CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022000/S-005

Trade Name: **LIALDA**

Generic Name: **Mesalamine**

Sponsor: **Shire Development Inc.**

Approval Date: 07/14/2011

Indications: LIALDA is a locally acting 5-aminosalicylic acid (5ASA) indicated for the induction of remission in adults with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22000/S-005

SUPPLEMENT APPROVAL

Shire Development Inc
Attention: Harris Rotman, Ph.D.
Global Regulatory Affairs
725 Chesterbook Blvd
Wayne, PA 19087-5637

Dear Dr. Rotman:

Please refer to your Supplemental New Drug Application (sNDA) dated June 14, 2010, received June 14, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LIALDA (mesalamine) Delayed Release Tablets, 1.2 g.

We acknowledge receipt of your amendments dated June 25, 2010, July 02, 2010, July 15, 2010, September 10, 2010, September 20, 2010, September 24, 2010, October 01, 2010, October 08, 2010, October 26, 2010, November 02, 2010, November 19, 2010, December 16, 2010, February 22, 2011, April 06, 2011, June 22, 2011, July 11, 2011, July 12, 2011 and July 14, 2011.

This "Prior Approval" supplemental new drug application is approved to change the labeling to include: "*maintenance of remission of ulcerative colitis*". It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 4 years because necessary studies are impossible or highly impracticable.

We are deferring submission of your pediatric study for ages 5 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

731-2 Deferred pediatric study under PREA for the maintenance of remission of ulcerative colitis in pediatric patients 5 to 17 years of age.

Final Protocol Submission:	05/2013
Study/Trial Completion:	12/2017
Final Report Submission:	05/2018

You should submit clinical protocols to your IND for this product and submit final study reports to this NDA. Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ANDREW E MULBERG
07/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LIALDA safely and effectively. See full prescribing information for LIALDA.

LIALDA® (mesalamine) delayed-release tablets, for oral use

Initial U.S. Approval: 1987

----------RECENT MAJOR CHANGES----------

Indications and Usage (1), 07/2011

Dosage and Administration (2), 07/2011

----------INDICATIONS AND USAGE----------

LIALDA is a locally acting 5-aminosalicylic acid (5-ASA) indicated for the induction of remission in adults with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis. (1)

------DOSAGE AND ADMINISTRATION-----

For induction of remission of active, mild to moderate ulcerative colitis, two to four 1.2 g tablets taken once daily with food. (1, 2)

For maintenance of remission of ulcerative colitis, two 1.2 g tablets taken once daily with food. (1, 2)

-----DOSAGE FORMS AND STRENGTHS----

Delayed-Release Tablets: 1.2 g (3)

----------CONTRAINDICATIONS----------

Patients with known hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of LIALDA tablets. (4)

------WARNINGS AND PRECAUTIONS-----

- Renal impairment may occur. Assess renal function at the beginning of treatment and periodically during treatment. (5.1)
- Mesalamine-induced acute intolerance syndrome has been reported. Observe patients closely for worsening of these symptoms while on treatment. (5.2)
- Use caution when treating patients who are hypersensitive to sulfasalazine. (5.3)
- Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported. (5.3)
- Hepatic failure has been reported in patients with pre-existing liver disease. Use caution when treating patients with liver disease. (5.4)
- Upper GI tract obstruction may delay onset of action. (5.5)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence ≥ 2 %) are ulcerative colitis, headache, flatulence, liver function test abnormality, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Nephrotoxic agents including NSAIDs: renal reactions have been reported. (7.1)
- Azathioprine or 6-mercaptopurine: blood disorders have been reported. (7.2)

-----USE IN SPECIFIC POPULATIONS-----

- Renal impairment: Use LIALDA with caution in patients with a history of renal disease. (5.1, 7.1, 8.5, 13.2)
- Nursing Women: Caution should be exercised when administered to a nursing woman. (8.3)
- Geriatric Patients: Monitor blood cell counts in geriatric patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: July 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LIALDA is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

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

3 DOSAGE FORMS AND STRENGTHS

The red-brown ellipsoidal delayed-release tablet containing 1.2 g mesalamine is debossed on one side and imprinted with S476.

4 CONTRAINDICATIONS

LIALDA is contraindicated in patients with known hypersensitivity to salicylates or aminosalicylates or to any of the ingredients of LIALDA *[*see *Warnings and Precautions (5.3), Description (11) Adverse Reactions (6.2)*]*.*

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products such as LIALDA that contain mesalamine or are converted to mesalamine.

It is recommended that patients have an evaluation of renal function prior to initiation of LIALDA therapy and periodically while on therapy. Exercise caution when using LIALDA in patients with known renal dysfunction or a history of renal disease.

In animal studies, the kidney was the principal organ for toxicity. *[See Drug Interactions (7.1) and Nonclinical Toxicology (13.2)]*

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash. Observe patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with LIALDA.

5.3 Hypersensitivity Reactions

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to LIALDA tablets or to other compounds that contain or are converted to mesalamine.

Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with LIALDA and other mesalamine medications. Caution should be taken in prescribing this medicine to patients with conditions predisposing them to the development of myocarditis or pericarditis.

5.4 Hepatic Impairment

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Caution should be exercised when administering LIALDA to patients with liver disease.

5.5 Upper GI Tract Obstruction

Pyloric stenosis or other organic or functional obstruction in the upper gastrointestinal tract may cause prolonged gastric retention of LIALDA which would delay mesalamine release in the colon.

6 ADVERSE REACTIONS

The most serious adverse reactions seen in Lialda clinical trials or with other products that contain or are metabolized to mesalamine are:

- Renal impairment, including renal failure *[See Warnings and Precautions (5.1)]*
- Mesalamine-induced acute intolerance syndrome *[See Warnings and Precautions (5.2)]*
- Hypersensitivity reactions *[See Warnings and Precautions (5.3)]*
- Hepatic impairment, including hepatic failure *[See Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

LIALDA has been evaluated in 1368 ulcerative colitis patients in controlled and open-label trials.

Induction of Remission

In two 8-week placebo-controlled clinical trials involving 535 ulcerative colitis patients, 356 received 2.4 g/day or 4.8 g/day LIALDA tablets and 179 received placebo. The most frequent adverse reaction leading to discontinuation from LIALDA therapy was exacerbation of ulcerative colitis (0.8%). Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with LIALDA in patients experiencing this event.

Adverse reactions occurring in LIALDA or placebo groups at a frequency of at least 1% in two 8-week, double blind, placebo-controlled trials are listed in Table 1. The most common adverse reactions with LIALDA 2.4 g/day and 4.8 g/day were headache (5.6% and 3.4%, respectively) and flatulence (4% and 2.8%, respectively).

Table 1: Adverse Reactions in Two Eight-Week Placebo-Controlled Trials Experienced by at Least 1% of the LIALDA Group and at a Rate Greater than Placebo[a]

Adverse Reaction	LIALDA 2.4 g/day (n = 177)	LIALDA 4.8 g/day (n = 179)	Placebo (n = 179)
Headache	10 (5.6%)	6 (3.4%)	1 (0.6%)
Flatulence	7 (4%)	5 (2.8%)	5 (2.8%)
Liver Function Test Abnormal	1 (0.6%)	4 (2.2%)	2 (1.1%)
Alopecia	0	2 (1.1%)	0
Pruritus	1 (0.6%)	2 (1.1%)	2 (1.1%)
a: Adverse reactions for which the placebo rate equalled or exceeded the rate for at least one of the LIALDA treatment groups were abdominal pain, dizziness, dyspepsia, and nausea.			

The following adverse reactions, presented by body system, were reported infrequently (less than 1%) by LIALDA-treated ulcerative colitis patients in the two controlled trials.

Cardiac Disorder: tachycardia

Vascular Disorders: hypertension, hypotension

Skin and Subcutaneous Tissue Disorders: acne, prurigo, rash, urticaria

Gastrointestinal Disorders: abdominal distention, colitis, diarrhea, pancreatitis, rectal polyp, vomiting

Investigations: decreased platelet count

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain

Nervous System Disorders: somnolence, tremor

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain

General Disorders and Administrative Site Disorders: asthenia, face edema, fatigue, pyrexia

Ear and Labyrinth Disorders: ear pain

Maintenance of Remission of Ulcerative Colitis

The dose evaluated in three studies of LIALDA given for the maintenance of remission in patients with ulcerative colitis was 1.2 g twice daily or 2.4 g/once daily. One of these studies was a 6-month double-blind comparator study while two were 12- to 14-month open-label studies.

The most common adverse reactions with LIALDA in the maintenance arms of long-term trials were colitis ulcerative (5.8%), headache (2.9%), liver function test abnormal (2.3%), and abdominal pain (2.2%). Of the 1082 subjects in the all maintenance studies pooled, 1.9% had severe adverse reactions. The most common

severe adverse reactions were gastrointestinal disorders; these were mainly symptoms associated with ulcerative colitis.

Table 2: Adverse Reactions in Three Maintenance Trials Experienced by at Least 1% of the LIALDA Group (maintenance phases of trials)

	All LIALDA (n=1082)	
Adverse Reaction	n	%
Colitis ulcerative	63	(5.8%)
Headache	31	(2.9%)
Liver function test abnormal	25	(2.3%)
Abdominal pain	24	(2.2%)
Diarrhea	18	(1.7%)
Abdominal distension	14	(1.3%)
Abdominal pain upper	13	(1.2%)
Dyspepsia	13	(1.2%)
Back pain	13	(1.2%)
Rash	13	(1.2%)
Arthralgia	12	(1.1%)
Fatigue	11	(1.0%)
Hypertension	10	(1.0%)

The following adverse reactions, presented by body system, were reported infrequently (less than 1%) by LIALDA-treated ulcerative colitis patients in the three long-term maintenance trials (maintenance phases of these trials):

Cardiac Disorder: tachycardia

Skin and Subcutaneous Tissue Disorders: acne, alopecia, pruritis, urticaria

Gastrointestinal Disorders: colitis, flatulence, nausea, pancreatitis, rectal polyp, vomiting

Nervous System Disorders: dizziness

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain

General Disorders and Administrative Site Disorders: asthenia, pyrexia

Ear and Labyrinth Disorders: ear pain

6.2 Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving LIALDA, the adverse reactions listed below have been identified during post-approval use of LIALDA and other mesalamine-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: lupus-like syndrome, drug fever

Cardiac Disorders: pericarditis, pericardial effusion, myocarditis

Gastrointestinal: pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer

Hepatic: jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes

Hematologic: agranulocytosis, aplastic anemia

Neurological/Psychiatric: peripheral neuropathy, Guillain-Barre syndrome, transverse myelitis

Renal Disorders: interstitial nephritis

Respiratory, Thoracic and Mediastinal Disorders: hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis)

Skin: psoriasis, pyoderma gangrenosum, erythema nodosum

Urogenital: reversible oligospermia

7 DRUG INTERACTIONS

No investigations of interaction between LIALDA and other drugs have been performed. However, the following interactions between mesalamine medications and other drugs have been reported.

7.1 Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions.

7.2 Azathioprine or 6-mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine may increase the risk for blood disorders.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies with mesalamine have been performed in rats at doses up to 1000 mg/kg/day (1.8 times the maximum recommended human dose based on a body surface area comparison) and rabbits at doses up to 800 mg/kg/day (2.9 times the maximum recommended human dose based on a body

surface area comparison) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Mesalamine is known to cross the placental barrier.

8.3 Nursing Mothers

Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. The clinical significance of this has not been determined and there is limited experience of nursing women using mesalamine. Caution should be exercised if LIALDA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of LIALDA in pediatric patients have not been established.

8.5 Geriatric Use

Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias, i.e., neutropenia and pancytopenia in patients who were 65 years or older who were taking mesalamine-containing products such as LIALDA. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

Clinical trials of LIALDA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic exposures are increased in elderly subjects. *[see Clinical Pharmacology (12.3)].* In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy in elderly patients.

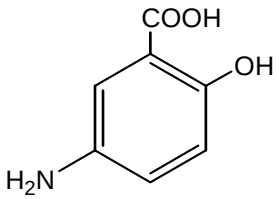
10 OVERDOSAGE

LIALDA is an aminosalicylate, and symptoms of salicylate toxicity may include tinnitus, vertigo, headache, confusion, drowsiness, sweating, seizures, hyperventilation, dyspnea, vomiting, and diarrhea. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, dehydration, and end organ damage.

There is no specific known antidote for mesalamine overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

11 DESCRIPTION

Each LIALDA delayed-release tablet for oral administration contains 1.2 g 5-aminosalicylic acid (5-ASA; mesalamine), an anti-inflammatory agent. Mesalamine also has the chemical name 5-amino-2-hydroxybenzoic acid and its structural formula is:



Molecular formula: $C_7H_7NO_3$
Molecular weight: 153.14

The tablet is coated with a pH dependent polymer film, which breaks down at or above pH 6.8, normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients and provides for extended release of mesalamine.

The inactive ingredients of LIALDA are sodium carboxymethylcellulose, carnauba wax, stearic acid, silica (colloidal hydrated), sodium starch glycolate (type A), talc, magnesium stearate, methacrylic acid copolymer types A and B, triethylcitrate, titanium dioxide, red ferric oxide and polyethylene glycol 6000.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mesalamine is not fully understood, but appears to have a topical anti-inflammatory effect on the colonic epithelial cells. 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.

Mesalamine has the potential to inhibit the activation of nuclear factor kappa B (NFκB) and consequently the production of key pro-inflammatory cytokines. It has been proposed that reduced expression of PPARγ nuclear receptors (γ-form of peroxisome proliferator-activated receptors) may be implicated in ulcerative colitis. There is evidence that mesalamine produces pharmacodynamic effects through direct activation of PPARγ receptors in the colonic/rectal epithelium.

12.2 Pharmacodynamics

The pharmacodynamic actions of mesalamine occur in the colonic/rectal mucosae local to the delivery of drug from LIALDA into the lumen. There is information suggesting that severity of colonic inflammation in ulcerative colitis patients treated with mesalamine is inversely correlated with mucosal concentrations of mesalamine. Plasma concentrations representing systemically absorbed mesalamine are not believed to contribute extensively to efficacy.

12.3 Pharmacokinetics

Absorption

The total absorption of mesalamine from LIALDA 2.4 g or 4.8 g given once daily for 14 days to healthy volunteers was found to be approximately 21-22% of the administered dose.

Gamma-scintigraphy studies have shown that a single dose of LIALDA 1.2 g (one tablet) passed intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labeled tracer in the colon, suggesting that mesalamine had distributed through this region of the gastrointestinal tract.

In a single dose study, LIALDA 1.2 g, 2.4 g and 4.8 g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalamine were detectable after 2 hours and reached a maximum by 9-12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects (Table 3). Mesalamine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was slightly more than dose proportional between 1.2 g and 4.8 g LIALDA. Maximum plasma concentrations (C_{max}) of mesalamine increased approximately dose proportionately between 1.2 g and 2.4 g and sub-proportionately between 2.4 g and 4.8 g LIALDA, with the dose normalized value at 4.8 g representing, on average, 74% of that at 2.4 g based on geometric means.

Table 3: Mean (SD) PK Parameters for Mesalamine Following Single Dose Administration of LIALDA Under Fasting Conditions

Parameter[1] of Mesalamine	LIALDA 1.2 g (N=47)	LIALDA 2.4 g (N=48)	LIALDA 4.8 g (N=48)
AUC_{0-t} (ng.h/mL)	9039[+] (5054)	20538 (12980)	41434 (26640)
$AUC_{0-\infty}$ (ng.h/mL)	9578[•] (5214)	21084 (13185)	44775[#] (30302)
C_{max} (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
T_{max}* (h)	9.0**(4.0-32.1)	12.0 (4.0-34.1)	12.0 (4.0-34.0)
T_{lag}* (h)	2.0** (0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
$T_{1/2}$ (h) (Terminal Phase)	8.56[•] (6.38)	7.05[§] (5.54)	7.25[#] (8.32)

[1] Arithmetic mean of parameter values are presented except for T_{max} and T_{lag}.

*Median (min, max); [+]N=43, [•]N=27, [§]N=33, [#]N=36, **N=46

Administration of a single dose of LIALDA 4.8 g with a high fat meal resulted in further delay in absorption, and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, a high fat meal increased systemic exposure of mesalamine (mean C_{max}: ↑91%; mean AUC: ↑16%) compared to results in the fasted state. LIALDA was administered with food in the controlled clinical trials that supported its approval.

In a single and multiple dose pharmacokinetic study of LIALDA, 2.4 g or 4.8 g was administered once daily with standard meals to 28 healthy volunteers per dose group.

Plasma concentrations of mesalamine were detectable after 4 hours and were maximal by 8 hours after the single dose. Steady state was achieved generally by 2 days after dosing. Mean AUC at steady state was only modestly greater (1.1- to 1.4-fold) than predictable from single dose pharmacokinetics.

In a single dose pharmacokinetic study of LIALDA, 4.8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young (18-35yrs); 28 elderly (65-75yrs); 15 elderly (>75yrs)). Increased age resulted in increased systemic exposure (approximately 2-fold in C_{max}), to mesalamine and its metabolite N-acetyl-5-aminosalicylic acid. Increased age resulted in a slower apparent elimination of mesalamine, though there was high between-subject variability. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Table 4: Mean (SD) PK Parameters for Mesalamine Following Single Dose Administration of LIALDA 4.8 g under Fasting Conditions to Young and Elderly Subjects

Parameter of 5-ASA	Young Subjects (18-35 yrs) (N=28)	Elderly Subjects (65-75 yrs) (N=28)	Elderly Subjects (>75 yrs) (N=15)
AUC_{0-t} (ng.h/mL)	51570 (23870)	73001 (42608)	65820 (25283)
$AUC_{0-\infty}$ (ng.h/mL)	58057[b] (22429)	89612[c] (40596)	63067[d] (22531)
C_{max} (ng/mL)	2243 (1410)	4999 (4381)	4832 (4383)
t_{max}[a] (h)	22.0 (5.98 – 48.0)	12.5 (4.00 – 36.0)	16.0 (4.00 – 26.0)
t_{lag}[a] (h)	2.00 (1.00 – 6.00)	2.00 (1.00 – 4.00)	2.00 (2.00 – 4.00)
$t_{½}$ (h), terminal phase	5.68[b] (2.83)	9.68[c] (7.47)	8.67[d] (5.84)
Renal clearance (L/h)	2.05 (1.33)	2.04 (1.16)	2.13 (1.20)

Arithmetic mean (SD) data are presented, N = Number of subjects
[a] Median (min - max), [b]N=15, [c]N=16, [d]N=13

Distribution

Mesalamine is approximately 43% bound to plasma proteins at the concentration of 2.5 µg/mL.

Metabolism

The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and intestinal mucosa cells, principally by NAT-1.

Elimination

Elimination of mesalamine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). However, there is also limited excretion of the parent drug in urine. Of the approximately 21-22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The apparent terminal half-lives for mesalamine and its major metabolite after administration of LIALDA 2.4 g and 4.8 g were, on average, 7-9 hours and 8-12 hours, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week dietary carcinogenicity study in CD-1 mice, mesalamine at doses up to 2500 mg/kg/day was not tumorigenic. This dose is 2.2 times the maximum recommended human dose (based on a body surface area comparison) of LIALDA. Furthermore, in a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose is 1.4 times the recommended human dose (based on a body surface area comparison) of LIALDA.

Mutagenesis

No evidence of mutagenicity was observed in an *in vitro* Ames test or an *in vivo* mouse micronucleus test.

Impairment of Fertility

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.7 times the maximum recommended human dose based on a body surface area comparison).

13.2 Animal Toxicology and/or Pharmacology

In animal studies with mesalamine, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis.

14 CLINICAL STUDIES

14.1 Active, Mild to Moderate Ulcerative Colitis

Two similarly designed, randomized, double blind, placebo-controlled trials were conducted in 517 adult patients with active, mild to moderate ulcerative colitis. The study population was primarily Caucasian (80%), had a mean age of 42 years (6% age 65 years or older), and was approximately 50% male. Both studies used LIALDA doses of 2.4 g/day and 4.8 g/day administered once daily for 8 weeks except for the 2.4 g/day group in Study 1, which was given in two divided doses (1.2 g twice daily). The primary efficacy end-point in both trials was to compare the percentage of patients in remission after 8 weeks of treatment for the LIALDA treatment groups

versus placebo. Remission was defined as an Ulcerative Colitis Disease Activity Index (UC-DAI) of ≤ 1, with scores of zero for rectal bleeding and for stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

In both studies, the LIALDA doses of 2.4 g/day and 4.8 g/day demonstrated superiority over placebo in the primary efficacy endpoint (Table 5). Both LIALDA doses also provided consistent benefit in secondary efficacy parameters, including clinical improvement, treatment failure, clinical remission, and sigmoidoscopic improvement. LIALDA 2.4 g/day and 4.8 g/day had similar efficacy profiles.

Table 5: Patients in Remission at Week 8

Dose	Study 1 (n=262) n/N (%)	Study 2 (n=255) n/N (%)
LIALDA 2.4 g/day	30/88 (34.1)	34/84 (40.5)
LIALDA 4.8 g/day	26/89 (29.2)	35/85 (41.2)
Placebo	11/85 (12.9)	19/86 (22.1)

14.2 Maintenance of Remission in Patients with Ulcerative Colitis

A multicenter, randomized, double-blind, active comparator study was conducted in a total of 826 adult patients in remission from ulcerative colitis. The study population had a mean age of 45 years (8% age 65 years or older), were 52% male, and were primarily Caucasian (64%).

Maintenance of remission was assessed using a modified Ulcerative Colitis Disease Activity Index (UC-DAI). For this trial, maintenance of remission was based on maintaining endoscopic remission defined as a modified UC-DAI endoscopy subscore of ≤1. An endoscopy subscore of 0 represented normal mucosal appearance with intact vascular pattern and no friability or granulation. For this trial the endoscopy score definition of 1 (mild disease) was modified such that it could include erythema, decreased vascular pattern, and minimal granularity; however, it could not include friability.

Subjects were randomized in a 1:1 ratio to receive either LIALDA 2.4 g/day administered once daily or mesalamine delayed release 1.6 g/day administered as 0.8 g twice daily. The proportion of patients who maintained remission at Month 6 in this study using LIALDA 2.4 g once daily (83.7%) was similar to that seen using the comparator (mesalamine delayed release) 1.6 g/day (81.5%).

16 HOW SUPPLIED/STORAGE AND HANDLING

LIALDA is available as red-brown ellipsoidal film coated delayed-release tablets containing 1.2 g mesalamine, and debossed on one side imprinted with S476.

NDC 54092-476-12 HDPE Bottle with a child-resistant closure of 120 delayed-release tablets.

Store at room temperature 15°C to 25°C (59°F to 77°F); excursions permitted to 30°C (86°F).

See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

- Instruct patients not to take LIALDA if they have hypersensitivity to salicylates (e.g., aspirin) or other mesalamines.
- Inform patients to let their physicians know all medications they are taking and if they:
    - are allergic to sulfasalazine, salicylates or mesalamine;
    - are taking non-steroidal anti-inflammatory drugs (NSAIDs) or other nephrotoxic agents;
    - are taking azathioprine, or 6-mercaptopurine;
    - experience cramping, abdominal pain, bloody diarrhea, fever, headache or rash;
    - have a history of myocarditis or pericarditis;
    - have kidney or liver disease;
    - have a history of stomach blockage;
    - are pregnant, intend to become pregnant or are breast-feeding.
- Patients should be instructed to swallow LIALDA delayed-release tablets whole, taking care not to break the outer coating. The outer coating needs to remain intact so that LIALDA is absorbed properly.

Manufactured for Shire US Inc., 725 Chesterbrook Blvd., Wayne, PA 19087, USA by Cosmo S.p.A., Milan, Italy. By license of Giuliani S.p.A., Milan, Italy.

U.S. Patent No. 6,773,720.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # Supplement #	022-000
Applicant Name	Shire
Date of Submission	June 14, 2010
PDUFA Goal Date	April 16, 2011-original; July 16, 2011-extension
Proprietary Name / Established (USAN) Name	Lialda/mesalamine
Dosage Forms / Strength	1.2 gram tablet
Proposed Indication(s)	Maintenance of remission (b) (4) UC
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Aisha Peterson Johnson, MD, MPH, MBA, Reviewer
CDTL Review	Anil Rajpal, MD
Nonclinical Reviewer	Sushanta Chakder
Epidemiology	Christian Hampp
SEALD	Jeanne Delasko
ONDQA	Thomas Oliver
Clinical Pharmacology Team Leader	Sue Chih Lee
Clinical Pharmacology Reviewer	Kris Estes
CMC Team Leader	Marie Kowblansky
CMC Reviewer	Yong Wang
DSI	Khairy Malek
DDMAC	Kathleen Klemm
DMEPA	Denise Baugh

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

In this NDA supplement, the applicant proposes to expand the indication for Lialda to the following indication:

1) maintenance of remission (b) (4) UC.

Mesalamine is a locally acting 5-aminosalicylic acid indicated for the induction of remission in adults with active, mild to moderate ulcerative colitis. The current dosing regimen is two to four 1.2 g tablets once daily with food for up to 8 weeks. This supplemental 505(b)(1) NDA application included the final report of the pivotal study, SPD476-304 (Study 304). This study was a Phase 3, randomized, double-blind, parallel-group, active comparator study, conducted globally in subjects with ulcerative colitis (UC) in endoscopic remission conducted at multiple centers in 27 countries worldwide. The study was designed to show that LIALDA 2.4g/day given once daily is non-inferior to ASACOL 1.6g divided twice daily in maintaining endoscopic remission of UC (mucosal healing). ASACOL was selected as the comparator. The primary efficacy variable for this study was the maintenance of mucosal healing. A modified UCDAI score was used to assess efficacy and was comprised of four indices of disease: stool frequency, rectal bleeding, mucosal appearance, and a physician's rating of disease severity. Each index is evaluated on a scale of 0 to 3, with a maximum total score of 12. To improve the clarity of the UCDAI, the scale was amended such that an endoscopy score of 1 (mild disease) did not include the term friability. Instead, friability was scored 2 (moderate disease). Mucosal healing for this study was defined as an endoscopy score of ≤1 at Month 6. All patients who entered the study were to have a previous diagnosis of UC confirmed by histology that was considered in remission for ≥30 days. Specifically, on admission to the study, patients had to have both an endoscopy score of ≤1 and a combined symptom score (stool frequency and rectal bleeding) of ≤1.

The primary efficacy variable was the proportion of subjects in endoscopic remission (maintenance of mucosal healing) at Month 6 in each treatment group as defined by an endoscopy score of ≤1. Study 304 was planned as a non-inferiority study and the SAP specified that the per protocol (PP) population was to be used for the primary analysis. The per protocol population excluded all patients who withdrew for reasons other than lack of efficacy or adverse events and/or had missing endoscopy data at Month 6. Patients who withdrew early for other reasons were considered treatment failures (i.e. not in remission). Additionally, PP patients could not have had any major protocol deviations.

According to the Applicant, the study was designed to test the null hypothesis that the difference in proportion of patients in remission between the Lialda and Asacol groups was less than or equal to -10%. Non-inferiority was to be concluded if the lower limit of the 95% CI of the difference was above the non-inferiority margin of -10%. Superiority was to be concluded if the 95% CI of the difference was above -10 and above 0.

After planned enrollment was completed, the applicant submitted Amendment #2: To change the clinical assumption of the 1.6 g/day Asacol response rate from 65% to 70% based on the results of the ITT population of the Mesalamine Study Group[1]. This change increased the study size from 416 to 832 patients and increased the number of study centers from 65 to 130 and increased the number of countries by 5. There were a total of 6 amendments to the protocol submitted to the FDA.

Several concerns were raised during the review of this application as addressed by the Clinical and Statistical Reviewers, Drs. Johnson and Fan, which resulted in multiple internal discussions regarding approvability. Several critical issues affecting the level of statistical evidence included an unplanned sample size adjustment and the interpretation of the non-inferiority comparisons. Protocol conduct was characterized by major protocol violations of the ITT population which required a review of its impact on the analysis population (ITT versus PP) to make a non-inferiority assessment and an assessment of effectiveness. The Statistical Team Leader, Dr. Welch, is of the opinion that analyses of the overall study population are most relevant and that separate analyses based on enrollment phases 1 and 2 should be considered "sensitivity analyses and it should not be expected that they individually meet the (more rigid) non-inferiority criteria." This issue is discussed in Section 8 Clinical more fully.

Having considered all the issues raised, I conclude and agree with the Dr. Johnson's and Rajpal's reviews for Approval of this NDA supplement. The data provided offer sufficient evidence of efficacy and safety for the proposed use of Lialda for the maintenance of remission of ulcerative colitis. Dr. Welch also provided the critical perspective that "approvability is supported generally based on the combined results where both the ITT and the PP analyses argue in favor of the similarity of the two products." Despite the issues surrounding the interpretation of the noninferiority margins, the data support effectiveness of the product.

In summary the data in this application do establish that Lialda 1.2 gram tablets are effective and safe for the maintenance of remission of patients with ulcerative colitis. My review will focus on the salient issues related to this risk/benefit assessment.

2. Background

Lialda has been previously approved as a locally acting 5-aminosalicylic acid indicated for the induction of remission in adults with active, mild to moderate ulcerative colitis. The Applicant proposes that this high-strength formulation of 5-ASA (1.2 g tablet) utilizes MMX Multi Matrix System® technology comprising lipophilic and hydrophilic excipients enclosed within a gastro-resistant, pH-dependent coating. The gastroresistant film, covering the tablet core, delays the initial release of 5-ASA until the tablet is exposed to pH 7 or higher, normally in the terminal ileum. As the gastro-resistant coating disintegrates, it is thought that intestinal fluids interact with the hydrophilic excipient causing the tablet to swell (much like a sponge in water) and form an outer viscous gel mass. The viscous gel mass is believed to slow diffusion of the

[1] The Mesalamine Study Group. An Oral Preparation of Mesalamine as Long Term Maintenance therapy for Ulcerative Colitis. Ann Intern Med, 1996;124:204-211.

5-ASA from the tablet core into the colonic lumen. As the tablet core and its surrounding gel mass progress through the colon, it is thought that pieces of the gel mass gradually break away from the core, releasing 5-ASA. It is presumed that the lipophilic excipient slows the penetration of aqueous fluids into the tablet core, reducing the rate of dissolution and thus prolonging therapeutic activity. Final labeling reflects altered wording related to the proposed mechanism of release as the CMC and ONDQA reviewers believed that this was promotional in nature and not supported by data provided by the Applicant (see section 12, Labeling for further discussion of this issue.)

There are a number of competing mesalamine based products approved for induction and maintenance therapy in ulcerative colitis with variant formulations and delivery systems as outlined below in Table 1: Marketed Formulations of Mesalamine. The active moiety remains the same, which is a mesalamine molecule or a derivatization of the mesalamine structure:

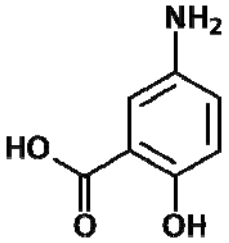
Mesalamine (5-ASA): 

Table 1: Marketed Formulations of Mesalamine

Drug Name	Approval	Applicatior	Sponsor	Strength	Dosage	Frequency	Route	Delivery System
ROWASA	12/24/1987	19618	ALAVEN PHARM	4GM/60ML	4GM/60ML	once daily	rectal	n/a
ASACOL	1/31/1992	19651	WARNER CHILCOTT	400 mg	3-4 g	divided doses	oral	Eudragit S (methacrylic acid copolymer B, NF)
PENTASA	5/10/1993	20049	SHIRE	500 mg	4 g	qid	oral	prolonged-release microgranules
CANASA	5/1/2001	21252	AXCAN	500/1000 mg		bid or qd	rectal	suppository vehicle
MESALAMINE	9/17/2004	76751	PERRIGO ISRAEL	4GM/60ML	4GM/60ML	once daily	rectal	n/a
MESALAMINE	9/30/2004	76841	TEVA	4GM/60ML	4GM/60ML	once daily	rectal	n/a
LIALDA	1/16/2007	22000	SHIRE	1.2 g	2.4-4.8 g	once daily	oral	MMX: polymer matrix with enteric coating
ASACOL HD	5/29/2008	21830	WARNER CHILCOTT INC	800 mg	4.8 g	tid	oral	Eudragit S (methacrylic acid copolymer B, NF)
APRISO	10/31/2008	22301	SALIX	375 mg	1.5 g	once daily	oral	Intellicor: polymer matrix with enteric coating

Active Controlled Trials and Non-Inferiority Assumptions:
This application requires an understanding of the use and definition of an active controlled trial and be interpreted in light of the need for testing against placebo comparator. Temple and Ellenberg (2000) have commented on the ethical basis for placebo-controlled studies and potential weaknesses of active controlled trials. Temple states: "Clinical trials that, because of deficiencies in study design or conduct, are unlikely to provide scientifically valid and clinically meaningful results raise their own ethical issues. If active controlled equivalence trials (ACETs) were always adequate substitutes for placebo-controlled trials, the ethical issue might not arise. Unfortunately, ACETs are often uninformative. They can neither demonstrate the effectiveness of a new agent nor provide a valid comparison to control therapy unless assay sensitivity can be assured, which often cannot be accomplished without inclusion of a

concurrent placebo group."[2] The Non-inferiority Clinical trials guidance further states, "Although a successful superiority trial (e.g., placebo-controlled) is readily interpreted, a failed trial of this design is not. Failure to show superiority to placebo can mean that the drug is ineffective or that the trial lacked assay sensitivity. To distinguish between these two possibilities, it is often useful to include an active control in placebo-controlled studies of drugs in a class or condition where known effective drugs often cannot be distinguished from placebo (e.g., depression, allergic rhinitis, angina, and many other symptomatic conditions). If the active control is superior to placebo but the test drug is not, one can conclude that the test drug lacks effectiveness (or at least is less effective than the active control). If neither the active control nor the test drug is superior to placebo, the trial lacked assay sensitivity and is uninformative about the effect of the test drug."[3]

There is a critical need to review the background of other published study designs as they relate to the current review. The historical controls that are referenced need to be analyzed in terms of assay sensitivity of the active against placebo comparator to lay the groundwork for interpreting the Lialda dataset. If the chosen M_1 does in fact represent the entire effect of the active control drug in the NI study, a finding of non-inferiority means that the test drug has an effect greater than 0. Assay sensitivity (AS) means that the control drug had at least the effect that it was expected to have (i.e. M_1).[4] The choice of M_1, and the decision on whether a trial will have AS (i.e., the active control would have had an effect of at least M_1), is based on three considerations: (1) historical evidence of sensitivity to drug effects; (2) the similarity of the new NI trial to the historical trials (the constancy assumption), and (3) the quality of the new trial (ruling out defects that would tend to minimize differences between treatments). As stated in the Non-inferiority Clinical Trials Guidance, 21 CFR 92 314.126(a)(2)(iv), says: "If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug."[5] The conclusion of effectiveness of Lialda in maintenance of remission of ulcerative colitis is mostly supported by the demonstration of acceptance of the M_1 margin which is critical to concluding treatment efficacy. A conclusion of non-inferiority from a statistical perspective is based on the margin M_2 which represents a clinical judgment. Therefore, there can be flexibility in interpreting the 95% upper bound of difference that is greater than M_2 as long as the upper bound is within M_1. These conditions have been satisfied with the PP results of Study 304. It is my opinion to conclude that the current application provides sufficient evidence for approval of Lialda. These issues are discussed more fully below.

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[2] Temple R and Ellenberger SS. **Placebo-Controlled Trials and Active-Control Trials in the Evaluation of** New I. Treatments. Part 1: Ethical and Scientific Issues Ann Int Med 2000;133:455-463.

[3] Non-inferiority Clinical Trials Gudiance,
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf

[4] Non-inferiority Clinical Trials Guidance.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf

[5] Non-inferiority Clinical Trials Guidance.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf

The following Table reproduced from Dr. Peterson's summary is a comparison of maintenance of remission rates of mesalamine or its derivatives against placebo from previously-published, randomized, placebo-controlled studies. These data show a statistically significant difference between placebo and mesalamine treatment for the maintenance of remission of UC. Two of the referenced studies of mesalamine products (Asacol and Apriso) were used in support of approval for the maintenance of UC indication for these two products. These studies had definitions of remission comparable to that used for Study 304 with similar study durations. Placebo remission rates for similar trials ranged from 40% to 68%. The remission rates for Lialda in the submitted trial, Study 304 ranged from 77% to 84% depending on which phase and population is analyzed. The statistical considerations impacting on determination of effectiveness and non-inferiority are discussed below in section 7.

Table 2: Cross-Study Comparison of Mesalamine Maintenance of Remission Rates
(Reproduced from Clinical Reviewer summary)

Study Drug	Definition of Remission	Time of Analysis	Maintenance of Remission Rate	
			Active Drug	Placebo
Lialda registration trial* NDA 22-000 S-005 (mesalamine) 2.4 g/day	endoscopy score ≤1 (intact vascular pattern, no friability or granulation; or erythema, decreased vascular pattern, minimal granularity)	6 months	ITT Ph1- 78.4% Ph2- 84.2%	n/a
			PP Ph1- 83.1% Ph2- 84.2%	
Mesalamine Study Group[i] Mesalamine 1.6 g/day	endoscopy score =0 (normal or mild granularity, edema, hyperemia, or erythema; mildly diminished vascular markings)	6 months	ITT 70.1%	ITT 48.2%
			Evaluable 65.5%	Evaluable 39.7%
Hawkey, et al.[ii] Mesalamine 1.6 g/day	endoscopy score=0 (not specifically defined in article) *and* <3 consecutive days of rectal bleeding *and* <1 week of liquid stools	6 months	Evaluable 62.8%	Evaluable 42.9%
Apriso registration trials[iii] (encapsulated mesalamine granules) 1.5 g/day	endoscopy score ≤1 (intact mucosa with preserved or distorted vessels; or erythema, decreased vascular pattern, granularity, and no mucosal hemorrhage) *and* rectal bleeding score =0 (absence of bleeding)	12 months	ITT Study 1- 78.9% Study 2- 79.9%	ITT Study 1- 58.3% Study 2- 67.7%
			PP Study 1- 78.5% Study 2- 80.1%	PP Study 1- 59.1% Study 2- 67.4%

3. CMC

Lialda is currently available in the U.S. in the form of 1.2 g tablets. No new dosage form or dose is planned for the proposed indication. Therefore, the Applicant did not submit any new CMC information, omitting Module 3 and Module 2 CMC QOS sections.

4. Nonclinical Pharmacology/Toxicology

This supplemental application presented no change to preclinical pharmacology/toxicology of the drug product; no new review issues are identified and no nonclinical issues were raised. Animal pharmacology/toxicology data were reviewed previously under the original NDA 22-000 and are described in the current Lialda label.

5. Clinical Pharmacology/Biopharmaceutics

This supplemental application presented no change to clinical pharmacology of the drug product; therefore no review was required.

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this supplemental application because the product is not an antimicrobial product.

7. Clinical/Statistical-Efficacy

I do concur with the reviews of Drs. Peterson, Welch and Rajpal who have disagreed with Dr. Fan regarding the demonstration of efficacy of Lialda for the maintenance treatment of ulcerative colitis. The pivotal study, SPD476-304 (Study 304), was a Phase 3, randomized, double-blind, parallel-group, active comparator study conducted at multiple centers in 27 countries worldwide. The study was designed to show that LIALDA 2.4g/day given once daily is non-inferior to ASACOL 1.6g/day given twice daily in maintaining endoscopic remission of UC (mucosal healing). This study enrolled subjects with ulcerative colitis (UC) in endoscopic remission. Subjects were randomized in a 1:1 ratio to receive either SPD476 2.4g/day administered QD or ASACOL 1.6g/day divided dose, administered as 0.8g BID). There were 5 study visits, starting with a screening visit up to 2 weeks prior to subject randomization onto study medication. The treatment period lasted for 6 months and involved 4 visits: baseline (Month 0), Month 1, Month 3, and Month 6 (end of study). Subjects may also have attended an unscheduled study visit at any time during the study if there was a return or worsening of UC symptoms. Subjects had a monthly telephone contact for safety assessments, and were contacted 30 days after the end-of-study visit for a safety follow-up call.

Several critical issues affecting the level of statistical evidence included an unplanned sample size adjustment and the interpretation of the non-inferiority comparisons. Protocol conduct was characterized by major protocol violations of the ITT population which required a review of its impact on the analysis population (ITT versus PP) to determine whether non-inferiority was achieved. Dr. Welch is of the opinion that analyses of the overall study population are most relevant and that separate analyses of Study 304 based on enrollment phases 1 and 2 should be considered "sensitivity analyses and it should not be expected that they individually meet the (more rigid) non-inferiority criteria." This issue is discussed below more fully.

a. Revision to Sample Size:

The study planned to enroll 410 subjects. Amendment #2 revised the clinical assumption of the 1.6 g/day Asacol response rate from 65% to 70% based on the results of the ITT population reported by the Mesalamine Study Group. The protocol amendment was submitted to FDA with the Statistical Analysis Plan finalized a few days after conclusion of study conduct. The increase in sample size was unplanned and was seriously questioned by Dr. Fan. In the NDA, the Applicant submitted the analysis population for Study 304 as the combined population and Statistics requested that the individual phases be analyzed separately. Table 3 below demonstrates the 2 different phases of the recruitment of subjects in this trial:

Table 3: Populations Used for Evaluation, Study 304 (Clinical Reviewer Summary)

POPULATION	PHASE 1		PHASE 2		COMBINED	
	Lialda	Asacol	Lialda	Asacol	Lialda	Asacol
Randomized	209	209	207	204	416	413
ITT/Safety	208	208	207	203	415	411
Per Protocol	178	179	165	157	343	336

b. Subject Disposition and Protocol Violations:

In the review of Dr. Johnson, there were a significant number of patients in the ITT population who had major protocol violations, as defined by the SAP. Of those patients randomized, 147 (17.8%) were excluded from the PP population for protocol violations. There were more protocol violations during phase 2 than during phase 1, 102 and 68, respectively. The proportion of patients treated with Lialda (across both phases) with protocol violations was similar to the proportion of Asacol-treated patients with protocol violations, 17.3% and 18.2% respectively. See Table 4 below:

Table 4: Failed Inclusion Criteria, by Phase

	PHASE 1			PHASE 2			COMBINED		
	Lialda	Asacol	Total	Lialda	Asacol	Total	Lialda	Asacol	Total
Total ITT patients	208	208	416	207	203	410	415	411	826
Failed Inclusion Criteria	n (%)								
Satisfactory medical assessment	2 (1.0)	0	2 (0.5)	0	0	0	2 (0.5)	0	2 (0.2)
Histology-confirmed dx of UC	0	0	0	3 (1.4)	7 (3.,4)	10 (2.4)	3 (0.7)	7 (1.7)	10 (1.2)
UC in remission for ≤30 days	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	4 (0.5)
Baseline endoscopy score ≥1	0	0	0	0	1 (0.5)	1 (0.2)	0	1 (0.2)	1 (0.1)
Baseline line combined sx score of ≥1	3 (1.4)	2 (1.0)	5 (1.2)	1 (0.5)	4 (2.0)	5 (1.2)	4 (0.1)	6 (1.5)	10 (1.2)
Stable dose of 5-ASA for ≥30 days prior to baseline	11 (5.3)	11 (5.3)	22 (5.3)	10 (4.8)	11 (5.4)	21 (5.1)	21 (5.1)	22 (5.6)	43 (5.2)
≥1 acute episode of UC in past 12 months	1 (0.5)	2 (1.0)	3 (0.7)	0	0	0	1 (0.2)	2 (0.5)	3 (0.4)

Adapted from Table 1 8 (p 266/464), SPD476-304 by Enrollment,, CSR SPD476-304, Final

Events categorized as major protocol violations were defined in the Statistical Analysis Plan and agreed upon prior to data lock and unblinding, according to the Applicant. The most common protocol violation was failure to meet all inclusion criteria. Of the inclusion criteria, the one most frequently not met was the requirement to be on a stable dose of 5-ASA of ≤2.4 g/day (or sulfasalazine ≤6.2 g/day) for 30 days prior to baseline evaluation for study enrollment. The implication of not being maintained on stable dose prior to enrollment would clearly impact on the interpretability of the data.

Table 5: Demographics, Study 304

Adapted from Table 2 (p 13/464), Table 12 (p 36/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

Demographic Subgroup	PHASE 1 N=416			PHASE 2		
	Lialda N= 208	Asacol N= 208	Phase 1 (All) N=416	Lialda N= 207	Asacol N= 203	Phase 2 (All) N=410
Sex (n,%)						
Male	101 (48.6%)	114 (54.8%)	215 (51.7%)	111 (53.6)	100 (49.3)	211 (51.5%)
Female	107 (51.4%)	94 (45.2%)	201 (48.3%)	96 (46.4%)	103 (50.7%)	199 (48.5%)
Age (years) (n,%)						
Mean (SD)	44.2 (13.5)	45.5 (13.4)	44.9 (13.5)	45.9 (14.5)	44.8 (13.5)	45.3 (14.0)
Median	44.0	45.5	45.0	46.0	45.0	45.0
min,max	18, 80	18, 85	18, 85	18, 85	19, 76	18, 85
Race^ (n,%)						
Caucasian	154 (74.0%)	156 (75.0%)	310 (74.5%)	118 (57.0%)	103 (50.7%)	221 (53.9%)
Black	4 (1.9%)	1 (0.5%)	5 (1.2%)	5 (2.4%)	3 (1.5%)	8 (2.0%)
Hispanic	5 (2.4%)	6 (2.9%)	11 (2.6%)	14 (16.8%)	17 (8.4%)	31 (7.6%)
Asian/ PI*	42 (20.2%)	40 (19.2%)	82 (19.7%)	61 (29.5%)	66 (32.5%)	127 (31.0%)
Other	3 (1.4%)	5 (2.4%)	8 (1.9%)	9 (4.3%)	14 (6.9%)	23 (5.6%)

The data represented in Table 5 demonstrate the demographic differences in the populations enrolled in Phases 1 and 2. There are particular differences between phases in the number of Asian/Pacific Islanders enrolled. There are data suggesting that genotype of N-acetyltransferase activity affecting slow acetylator status is not frequent in Asians.[6] The enzymes arylamine *N*-acetyltransferases (NAT) metabolize a range of hydrazines and arylamines, including mesalamine. There are 2 NAT isozymes in humans, NAT1 and NAT2, both of which are now known to be polymorphic. Both NAT1 and NAT2 activities have been described in intestine, and these enzymes catalyze the *N*-acetylation of mesalamine. NAT genes are encoded on chromosome 8p22; NAT polymorphisms may be associated with different responses to mesalamine therapy. A study that examined NAT1 and NAT2 polymorphisms in ulcerative colitis patients found no association with therapeutic responses to mesalamine although the study had a predominance of Caucasian population. Therefore, neither Dr. Johnson nor I believe that there are clinical implications to approvability of Lialda based on these population differences.

c. Non-inferiority Margin Assumptions:

The non-inferiority margin assumptions for Study 304 were changed during the conduct of the study by the Applicant. The Medical and Statistical reviews summarize the assumptions underlying the non-inferiority margin assumptions but are recapitulated briefly here. Dr. Fan believes that the sponsor's pre-specified non-inferiority margin of 10% was obtained by taking 50% of treatment effect of mesalamine relative to placebo but did not consider study-to-study variability of treatment effects of mesalamine.

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[6] Hein DW et al. Molecular Genetics and Epidemiology of the *NAT1* and *NAT2* Acetylation Polymorphism. Cancer Epidemiol Biomarkers Prev January 2000 *9;* 29

At the request of Dr. Fan, the applicant applied the new FDA non-inferiority guidance, and determined that, based on the PP results from the Mesalamine Study Group Trial, M1 would be defined as -8.6%. Assuming that at least 50% of M_1 would be maintained, M_2 would be defined -4.3%. In his review, Dr. Fan further discusses his rationale for the non-inferiority margin M_2 to be in the range of 3.8 - 4.3 and that the M_1 should be calculated as 7.6% (based on the ITT results from the Mesalamine Study Group Trial). Dr. Fan fully discusses his perspective that the trial does not meet non-inferiority criteria relative to the active comparator, Asacol, although clinical effectiveness was demonstrated.

Given the unplanned sample size adjustment, one could not rule out that there had been an interim examination of the results by the applicant, and therefore separate analyses of the overall results and the individual phases were considered. More statistical credibility was associated with Phase 1 of the trial according to Dr. Fan and drove the primary analyses for the overall population. Dr. Welch differed from the primary statistical reviewer in that the combined data from the entire trial based on both the ITT and PP populations were more appropriate. Analyses of the separate phases would be considered sensitivity analyses and would therefore not be expected to achieve separate criteria for non-inferiority. Support for this perspective is made by the higher precision from a larger sample size in a population (for further discussion see Statistical Team Leader Memorandum).

Dr. Fan concluded that the results from Phase 1 using M_2 as the NI margin were inconclusive for demonstration of non-inferiority. He added that if the M_1 was acceptable as the NI margin from a clinical perspective, then this study would have just barely met the non-inferiority criteria. As per Dr. Rajpal, Dr Johnson noted that the NI margin of 10% was pre-specified by the Applicant; i.e., the statistical analysis plan specified that non-inferiority of Lialda to Asacol would be concluded if the lower limit of the 95% CI for the difference (Lialda-Asacol) was above the NI margin of 10%. Dr. Welch stated that the unplanned sample increase does not necessarily invalidate the results. He recommends using the combined results and notes that both PP and ITT analyses argue in favor of the similarity of the two products if the NI margin recommended by the Clinical Reviewer (i.e., 6% to 7%) is used". To calculate an appropriate M_2, the lower bound of the 95% confidence interval (8.6%) of the active control from the Mesalamine Group Study should be chosen as the conservative choice for the active comparator effect size, M_1. Next, the largest clinically acceptable degree of inferiority of 20% to 30% is used to discount M_1 which leads to an M_2 of 6% to 7%. He further commented that "a "formal" conclusion of non-inferiority is not justified due to the *post hoc* nature of the "margin finding" exercises (where there seems to be some disagreement on what margin is more correct)." Further discussion of the impact of the non-inferiority margin on approvability and the effectiveness in PP and overall populations is in section **d** below.

d. ITT versus PP Analysis:

The per protocol (PP) population included all patients in the ITT population who either completed the study or withdrew for reasons related to lack of efficacy or adverse events (AEs) and were considered protocol-compliant. Specific details can be found in Table 13 in Dr. Johnson's review entitled, Patient Disposition. Table 6 reflected below demonstrates the efficacy of both populations tested as Phase 1 and Phase 2 as well as combined analysis.

Table 6: Proportion of Patients in Endoscopic Remission at Month 6, Study 304

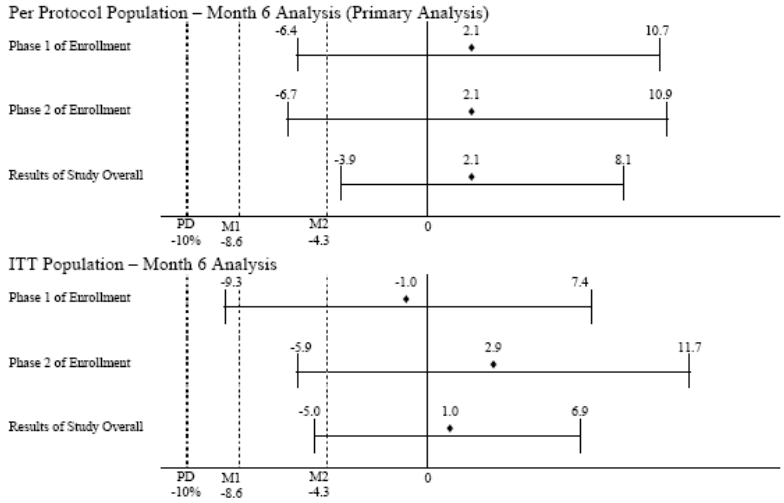
Reproduced from Dr. Johnson's summary

		PHASE 1	PHASE 2	COMBINED
Intent-to-Treat Population	Lialda 2.4 g/day	78.4% (163/208)	77.3% (160/207)	77.8% (323/415)
	Asacol 1.6 g/day	79.3% (165/208)	74.4% (151/203)	76.9% (316/411)
	Difference (Lialda-Asacol)	-1.0%	2.9%	0.9%
	95% Confidence Interval	-9.3%, 7.4%	-5.9%, 7.0%	-5.0%, 7.0%
Per Protocol Population	Lialda 2.4 g/day	83.1% (148/178)	84.2% (139/165)	83.7% (287/343)
	Asacol 1.6 g/day	81.0% (145/179)	82.2% (129/157)	81.5% (274/336)
	Difference (Lialda-Asacol)	2.1%	2.1%	2.1%
	95% Confidence Interval	-6.4%, 10.7%	-6.7%, 10.9%	-4.0%, 8.0%

The primary analyses for PP and ITT for Phase 1, 2 and overall study for the 6 month endpoint is represented graphically below. These data are presented to illustrate the support for the approvability of this supplement. As I discussed above, I agree with the Statistical Team Leader that the overall population reflects on the appropriate population for analysis. There are no discrete differences in the individual Phase 1 and 2 populations that would necessarily affect the assessment of effectiveness. Furthermore, as shown below, the only analysis that demonstrates lack of meeting non-inferiority margin criteria was that for the Phase 1 enrollment of the ITT population. All other analyses including Phases 1, 2 and overall study results for the PP population and Phase 2 and overall study results of the ITT population demonstrate meeting non-inferiority boundaries set forth in the protocol and support effectiveness.

If the chosen M_1 does in fact represent the entire effect of the active control drug in the NI study, acceptance of M_1 is critical to the conclusion of treatment efficacy. Therefore, if the M1 margin (i.e., 7.6% based on the ITT population of the Mesalamine Study Group trial or 8.6% based on the PP population of that trial), then the phase of enrollment and populations that meet effectiveness criteria are (see figure below):

Endoscopic Remission (Maintenance of Mucosal Healing) by Phase of Enrollment: SPD476 – ASA (Difference, 95% CI)



- Meet Effectiveness Criteria: Phase 1 (PP), Phase 2 (PP and ITT), Combined (PP and ITT)
- Do not Meet Effectiveness Criteria: Phase 1 (ITT)

It should be noted that Dr. Fan commented that if the M_1 was acceptable as the NI margin from a clinical perspective, and if only Phase 1 was analyzed, then this study would have "just barely met non-inferiority criteria." It should also be noted that the secondary statistical reviewer recommended that combined results be used and that a descriptive approach to labeling the results is appropriate. A conclusion though of non-inferiority is based on the margin M_2. Labeling of Lialda will include descriptive summary of complete trial dataset stating: "proportion of patients who maintained remission at Month 6 in this study using LIALDA 2.4 g once daily (83.7%) was similar to that seen using the comparator (mesalamine delayed release) 1.6 g/day ((b) (4) 81.5%)." Further support for this decision is discussed in section 9 of this summary which reviews the deliberations of the Senior Statistical leadership in review of definition of M_1 and M_2 margins.

Therefore, I conclude that Study 304 is supportive of efficacy and can be adequately described in the product labeling for Lialda.

8. Safety

Mesalamine products are generally associated with the following Warnings and Precautions as identified in the current label:

- Renal impairment may occur

(b) (4)

- Mesalamine-induced acute intolerance

(b) (4)

In her review of Study 304 by Dr. Johnson, the summary review of SAEs reported do not reflect any increased incidence of reported ADRs currently labeled as presented in Tables 7 and 8 below:

Table 7: Summary of Safety Results

	Study 304		All Lialda N=1082
	RCT Lialda N=415	Asacol N=411	
	n (%)	n (%)	n(%)
Any Adverse Event	155 (37.4)	148(36.0)	123 (59.1)
Any treatment-related AE	52 (12.6)	45 (10.9)	24 (11.5)
Any Severe AE	11 (2.7)	12 (2.9)	15 (7.2)
Serious Adverse Event (SAE)	6 (1.4)	3 (0.7)	9 (0.4)
Discontinuation due to Adverse Event (DAE)	8 (2.0)	4 (1.0)	15 (7.2)
Deaths	0	0	1 (0.0)

Table 8: Serious Adverse Events, Study 304

	SPD476 2.4g/day QD N=415		ASACOL 1.6g/day divided BID N=411	
MedDRA System Organ Class/Preferred Term	N	(%)	N	(%)
Gastrointestinal Disorders	2	(0.5)	1	(0.2)
Colitis	1	(0.2)	0	
Colitis ulcerative	1	(0.2)	1	(0.2)
Infections and Infestations	2	(0.5)	0	
Appendicitis	1	(0.2)	0	
Bronchitis	1	(0.2)	0	
Injury, Poisoning, and Procedural Complications	1	(0.2)	1	(0.2)
Fallopian tube perforation	0		1	(0.2)
Post procedural haemorrhage	1	(0.2)	0	
Musculoskeletal and Connective Tissue Disorders	0		1	(0.2)
Intervertebral disc protrusion	0		1	(0.2)
Nervous System Disorders	1	(0.2)	0	
Radiculitis brachial	1	(0.2)	0	
Pregnancy, Puerperium, and Perinatal Conditions	0		1	(0.2)
Ectopic pregnancy	0		1	(0.2)
Respiratory, Thoracic, and Mediastinal Disorders	1	(0.2)	0	
Asthma	1	(0.2)	0	
Subjects With ≥1 Treatment-emergent SAE	6	(1.4)	3	(0.7)

Adapted from Tables 6 and 7 (p 20/57) Section 2.7.4 Summary of Clinical Efficacy

I concur that no new safety issues were raised from this development program concerning Lialda.

9. Advisory Committee Meeting

No advisory meeting was held to discuss this application.

On June 24, 2011, Dr. Milton Fan presented this Application during a session of the Office of Biostatistics Statistical Rounds. The Rounds included discussion of some of the key statistical questions concerning this Application (for further detailed questions asked of this committee, the reader is referred to the Statistical review for full discussion of the rounds). For this efficacy supplement (NDA 22-000-005), **Lialda** 2.4 g/day dose was compared to **Asacol** 1.6 g/day dose with the intention of showing non-inferiority of Lialda to Asacol. Particularly, the responses to question #3 by Dr. Bob O'Neill and others support the decision of approvability of this application. The question stated: "For Case Study 1, the test drug and active control are in the same drug class, pharmacologically similar, and both have no safety issues from a clinical perspective. How much of a discount factor should be applied to M_1 for determining the non-inferiority margin M_2. Is a 50% discount overly conservative? The respondents stated that the "issue of discounting is done for M_1, not for M_2. Choice of M_2 is a clinical decision based on precedence of comparisons in CBER resulting from drugs associated with fatal events. Importantly the discounting is done in the context of changing scientific conditions. If nothing has changed, there is no discounting. In this case, since the endpoint is not a survival endpoint, flexibility could be exercised."

Further support for the decision on approvability of the NDA comes from considering intraluminal exposures of Lialda and Asacol. The exposures of Lialda and Asacol are distinct and the exposure from Lialda is greater than that reported from Asacol.[7,8] Therefore intraluminal exposure is greater for Lialda and supports the conclusion of effectiveness from a clinical pharmacological perspective.

10. Pediatrics

(b) (4)

[redacted]

[7] Asacol label. http://www.accessdata fda.gov/drugsatfda_docs/label/2010/019651s023lbl.pdf
[8] Lialda label. http://www.accessdata fda.gov/drugsatfda_docs/label/2010/022000s003lbl.pdf

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(b) (4)

The following deferred study has been modified and negotiated with the applicant and include the following:

731-2 Deferred pediatric study under PREA for the maintenance of remission of ulcerative colitis in pediatric patients 5 to 17 years of age.

Final Protocol Submission: 05/2013
Study/Trial Completion: 12/2017
Final Report Submission: 05/2018

11. Other Relevant Regulatory Issues

A. DSI audits

A site inspection was conducted by the Division of Scientific Investigations (DSI) of Site 205 of Study SPD476-304 (Location: Trivandrum, India; Investigator: K.T. Shenoy, M.D.) DSI recommended that data from the inspected site can be used in support of the NDA.

12. Labeling

For details regarding concerns over promotional content in labeling from DDMAC, the reader is referred to the CDTL memorandum. Issues that were in final negotiations concerned the use of the wording (b) (4) and concerns over release characteristics described in the label. Appropriate wording finalized with ONDQA agreement included the following: "The tablet is coated with a pH dependent polymer film, which breaks down at or above pH (b) (4) normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients." Particular reference to the (b) (4) was deleted from final labeling supported by CMC and ONDQA reviewers.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

[10] Background package, Shire Development Inc. 1 April 2011, IND 66,193 Version 1.0,= Meeting Request/Briefing Document, Type C Meeting

All of the review disciplines recommended the product for approval. I concur with the approval recommendation. In addition, the revised PREA-required study meets the statutory standard of meeting the needs of children and is appropriate scientifically. This study will answer clinically relevant questions on the role of Lialda treatment for induction and maintenance of remission of ulcerative colitis in the pediatric population. There is continued clarification of the primary endpoint for the study and this will be resolved in further discussions with Shire.

13.2 Risk Benefit Assessment:
All of the review disciplines recommended the product for approval. I concur with the approval recommendation.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
There are no requirements for postmarketing risk evaluation and mitigation strategies.

Recommendation for other Postmarketing Requirements and Commitments
Shire's deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B (a) (3) (B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

731-2 Deferred pediatric study under PREA for the maintenance of remission of ulcerative colitis in pediatric patients 5 to 17 years of age.

Final Protocol Submission: 05/2013
Study Completion: 12/2017
Final Report Submission: 05/2018

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/s/

ANDREW E MULBERG
07/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

OFFICER/EMPLOYEE LIST

Officer/Employee List
NDA 22000/S-005

Name	Role
Kevin Bugin	RPM
Andrew Mulberg	Deputy Director, Signatory
Donna Griebel	Director
Anil Rajpal	CDTL
Aisha Peterson Johnson	Clinical Reviewer
Mike Welch	Statistics Team Leader
Milton Fan	Statistics Reviewer
Sushanta Chakder	Nonclinical Reviewer
Sue Chih Lee	Clinical Pharmacology Team Leader
Kris Estes	Clinical Pharmacology Reviewer
Marie Kowblansky	CMC Team Leader
Yong Wang	CMC Reviewer
Khairy Malek	DSI
Kathleen Klemm	DDMAC
Denise Baugh	DMEPA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 14, 2011
From	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	NDA 22-000 S005
Applicant	Shire Development Inc.
Date of Submission	June 14, 2010
PDUFA Goal Date	July 14, 2011 (includes three-month extension for a major amendment)
Proprietary Name / Established (USAN) names	Lialda® / mesalamine
Dosage forms / Strength	1.2 g tablet
Proposed Indication	Maintenance of remission (b) (4) UC
Recommended Action:	Approval for Supplement S005

Table of Contents

1. Introduction

This application, received June 14, 2010, was submitted as an SE1 efficacy supplement to the NDA for Lialda (mesalamine) which is a delayed-release oral tablet formulation of

mesalamine (5-aminosalicylic acid). Lialda was originally approved on January 16, 2007, with the following indication: "...for the induction of remission in patients with active, mild to moderate ulcerative colitis."

The Applicant proposes the following addition to the indication statement: "…and for the maintenance of remission, (b) (4) ulcerative colitis." The Applicant also proposes additions to the Dosage and Administration, Adverse Reactions, and Clinical Studies sections.

2. Background

2.1 Regulatory History

2.1.1 Products Approved for Maintenance of Remission of UC

A listing of products approved for the maintenance of remission of UC is shown below along with the indication statement for the UC indication (emphasis added by this reviewer to the "maintenance" portion of the indication):

- Asacol (mesalamine): "…for the treatment of mildly to moderately active ulcerative colitis and for the ***maintenance of remission*** of ulcerative colitis."
- Apriso (encapsulated mesalamine granules): "…for the ***maintenance of remission*** of ulcerative colitis in patients 18 years of age and older."
- Azulfidine EN-tabs / Azulfidine(sulfasalazine): "a) in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis; and b) for the ***prolongation of the remission period between acute attacks*** of ulcerative colitis."
- Dipentum (olsalazine): "…***for the maintenance of remission*** of ulcerative colitis in patients who are intolerant of sulfasalazine."
- Remicade (infliximab): "…for reducing signs and symptoms, inducing and ***maintaining clinical remission and mucosal healing***, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

2.1.2 Regulatory History of Lialda

Original Approval: Lialda was approved on January 16, 2007 with the indication "...for the induction of remission in patients with active, mild to moderate ulcerative colitis." The reader is referred to the Team Leader Memo by Ruyi He for information about the regulatory history pertinent to the original application.[1]

[1] He, Ruyi, Team Leader Memo for NDA 22-000 Original Application, January 16, 2007.

Current Application: The table below summarizes the regulatory activity pertinent to the current SE1 efficacy supplement.

Table 1. Pertinent Regulatory History of Lialda (NDA 22-000, S005)*

Date	Action
January 16, 2007	Approval of original NDA (induction of remission in patients with active, mild to moderate UC)
March 11, 2010	Pre-sNDA Meeting (included discussion of non-inferiority margin for Study SPD476-304)
June 14, 2010	Submission of current SE1 Efficacy Supplement

*IND 66193

In the Pre-sNDA meeting held on March 11, 2010, the sponsor proposed a non-inferiority (NI) margin of 10%. The Agency advised the sponsor that the adequacy of the sponsor's data to support their efficacy conclusions will be a review issue. The sponsor's rationale for the proposed NI margin was that a difference of 20-25% in remission rate was observed between Asacol 1.6 g/day (0.8 g BID) and placebo in favor of Asacol in the Mesalamine Study Group, 1996[2] trial. The fraction of the standard treatment effect that was selected to be preserved was 0.5 with a resulting non-inferiority margin of 10%.

See also Section 10 Pediatrics of this review.

See the Clinical Review by Aisha Peterson Johnson for details of the Lialda regulatory history.

2.2 Current Application

The application was received on June 14, 2010. It was classified as a ten-month submission with a PDUFA deadline of April 14, 2011; because of a major amendment received on February 22, 2011, the PDUFA date was extended to July 14, 2011.

No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon were the following:

(1) Clinical Review by Aisha Peterson Johnson, dated July 11, 2011
(2) Statistics Reviews:
    a. Primary Statistical Review by Milton Fan, dated July 14, 2011
    b. Secondary (Team Leader) Statistical Review by Mike Welch, dated July 14, 2011
(3) Pharmacology/Toxicology Review by Sushanta Chakder, dated June 9, 2011
(4) DDMAC Reviews:

[2] The Mesalamine Study Group. An Oral Preparation of Mesalamine as Long Term Maintenance therapy for Ulcerative Colitis. Ann Intern Med, 1996;124:204-211.

a. DDMAC Labeling Review by Kathleen Klemm, dated June 22, 2011
b. DDMAC Supplemental Review of Section 11 of Label by Kathleen Klemm, dated July 1, 2011

(5) SEALD Labeling Review by Jeanne Delasko dated July 1, 2011
(6) Clinical Pharmacology Review by Kristina Estes dated July 8, 2011
(7) CMC Review by Yong Wang dated July 11, 2011
(8) Epidemiology Consult Review by Christian Hampp, dated November 10, 2010
(9) DSI Clinical Inspection Summary by Khairy Malek, dated February 9, 2011

The reviews should be consulted for more specific details of the current application. The reader is also referred to the CDTL Reviews for the original application (approved January 16, 2007), as well as to the primary review documents for that application.

This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current application.

3. CMC

There were no new CMC data presented in this application.

For a discussion of CMC issues during the review of the original application, the reader is referred to the review memo by Marie Kowblansky dated February 13, 2006, and the Team Leader memo by Ruyi He dated January 16, 2007.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical study data presented in this application.

For a discussion of nonclinical issues during the review of the original application, the reader is referred to the review memo by David Joseph dated August 3, 2006, and the Team Leader memo by Ruyi He dated January 16, 2007.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology data presented in this application.

For a discussion of clinical pharmacology issues during the review of the original application, the reader is referred to the review memo by Sue-Chih Lee dated December 21, 2006, and the Team Leader memo by Ruyi He dated January 16, 2007.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Lialda is not an antimicrobial agent.

7. Clinical/Statistical - Efficacy

7.1 Issues

The reader is referred to the Clinical Review by Aisha Peterson Johnson dated July 11, 2011, the Statistics Primary Review by Milton Fan dated July 14, 2011, and the Statistics Secondary Review by Mike Welch dated July 14, 2011, for complete information.

7.1.1 Study Design Overview

Study SPD476-304 was a randomized, double-blind, active comparator (non-inferiority) study of Lialda 2.4 g QD versus Asacol 0.8 g BID. Pertinent features of the study design are shown in Figure 1.

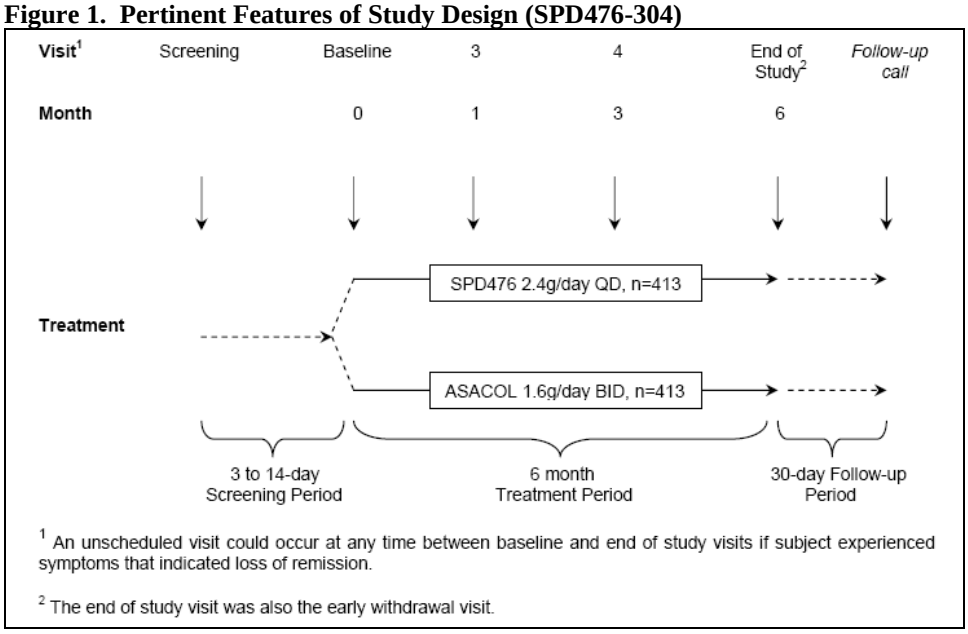
Key entry criteria were the following:

- History of acute UC episodes (≥ 1 in the past year; ≥ 2 in the patient's medical history)
- Stable dose of 5-ASA (≤ 2.4 g/day) or sulfasalazine (≤ 6.2 g/day) for ≥ 30 days
- UC in remission for ≥ 30 days
- Endosocopy score of ≤ 1
- Combined symptom score [stool frequency (SF) and rectal bleeding (RB)] of ≤ 1

Other pertinent features of the study design were the following:

- Treatment Duration: 6 months
- Primary Endpoint: Endosocopic remission (defined as an endoscopy score of ≤ 1) at Month 6
- Key Secondary Endpoints:
  - Clinical remission (defined as SF=0 and RB=0) at Month 6;
  - UCDAI score ≤ 1 and clinical remission (defined as SF=0 and RB=0) at Month 6.

Figure 1. Pertinent Features of Study Design (SPD476-304)



Patients were instructed to call an Interactive Voice Response System (IVRS) daily for one week prior to each visit except the Screening Visit.
From Clinical Review by Dr. Peterson Johnson. Source is SPD476-304 Final Study Report, p. 23/893.

Key assessments were the following:

- SF and RB symptoms: assessed by IVRS at Baseline, Month 1, Month 3, and Month 6
- Mucosal appearance: assessed by endoscopy at Baseline and Month 6

See Appendix 1 (SF, RB, and Mucosal Appearance Scoring).

7.1.2 Sample Size

The sample size estimation for Study SPD476-304 was based on the results of the placebo-controlled study of Asacol published by the Mesalamine Study Group.[3]

The results for the Asacol 1.6 g/day arm of the Mesalamine Study Group trial were as follows[4]:

- Per-Protocol: In the per-protocol (PP) analysis of the Mesalamine Study Group trial, the proportion of patients in the Asacol 1.6 g/day arm that met the primary endpoint (maintenance of remission as indicated by endoscopic evaluation) was 65.5%.
- Intent-to-Treat: In the intent-to-treat (ITT) analysis, the proportion of patients in the Asacol 1.6 g/day arm that met the primary endpoint was 70.1%.

[3] The Mesalamine Study Group. An Oral Preparation of Mesalamine as Long Term Maintenance therapy for Ulcerative Colitis. Ann Intern Med, 1996;124:204-211.
[4] The Mesalamine Study Group. An Oral Preparation of Mesalamine as Long Term Maintenance therapy for Ulcerative Colitis. Ann Intern Med, 1996;124:204-211.

The sample size planned in the original protocol was changed in an amendment to the protocol as described below:

- Original Protocol (November 25, 2004): In the original protocol, the sample size planned was 410. This sample size estimate was based on the PP results for the Asacol 1.6 g/day arm of the Mesalamine Study Group trial.
- Revised Protocol (protocol amendment dated March 20, 2007): In the revised protocol, the sample size was increased to 826. This sample size estimate was based on the ITT results for the Asacol 1.6 g/day arm of the Mesalamine Study Group trial.

It should be noted that although the sample size was increased based on the use of the ITT results rather than the PP results of the Mesalamine Study Group trial, there was not a change proposed to the NI margin (see Section 2.1.2).

The Statistical Reviewers requested that the applicant provide results separately from "Phase 1" (based on the pre-amendment sample size) and from "Phase 2" (based on the additional sample added by the protocol amendment; excludes the pre-amendment sample).[5] This information was received in an amendment dated February 22, 2011. See Primary Statistical Review for more details.

7.1.3 Results

Disposition:

Of the 829 patients randomized to treatment, 418 were randomized during Phase 1 of enrollment (i.e., prior to the protocol amendment dated March 20, 2007) and 411 were randomized during Phase 2 of enrollment (i.e., after the protocol amendment). The primary statistical reviewer noted that there was a 16 month gap from July 20, 2006, to Nov 22, 2007 (based on date of the first study medication dose) between the Phase 1 and Phase 2 periods.

Of the patients randomized, three did not receive study medication (one randomized to Lialda and one randomized to Asacol in Phase 1; one randomized to Asacol in Phase 2). The remaining 826 patients were included in the intent-to-treat (ITT) population.

Of the patients randomized, 81% (670) completed the study. The percentage of patients who completed the study was similar between those patients taking Lialda in Phase 1 (81%), those taking Asacol in Phase 1 (83%), those taking Lialda in Phase 2 (82%), and those taking Asacol in Phase 2 (77%). The most common reason for early discontinuation was lack of efficacy. See Clinical Review for additional information.

Protocol Violations***:***

Of the patients in the ITT population, 147 (17.8%) were excluded for protocol violations across both phases; the proportion of Lialda-treated patients with protocol violations was similar to the proportion of Asacol-treated patients with protocol violations, 17.3% and 18.2%, respectively. There were more protocol violations during Phase 2 than during Phase

[5] Information Request dated August 27, 2010 (NDA 22-000/S-005)

1, 102 (24.9%) and 68 (16.3%), respectively (see Clinical Review). The most common protocol violation was failure to meet all inclusion criteria (see table below).

Table 2. Failed Inclusion Criteria, by Phase (SPD476-304)

	Phase 1			Phase 2			Combined		
	Lialda	Asacol	Total	Lialda	Asacol	Total	Lialda	Asacol	Total
Total ITT patients	208	208	416	207	203	410	415	411	826
Failed Inclusion Criteria	n (%)								
Satisfactory medical assessment	2 (1.0)	0	2 (0.5)	0	0	0	2 (0.5)	0	2 (0.2)
Histology-confirmed dx of UC	0	0	0	3 (1.4)	7 (3.4)	10 (2.4)	3 (0.7)	7 (1.7)	10 (1.2)
UC in remission for ≤30 days	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	4 (0.5)
Baseline endoscopy score ≥1	0	0	0	0	1 (0.5)	1 (0.2)	0	1 (0.2)	1 (0.1)
Baseline line combined sx score of ≥1	3 (1.4)	2 (1.0)	5 (1.2)	1 (0.5)	4 (2.0)	5 (1.2)	4 (0.1)	6 (1.5)	10 (1.2)
Stable dose of 5-ASA for ≥30 days prior to baseline	11 (5.3)	11 (5.3)	22 (5.3)	10 (4.8)	11 (5.4)	21 (5.1)	21 (5.1)	22 (5.6)	43 (5.2)
≥1 acute episode of UC in past 12 months	1 (0.5)	2 (1.0)	3 (0.7)	0	0	0	1 (0.2)	2 (0.5)	3 (0.4)

Table above is taken from the Clinical Review by Aisha Peterson Johnson. Source is Table 1.8 (p. 266/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request.

Of the inclusion criteria, the one most frequently not met was the requirement to be on a stable dose of 5-ASA of ≤2.4 g/day (or sulfasalazine ≤6.2 g/day) for 30 days prior to baseline evaluation for study enrollment. The proportion of patients that failed this inclusion criterion was similar between the two treatments in each of the phases (see table above).

Demographic Characteristics:

Baseline demographic characteristics were well-balanced between the two treatments—Lialda and Asacol (see table below).

Table 3. Demographics (SPD476-304)

Demographic Subgroup	Phase 1 (N=416)			Phase 2 (N=410)		
	Lialda N= 208	Asacol N= 208	Phase 1 (All) N=416	Lialda N= 207	Asacol N= 203	Phase 2 (All) N=410
Sex (n,%)						
Male	101 (48.6%)	114 (54.8%)	215 (51.7%)	111 (53.6)	100 (49.3)	211 (51.5%)
Female	107 (51.4%)	94 (45.2%)	201 (48.3%)	96 (46.4%)	103 (50.7%)	199 (48.5%)
Age (years) (n,%)						
Mean (SD)	44.2 (13.5)	45.5 (13.4)	44.9 (13.5)	45.9 (14.5)	44.8 (13.5)	45.3 (14.0)
Median	44.0	45.5	45.0	46.0	45.0	45.0
min,max	18, 80	18, 85	18, 85	18, 85	19, 76	18, 85
Race (n,%)						
Caucasian	154 (74.0%)	156 (75.0%)	310 (74.5%)	118 (57.0%)	103 (50.7%)	221 (53.9%)
Black	4 (1.9%)	1 (0.5%)	5 (1.2%)	5 (2.4%)	3 (1.5%)	8 (2.0%)
Hispanic	5 (2.4%)	6 (2.9%)	11 (2.6%)	14 (16.8%)	17 (8.4%)	31 (7.6%)
Asian/ PI	42 (20.2%)	40 (19.2%)	82 (19.7%)	61 (29.5%)	66 (32.5%)	127 (31.0%)
Other	3 (1.4%)	5 (2.4%)	8 (1.9%)	9 (4.3%)	14 (6.9%)	23 (5.6%)

Table above taken from Clinical Review by Aisha Peterson Johnson Source is Table 2 (p 13/464), Table 12 (p 36/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

The proportion of Caucasian and Asian race patients was disparate between the two phases with more Asians being enrolled in Phase 2. In Phase 1, 74.5% of patients were Caucasian and 19.7% were Asian. However, in Phase 2, only 53.9% of patients were Caucasian and 31.0% of patients were Asian. This is explained by the additional study centers which were included after the protocol amendment. The Clinical Reviewer noted that epidemiologic research suggests that "the clinical course of IBD seems to be less severe in the Asia-Pacific region than in Western countries".[6] This reviewer agrees with the Clinical Reviewer that because Asian patients in both phases were split nearly equally between treatment groups (see table above), there is little potential for these differences to influence the overall efficacy results.

[6] Ouyang Q, Tandon R, Goh KL et al . Management consensus of inflammatory bowel disease for the Asia–Pacific region. J Gastroenterol Hepatol 2006; 21: 1772–82. [Review].

Endoscopic Remission:

The proportion of patients in endoscopic remission at Month 6 by phase of enrollment is shown in the table and figure below for the ITT and PP populations.

Table 4. Proportion of Patients in Endoscopic Remission at Month 6 (SPD476-304)

		Phase 1	Phase 2	Combined
Intent-to-Treat Population	Lialda 2.4 g/day	78.4% (163/208)	77.3% (160/207)	77.8% (323/415)
	Asacol 1.6 g/day	79.3% (165/208)	74.4% (151/203)	76.9% (316/411)
	Lialda-Asacol	-1.0%	2.9%	0.9%
	95% CI	-9.3%, 7.4%	-5.9%, 7.0%	-5.0%, 7.0%
Per Protocol Population	Lialda 2.4 g/day	83.1% (148/178)	84.2% (139/165)	83.7% (287/343)
	Asacol 1.6 g/day	81.0% (145/179)	82.2% (129/157)	81.5% (274/336)
	Lialda-Asacol	2.1%	2.1%	2.1%
	95% CI	-6.4%, 10.7%	-6.7%, 10.9%	-4.0%, 8.0%

Table above is taken from the Clinical Review by Aisha Peterson Johnson Source is Table 7 (p 28/464) and Table 8 (p 30/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

Figure 2. Endoscopic Remission (Maintenance of Mucosal Healing) by Phase of Enrollment: Lialda - Asacol (Difference, 95% CI)

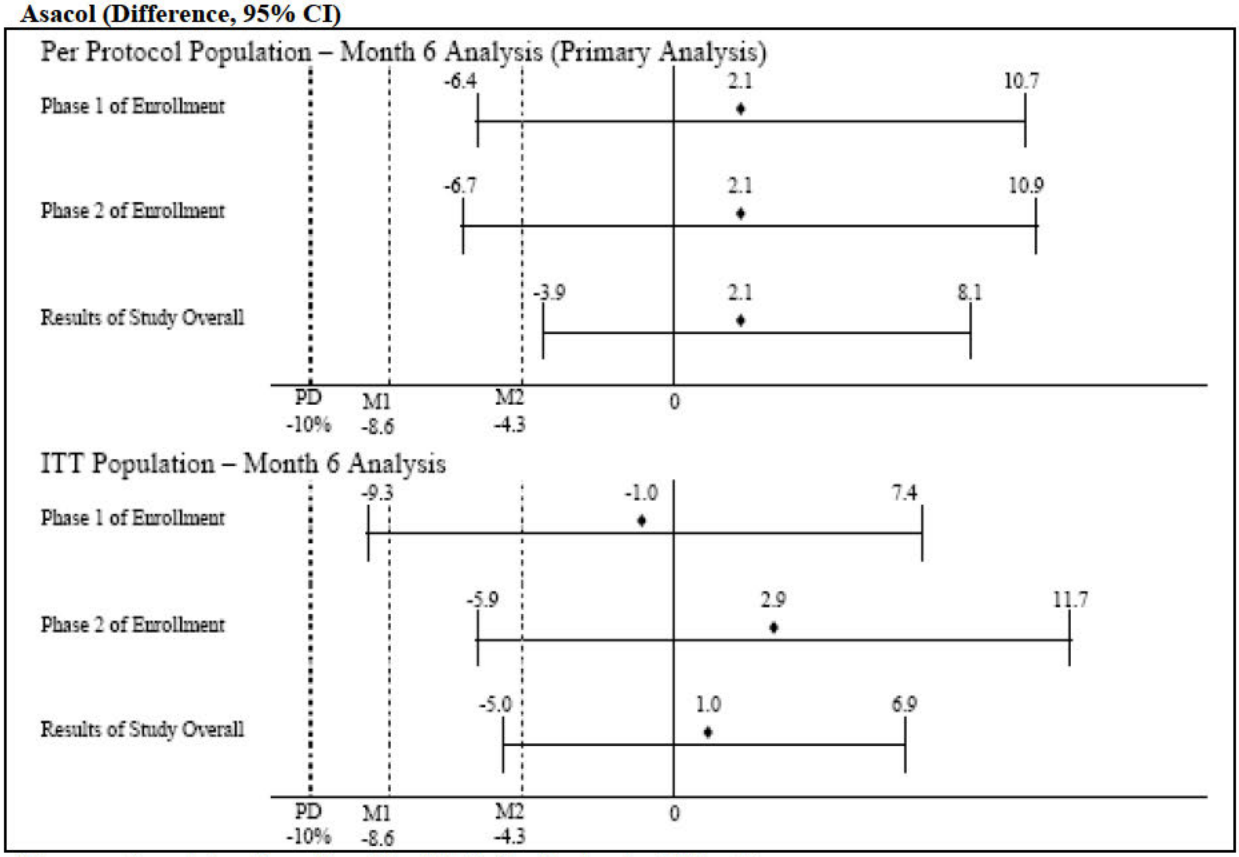


Diagram above taken from Page 27 of Statistics Review by Milton Fan

7.1.4 Discussion

The Clinical Reviewer noted that the Non-Inferiority Guidance states the following: "…the NI study is dependent on knowing something that is not measured in the study, namely, that the active control had its expected effect in the NI study."[7] This reviewer agrees with the Clinical Reviewer that the active control (Asacol) demonstrated its expected effect in Study SPD476-304 (see Table 4 above). In the Mesalamine Study Group trial, the proportion of patients that met the primary endpoint (maintenance of remission as indicated by endoscopic evaluation at Month 6) was 70.1% in the Asacol 1.6 g/day group compared to 48.3% in the placebo group (p=0.005).[8]

The Clinical Reviewer noted that the NI margin of 10% was pre-specified by the Applicant; i.e., the statistical analysis plan specified that non-inferiority of Lialda to Asacol would be concluded if the lower limit of the 95% CI for the difference (Lialda-Asacol) was above the NI margin of 10%. (See Section 2.1.2 for the basis of the initially proposed NI margin.)

In an Information Request (IR) written by the Statistical Reviewer, the Applicant was requested to re-evaluate the NI margin "taking into account the study-to-study variability of treatment effects and apply a 50% discount for the 'constancy assumption.'"[9] In the response to the IR (dated September 20, 2010), the Applicant applied the "fixed margin" method described in the Non-Inferiority Guidance as follows:

> "…in the fixed margin method, the margin M1 is based upon estimates of the effect of the active comparator in previously conducted studies, making any needed adjustments for changes in trial circumstances. The NI margin is then pre-specified and it is usually chosen as a margin smaller than M1 (i.e., M2), because it is usually felt that for an important endpoint a reasonable fraction of the effect of the control should be preserved."

The Clinical Reviewer commented that for this method, "the lower bound of the 95% CI of the active control effect size in past placebo-controlled studies is selected as a conservative choice for the active comparator effect size, M1." In the Mesalamine Study Group Trial the difference in remission rate between patients taking Asacol 1.6 g/day and placebo was 25.8% (95% CI: 8.6%, 43.0%) for the PP population and 21.8% (95% CI: 7.6%, 36.1%) for the ITT population. In the response to the IR, the applicant, using the PP population, calculated 8.6% for M1, and 4.3% for M2 (50% discount of M1).

7.1.5 Conclusions

The Primary Statistical Reviewer (Milton Fan) noted that using the ITT population, M1 would be calculated as 7.6%, and M2 as 3.8%; he commented that the M2 should be in the range of 3.8% to 4.3%. He commented that only the results from Phase 1 could be interpreted statistically. He concluded that the results from Phase 1 using M2 as the NI

[7] Guidance for Industry, Non-Inferiority Clinical Trials, March 2010
[8] The Mesalamine Study Group. An Oral Preparation of Mesalamine as Long Term Maintenance therapy for Ulcerative Colitis. Ann Intern Med, 1996;124:204-211.
[9] Information Request dated August 27, 2010 (NDA 22-000/S-005)

margin were inconclusive for demonstration of non-inferiority. Dr. Fan added that if the M1 was acceptable as the NI margin from a clinical perspective, then this study would have just barely met the non-inferiority criteria.

Dr. Fan presented this Application during a session of the Office of Biostatistics Statistical Rounds (see Section 9 of this review). In that meeting, a view was expressed that including more patients in a study (i.e., "overpowering" a study) would give a more precise confidence interval. Also, there was no consensus from the audience regarding which population should be used for analysis (ITT vs. PP). Finally, there was a discussion of M1 and of M2. Whereas M1 is derived historically and is the treatment difference between the active comparator and placebo, M2 is derived clinically and should reflect what degree of the treatment difference between placebo and the active comparator needs to be preserved; a view was expressed that in certain situations no discount of M1 is needed.

Dr. Johnson notes that there can be flexibility in the M2 margin, for example when "the primary endpoint does not involve an irreversible outcome such as death."[10] Dr. Johnson also notes that in situations where the test drug is pharmacologically similar to the active control, "…the expectation of similar performance (but still requiring confirmation in a trial) might make it possible to accept a single trial and perhaps could also allow less conservative choices in choosing the non-inferiority margin."[11] Dr. Johnson commented that each of these situations apply to Study SPD476-304. First, the endpoint of Study SPD476-304 does not involve an irreversible outcome. Second, Lialda is pharmacologically similar to Asacol. Dr. Johnson concluded that the appropriate M2 for this study would be 6% to 7%; this M2 is calculated by using a discount of 20% to 30% of the M1 of 8.6%. Dr. Johnson also commented that there is no consensus as to which population should be used (PP versus ITT).

The Secondary Statistical Reviewer (Mike Welch) stated that the unplanned sample increase does not necessarily invalidate the results. He recommends using the combined results based both on the ITT and PP populations. He notes that "the separate analyses based on phase 1 and phase 2 should be considered sensitivity analyses, and it should not be expected that they individually meet the (more rigid) non-inferiority criteria." Regarding the NI margin, he comments that "the choice of M2 is largely moot and should not be decided at the analysis stage" and that "the focus should be more on what the data show rather than a formal test of a (post hoc) hypothesis." He concludes that the lower confidence bounds of the treatment differences for the ITT population (-5.0%) and PP population (-4.0%) (see Table 4) "not only rule out M1 but preserve (1 - 5/8.6) = 42% of M1" [redacted] (b) (4) He recommends a descriptive summary of complete trial data in the clinical trials section of the label.

If the M1 margin (i.e., 7.6% based on the ITT population of the Mesalamine Study Group trial or 8.6% based on the PP population of that trial) is used as the criteria for effectiveness,

[10] Guidance for Industry, Non-Inferiority Clinical Trials, March 2010
[11] Guidance for Industry, Non-Inferiority Clinical Trials, March 2010

then the phase of enrollment and populations that meet this criteria and do not meet this criteria would be the following (see Table 4 and Figure 2):

- Meet Effectiveness Criteria: Phase 1 (PP), Phase 2 (PP and ITT), Combined (PP and ITT)
- Do not Meet Effectiveness Criteria: Phase 1 (ITT)

This reviewer believes that M1 should be used as the criteria for effectiveness, and that based on the above results effectiveness has been demonstrated. It should be noted that Dr. Fan commented that if the M1 was acceptable as the NI margin from a clinical perspective, and if only Phase 1 was analyzed, then this study would have "just barely met non-inferiority criteria." This reviewer agrees with Dr. Welch that a formal conclusion of non-inferiority cannot be made based on the results of this trial, and that a descriptive approach to labeling the results is appropriate.

7.2 Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical standpoint; see Sections 7.1.4 and 7.1.5 above for individual reviewer's conclusions and Section 9 of this review for a summary of discussion at an Office of Biostatistics rounds where this application was presented.

8. Safety

8.1 Issues

The reader is referred to the Clinical Review by Aisha Peterson Johnson dated July 11, 2011 for complete information.

In addition to Study SPD476-304 (described in Section 7 above), there were two long-term open label trials:

- Study SPD476-404: This was a Phase 4, open-label, 12-14 month study in patients using Lialda. In addition to the maintenance of remission phase, the study also had an 8-week acute phase. Only results from the maintenance phase are included in the safety summary.
- Study SPD476-303: This was a Phase 3, open-label, 12-14 month study in patients using Lialda. During this study, patients were randomized to once daily or twice treatment. Study 303 was an extension of two acute UC trials. The total planned daily dose for all 3 studies in the safety analyses was 2.4 g/day.

8.1.1 Exposure

Lialda was evaluated in 1,082 patients whose UC was in remission.

- Controlled Trial (SPD476-304): 415 patients exposed to Lialda
- Open Label Trials (SPD476-303 and SPD476-304): 667 patients exposed to Lialda

Across the studies (304, 303, and 404), 1,082 patients received Lialda of 2.4 g/day (once daily or twice daily) for a mean duration of exposure of approximately 41 weeks. See Table below.

Table 5. Extent of Exposure (Weeks)

Weeks of Exposure	RCT Lialda n=415	Asacol N=411	All Lialda n=1082
0-<12	42 (10.1%)	41 (10.0%)	72 (6.7%)
12-<24	28 (6.7%)	30 (7.3%)	62 (5.7%)
≥24	340 (81.9%)	329 (80.0%)	
24-<48			413 (38.2%)
≥48			527 (48.7%)
Mean (SD)	23.5 (6.8)	23.5 (6.7)	40.7 (18.9)
Median	26.1	26.0	45.5
Range	0, 29	0, 30	1, 80

Table above taken from Clinical Review by Dr. Peterson Johnson. Source is Adapted from Table 1 (p 14/57) 2.7.4 Summary of Clinical Efficacy and Table 3.1 (p 28/893) Clinical Study Report SPD476-304.

8.1.2 Safety Findings

Safety findings are summarized below. See also the table below.

Table 6. Summary of Safety Results

	Study 304		All Lialda N=1082
	RCT Lialda N=415	Asacol N=411	
	n (%)	n (%)	n(%)
Any Adverse Event	155 (37.4)	148(36.0)	123 (59.1)
Any treatment-related AE	52 (12.6)	45 (10.9)	24 (11.5)
Any Severe AE	11 (2.7)	12 (2.9)	15 (7.2)
Serious Adverse Event (SAE)	6 (1.4)	3 (0.7)	9 (0.4)
Discontinuation due to Adverse Event (DAE)	8 (2.0)	4 (1.0)	15 (7.2)
Deaths	0	0	1 (0.0)

Table above taken from Clinical Review by Aisha Peterson Johnson. Source is Tables 6 and 7 (p 20/57) Section 2.7.4 Summary of Clinical Efficacy

Deaths:

- There were no deaths reported in Studies 304 and 404.
- There was one death reported in Study 303; this was a 25 year old Caucasian female randomized to Lialda 1.2 g BID who was exposed to Lialda for approximately 9.5 months. The patient died from an electric shock while cleaning her car with an electric vacuum cleaner. The patient had a history of mitral insufficiency (grade 1-2), mitral valve prolapse, nephrolithiasis, and erythema nodosum.

SAEs:

In Study 304, 6 patients in the Lialda group and 3 patients in the Asacol group experienced SAEs.

- In the Lialda group, the SAEs were worsening of UC, appendicitis, lower GI bleed, severe pancolitis, brachial neuritis, and asthma attack precipitated by bronchitis.
- In the Asacol group, the SAEs were intervertebral disc protrusion, ruptured right fallopian tube due to an ectopic pregnancy, and flare of UC.

In the All Lialda population, the incidence of SAEs was 3.0%.

- In this population, 33 patients had a total of 39 SAEs.
- The only SAEs that occurred in more than one patient was UC (10 patients) and pneumonia (2 patients).
- Two SAEs were considered by investigators to be related to study treatment – pancreatitis (Study 404) and liver function test abnormality (Study 303)

See details in Clinical Review.

Dropouts and/or Discontinuations:
During Study 304, 12 patients had a total of 13 AE's that led to withdrawal (9 events in the Lialda group and 4 events in the Asacol group). In the All Lialda population, 43 patients had a total of 49 AE's that led to withdrawal. Most of these were recurrence of UC symptoms.

Common Adverse Events:
The Clinical Reviewer commented that the most common AE's were UC, headache, and (b) (4) and that each of these AE's is currently included in the Lialda labeling. The Clinical Reviewer provided recommendations for a table of common adverse reactions to include in labeling, as well as recommendations for adverse reactions to be included in the listing of less common events of significance.

8.1.3 Conclusion

The Clinical Reviewer concluded that, overall, Lialda appears to have a safety profile comparable to other mesalamine products when used at the recommended dose of 2.4 g/day.

8.2 Recommendation

An Approval Action is the final recommendation from a Clinical standpoint.

9. Advisory Committee Meeting

This efficacy supplement application was not presented to an Advisory Committee.

However, on June 24, 2011, Milton Fan, the statistical reviewer, presented this Application during a session of the Office of Biostatistics Statistical Rounds.

The following questions were discussed:

Question 1: Which analysis population, phase 1, phase 2, or pooled analysis (ITT or PP) should be considered as the primary analysis population from a statistical perspective? Are the results sufficient to show non-inferiority from a statistical perspective?

Question 2: For this Application, the test drug and active control are in the same drug class, are pharmacologically similar, and both have similar safety profiles. How much of a discount factor should be applied to M_1 for determining the non-inferiority margin M_2 ? Is a 50% discount overly conservative?

Key discussion points were the following (taken from the Clinical Review):

- The concept of "overpowering" a study was discussed (in the context of the Applicant's rationale for doubling the patient population); Dr. Thomas Permutt expressed his view that including more patients in a study would gives a more precise confidence interval, and thus would always be a positive thing.
- There was no consensus from the audience regarding which population should be used for analysis (ITT vs. PP).
- Dr. Bob O'Neill addressed the question of M_2 in detail. He clarified that the M_1 and M_2 should be approached separately. Whereas M_1 is derived historically and is the treatment difference between the active comparator and placebo, M2 is derived clinically and should reflect what degree of the treatment difference between placebo and the active comparator needs to be preserved. Dr. O'Neill specifically stated that in certain situations no discount of M_1 is needed.

10. Pediatrics

Current Efficacy Supplement (maintenance of remission in UC):

Because the adult indication is ready to be approved, the requirement for pediatric studies is eligible for deferral. Due to the low incidence of UC in pediatric patients below age 5 years, the Division has previously waived requirements for pediatric studies of UC treatment for this age group. Dr. Johnson recommended that the Applicant be required to evaluate safety and effectiveness in pediatric patients age 5 years and older who are in remission of UC, but that the PREA requirement for studies in patients under 5 years could be waived.

The application was presented to the Pediatric Research Committee (PeRC) on December 15, 2010, and the committee agreed with the proposals for partial waiver and deferral.

An acceptable timeline for the pediatric development program was negotiated with the Applicant.

See Section 13.4 of this review.

Prior Regulatory History Relevant to Pediatrics:

Table 7. Prior Regulatory History Relevant to Pediatrics

Date	Activity
September 4, 2007	▪ Waiver of pediatric studies for patients <5 years of age granted ▪ Deferral for patients 5-17 years of age until December 2010 (final report submission). (See Appendix 2: Original PREA PMR.)
(b) (4)	

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. Mesalamine products have been approved and marketed since 1987. Preclinical studies have not pointed to any problems with QT prolongation due to mesalamine, and postmarketing experience with several marketed products similar to the present one have not identified a concern regarding QT prolongation.

11.2 Division of Scientific Investigations (DSI) Audits

A site inspection was conducted by the Division of Scientific Investigations (DSI) of Site 205 of Study SPD476-304 (Location: Trivandrum, India; Investigator: K.T.Shenoy, M.D.) This site was among the top four centers in total patient enrollment, and was the only site among the high-enrolling sites in which all patients were found to be in endoscopic remission at 6

[12] Results for Orphan Drug Product Designations Search, http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm (accessed July 7, 2011)

months with both the study drug (Lialda) and the active comparator (Asacol). DSI recommended that data from the inspected site can be used in support of the NDA (see DSI Clinical Inspection Summary by Khairy Malek dated February 9, 2011).

12. Labeling

12.1 Proprietary name

Current SE1 Efficacy Supplement (Maintenance Indication for UC): For the current SE1efficacy supplement, a consult from DMEPA was not requested, and a review by DMEPA was not conducted.

Original Application (Induction Indication for UC): The proprietary name "Lialda" was deemed acceptable by Walter Fava in the Division of Medication Errors and Technical Support (DMETS), Office of Surveillance and Epidemiology (OSE) during the review of the original application. (For a discussion of proprietary name issues during the review of the original application, the reader is referred to the DMETS Proprietary Name Review by Walter Fava dated December 20, 2006, and the TL memo by Ruyi He dated January 16, 2007.)

12.2 Division of Drug Marketing, Advertising, and Communications (DDMAC) Comments

June 22, 2011 Review: The Division of Drug Marketing, Advertising and Communications (DDMAC) made several recommendations regarding labeling; many involved changes to currently approved sections to reduce potential for misinterpretation or to improve compliance with current labeling practice. (See the DDMAC labeling review by Kathleen Klemm dated June 22, 2011 for details.) The review team decided to adopt several of the recommendations, but the team felt that the precedent of the currently approved labeling wording precluded implementing some of the recommendations.

July 1, 2011 Review: In addition, the DDMAC Reviewer wrote a separate review for Section 11 of the label (Description). (See the DDMAC labeling review by Kathleen Klemm dated July 1, 2011 for details.) The following text was proposed by the Applicant (in the course of labeling negotiations):

[redacted] (b) (4)

The DDMAC reviewer stated that DDMAC is concerned that this text may be used in a promotional context to overstate the efficacy of the drug and imply superiority over other available mesalamine products. [redacted] (b) (4) The DDMAC

Reviewer agreed with ONDQA's recommendation to revert to the text proposed by FDA in version 9:

> The tablet is coated with a pH dependent polymer film, which breaks down at or above (b) (4) normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The Applicant proposed revisions to the Indications and Usage, Dosage and Administration, Adverse Reactions, and Clinical Studies sections. There were no major disagreements with the Applicant about revisions to any of these sections. The revisions made to each of these sections are summarized below:

- Indications and Usage (Section 1 of label):
  - The Applicant proposed an indication statement that included "maintenance of remission (b) (4) ulcerative colitis."
  - The Clinical Reviewer recommended that the maintenance indication for Lialda include only "maintenance of remission of ulcerative colitis" noting that (b) (4)

- Dosage and Administration (Section 2 of label): The following recommended dosage for the maintenance of remission was added: "…two 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g."

- Adverse Reactions (Section 6.1 of label): A description of the three maintenance trials, the most common adverse reactions, and the most common severe adverse reactions were added to this section of the label. Adverse reactions occurring in at least 1% of Lialda-treated patients in the maintenance trials were summarized in a table.

- Clinical Studies (Section 14.2 of label): Section 14.2 titled (b) (4) was added. The section includes a summary of Study SPD476-304 including demographic information and key design features such as the primary endpoint and the dose of Lialda and the comparator. The presentation of results

of the trial (i.e., the proportion of patients that maintained remission at Month 6 in each of the treatment arms) is descriptive.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The Primary Clinical Reviewer and Secondary Statistical Reviewer each recommended an Approval action (see Sections 7.1.4 and 7.1.5 of this review). The Primary Statistical Reviewer recommended an Approval action if the M1 was acceptable as the NI margin from a clinical perspective (see Sections 7.1.4 and 7.1.5). This Reviewer concurs with each of the recommendations from individual reviewers above.

The CMC Reviewer recommends approval only if the applicant revises the label wording to remove the [redacted] (b) (4) This Reviewer concurs with the CMC Reviewer's recommendation.

13.2 Risk Benefit Assessment

The risk and benefit characteristics appear similar to those of already approved and marketed oral mesalamine products for treatment of ulcerative colitis.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

PREA PMR (for current efficacy supplement):

Postmarketing required pediatric studies under PREA are recommended for the current efficacy supplement application, with the following language for the Approval Letter:

> Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 4 years because necessary studies are impossible or highly impracticable.

We are deferring submission of your pediatric study for ages 5 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

731-2 Deferred pediatric study under PREA for the maintenance of remission of ulcerative colitis in pediatric patients 5 to 17 years of age.

Final Protocol Submission: 05/2013
Study/Trial Completion: 12/2017
Final Report Submission: 05/2018

Reports of this/these required pediatric postmarketing study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

Original PREA PMR:

In addition, it should be noted that the Applicant's earlier pediatric study requirements under PREA are delayed. Although the Applicant has proposed a revised schedule (see Section 10 of this review), the original schedule (i.e., Final Report Submission by December 2010) will serve as the basis for defining the status of the postmarketing requirement.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

None of the primary review disciplines had recommendations for postmarketing study requirements. No postmarketing study requirements are recommended for this Application.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

None of the primary review disciplines had recommendations for postmarketing study commitments. No postmarketing study commitments are recommended for this Application.

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: SF, RB, and Mucosal Appearance Scoring

The following tables are taken from the Clinical Review by Aisha Peterson Johnson:

Table 8. IVRS Symptom Assessment Scores

Parameter	Assessment	Score
Stool Frequency	Normal	0
	1-2 more than normal/day	1
	3-4 more than normal /day	2
	>4 more than normal /day	3
Rectal bleeding	No rectal bleeding	0
	Streaks of blood	1
	Obvious blood	2
	Mostly blood	3

Table 9. Mucosal Appearance Scoring

Score	Disease Severity	Characteristics
0	Normal	Intact Vascular Pattern No Friability or Granulation
1	Mild	Erythema Decreased Vascular Pattern Minimal Granularity
2	Moderate	Marked Erythema Granularity Friability Absent Vascular Pattern
3	Severe	Ulceration Spontaneous Bleeding

APPENDIX 2: Original PREA PMR

The "Partial Waiver Granted" Letter dated September 4, 2007, included the following:

> Please refer to your submission dated May 4, 2007, requesting a waiver under 505B(a)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) for pediatric studies for Lialda.
>
> We have reviewed your submission and agree that a waiver of pediatric studies is justified for patients less than 5 years old for Lialda for the treatment of ulcerative colitis. The reason for granting the waiver is the low incidence of disease in this age group.
>
> We also agree that a deferral of pediatric studies in patients aged 5 – 17 years old is justified for the treatment of ulcerative colitis until December, 2010.
>
> Your deferred pediatric studies required by section 2 of the Pediatric Research Equity Act (PREA) are required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.
>
> 1. Deferred pediatric study under PREA for the treatment of ulcerative colitis in pediatric patients ages 5 to 17.
>
>   Final Report Submission: December, 2010
>
> Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) should be clearly designated "**Required Pediatric Study Commitments**".


(b) (4)

APPENDIX 4: Delayed Original PREA PMR

A General Advice Letter dated February 4, 2011, included the following:

731-1 Deferred pediatric study under PREA for the treatment of ulcerative colitis in pediatric patients of all ages

Final Report Submission: 12/2010

Study/Trial Status: Pending

The new proposed dates for the study would be as follows:

Study initiation and enrollment:	Aug 2012
Study completion:	Oct 2015
Study data available for anlaysis:	Jan 2016
Final report submission:	May 2016

We have reviewed the referenced material and have the following comments.

Please note that the original schedule serves as the basis for defining the status of a postmarketing requirement. Your annual progress reports, required under 21 CFR 314.81(b)(2)(vii), should include the original schedules. Because the requested submission date differs from that specified in the milestones listed in the January 16, 2007 approval letter, we consider this postmarketing requirement delayed. This status will be posted on the FDA Postmarketing Requirement and Commitments website: http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

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

/s/

ANIL K RAJPAL
07/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022-000
Priority or Standard	Standard
Submit Date(s)	14 June 2010
Received Date(s)	14 June 2010
PDUFA Goal Date	16 April 2011 (original) 16 July 2011 (extension)
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)/ Office of Drug Evaluation III
Reviewer Name(s)	Aisha Peterson Johnson MD, MPH, MBA
Review Completion Date	11 July 2011
Established Name	Mesalamine
Trade Name	Lialda
Therapeutic Class	Locally acting aminosalicylate
Applicant	Shire
Formulation	1.2 g Tablet
Dosing Regimen	2.4 g once daily
Indication(s)	Maintenance of remission (b) (4) UC
Intended Population(s)	Adults

Template Version: March 6, 2010

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of US marketing approval for Lialda for the indication of the maintenance of ulcerative colitis. The recommended dose is 2.4 g once daily.

1.2 Risk Benefit Assessment

Review of the current Application reveals that the benefit of Lialda for the maintenance of remission of ulcerative colitis outweighs the risk of Lialda in an appropriate patient population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

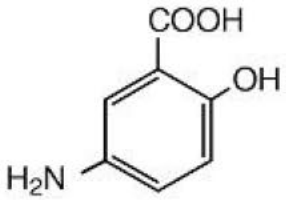
Shire has a deferred postmarketing study commitment for pediatric patients ages 5 to 17 years of age for the maintenance of remission of ulcerative colitis. The final protocol is due May 2013. The required study completion date is December 2017 with the final study report due May 2018.

2 Introduction and Regulatory Background

2.1 Product Information

Trade Name:	Lialda
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: Delayed-release tablets containing 1.2 g mesalamine
Proposed indication: Maintenance of remission (b) (4) UC

The exact mechanism of action of mesalamine is unknown, but it appears to act topically rather than systemically. Oral mesalamine formulations have been accepted as a first line treatment for the induction and maintenance of remission of ulcerative colitis for over 40 years.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several products currently approved by the FDA for the maintenance of remission of UC. Specific products are included in the table below.

Trade Name (generic name)	Dosing Regimen for Maintenance Indication
Asacol (mesalamine)	1.6 g/day by mouth in two divided doses
Apriso (encapsulated mesalamine granules)	1.5 g/day by mouth once daily in the morning
Azulfidine EN-tabs, Azulfadine (sulfasalazine)	30 mg/kg/day by mouth in four divided doses
Dipentum (olsalazine)	1.0 g/day in two divided doses
Remicade (infliximab)	3.0 mg/kg IV every 8 weeks (for moderate to severe 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 Safety Issues With Consideration to Related Drugs

The current labeling of other mesalamine products includes the following warnings and precautions:

- Renal impairment, including renal failure
- Hepatic impairment
- Acute exacerbation of colitis
- Hypersensitivity reactions
- Pyloric stenosis

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1. Pre-submission Regulatory History, NDA 22-000, s005

Date	Regulatory Action(s)
June 16, 2010	sNDA 005 submitted for maintenance of remission indication
March 11, 2010 Type B, Pre-sNDA Meeting	Sponsor proposed using NI margin of 10%. FDA advised that the data to support that conclusion would need to be reviewed as part of the Application.
[redacted] (b) (4)	
September 4, 2007	Shire was granted waiver of pediatric studies for patients <5 years of age and granted deferral for patients 5-17 years of age until December 2010
January 16, 2007	Lialda (mesalamine) Delayed Release Tablets 1.2 g approved for the induction of remission in adults of mild to moderate ulcerative colitis.

2.6 Other Relevant Background Information

Mesalamine has been available worldwide for the treatment of inflammatory bowel disease (IBD) for more than 20 years and as the active component in sulfasalazine for more than 50 years.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well-organized and easily navigable.

The Division of Scientific Investigations (DSI) performed a single clinical site audit for this application. The international site chose was site 205 of the pivotal trial, SPD476-304. This site, in Trivandrum, India, was among the top four centers in total patient enrollment. Additionally, site 205 was the only site among the high-enrolling sites in which all patients were found to be in endoscopic remission at 6 months with both the study drug (Lialda) and the active comparator (Asacol).

DSI recommended that data from the inspected site can be used in support of the NDA. (See DSI Clinical Inspection Summary dated 09 February 2011).

3.2 Compliance with Good Clinical Practices

According to the Applicant, all of the studies were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human patients (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). All studies were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

3.3 Financial Disclosures

For studies 303, 304, and 404 the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

For Study 304, two investigators provided financial disclosures. The principal investigator, (b) (6) disclosed that he received $25,225 from Shire for consult work. He enrolled (b) (6) patients in Study 304. This represents (b) (6) of the patients for that study. Also, (b) (6) disclosed that he received $531,437 from Shire for consult work. He enrolled (b) (6) of patients for Study 304.

Clinical Reviewer Comment:
(b) (6) disclosed that he received over half a million dollars from Shire for consult work. This is a significant amount of money and far greater than the amounts disclosed by other investigators. However, because he enrolled less than (b) (6) of the patients in Study 304 (the pivotal study), (b) (6) has limited potential to impact the outcome of the study.

Table 2. Financial Disclosures, by Study

	Investigator	Site #	Description of Financial Disclosure	Number of Patients Enrolled
Study 304	(b) (6)		Received $25,225 from Shire for consult work	(b) (6)
			Received $531,437 from Shire for consult work	
Study 404			Received $46,682 for partial payments ($1,992) and the IST study ($44,690)	
			Received $142,050 for partial payments ($7,050) and the IST study ($135,000)	
			Received $180,100 for speaker training ($4,500) and the IST study ($175,600)	

For Study 404, three investigators provided financial disclosures. The amounts of these disclosures ranged from $46,682 to $180,100. The disclosures totaled $368,832.

There were no financial disclosures or non-disclosures on file for three investigators who participated in Study 303. See Table 3, below.

Table 3. Investigators Without Financial Disclosures or Non-disclosures on File

Investigator	Site #	Number of Patients Enrolled
(b) (6)		

Clinical Reviewer Comment:
Study 303 was an uncontrolled study and as such the results were not used to make the efficacy determination regarding Lialda in this Application. Only the safety results from Study 304 were used.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Lialda is currently available in the U.S. in the form of 1.2g tablets. No new dosage form or dose is planned for the proposed indication. Therefore, the Applicant did not submit any new CMC information, omitting Module 3 and Module 2 CMC QOS sections.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No animal pharmacology/toxicology data was submitted as part of this supplemental NDA. Animal pharmacology/toxicology data were reviewed previously under the original NDA 22-000 and are described in the current Lialda label.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The exact mechanism of action of mesalamine is unknown, but it appears to act topically rather than systemically as an anti-inflammatory agent.

4.4.2 Pharmacodynamics

Mesalamine is thought to exert its pharmacologic effects topically on the GI tract. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, i.e.,prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

4.4.3 Pharmacokinetics

No new pharmacokinetic studies were submitted with this Application

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4. Clinical Trials Submitted in Support of the Current Application

Study	Design	Treatment Duration	Patients enrolled (completed)	Primary Endpoint
304*	Phase 3, double-blind, active comparator, non-inferiority study of efficacy and safety LIALDA 2.4g once daily vs. ASACOL 0.8 g twice daily	6 months	829 (670)	Primary endpoint: Comparison of proportion of subjects in endoscopic remission (maintenance of mucosal healing) at 6 months.
404	Phase 4, open-label, long-term safety and efficacy study with both acute and maintenance phases. Acute: LIALDA 2.4g-4.8g once daily Maintenance: LIALDA 2.4g once daily	Acute: 8 Weeks Maintenance: 12 months	Acute: 138 (56) Maintenance: 208 (138)	Primary endpoint: To evaluate the proportion of subjects with clinical recurrence at 6 months.
303	Phase 4, open-label, long-term safety and efficacy study with an acute phase Acute: LIALDA 2.4g twice daily Maintenance: LIALDA 2.4g once daily or 1.2 g twice daily	Acute: 8 weeks Maintenance: 12 months	Acute: 312 (250) Maintenance: 459 (377)	Primary endpoint: Safety and tolerability over 12 months. Efficacy assessments included as secondary endpoints.

*Pivotal efficacy trial.

5.2 Review Strategy

For this NDA submission, Study 304 was reviewed in detail and the results are discussed in this document. In the initial submission of this NDA (14 June 2010), for Study 304 the Applicant provided efficacy results only for Study 304 (as a whole). Protocol Amendment 2 (20 March 2007) increased the study population substantially from 410 to 829 randomized patients.

After review team discussions, an information request (IR) was sent to the Applicant on 08 December 2010 for the following information:

1. Details of any correspondence between Shire and FDA regarding clinical study SPD476-304 regarding the study sample size amendment and dates of relevant submissions.

2. Separate Clinical Study Reports for the two phases (i.e., "phase 1" and "phase 2") of study SPD476-304. Phase 1 is based on the pre-amendment sample size; phase 2 is based on the additional sample added by the amendment (excludes the pre-amendment sample).
3. Separate analyses of the primary efficacy endpoint in the ITT (all patients randomized) population for phase 1, phase 2, and phase 1 and 2 combined.
4. Separate analyses of the secondary efficacy endpoints in the ITT population for phase 1, phase 2, and phase 1 and 2 combined.

The Applicant responded to our request for information on 22 February 2011. This large submission was considered a major amendment and the review clock was extended by 3 months.

In this review, efficacy data are presented for phase 1, phase 2, and the combination of these populations.

An additional information request was sent to the Applicant on 04 March 2011. In this request, the FDA asked Shire to explain the following:

1. The reason for the delay in enrollment between phases 1 and 2. Specifically, the FDA requested an explanation for why no new patients were enrolled in Study 304 for approximately 16 months after the estimated date of dosing of the last patient in phase
2. A description of the procedures used to ensure that the data were blinded during the period of the enrollment delay.

Shire responded to the first part of the IR on 17 March 2011. In their response, Shire explained that a 16-month delay was necessary to assess the availability of countries and study sites for phase 2, remanufacture placebo-matching ASACOL tablets, transition to a new Contract Research Organization (CRO), and label study medication.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title
MATRx Maintenance: A Phase 3, Randomized, Multicenter, Double-blind, Parallel Group, Active Comparator Study to Compare the Efficacy and Safety of SPD476 (Mesalamine) 2.4g/day Once Daily With Asacol 1.6g/day Twice Daily (BID) in the Maintenance of Remission in Patients with Ulcerative Colitis

Study Centers

This study was conducted in 133 centers in 27 countries. For analysis, the Applicant chose to pool certain countries geographically (see Table 2 for pooling details). Russia, India, South Africa, USA, and Canada were not pooled.

Table 5. Geographic Pooling

Pooling	Countries
Central And South America	Argentina, Brazil, Chile, Peru, Mexico
Australasia	New Zealand, Australia
Western Europe	Belgium, Denmark, France, Germany, Spain, Sweden, the Netherlands, United Kingdome
Eastern Europe	Hungary, Poland, Romania, Czech Republic
Asia	Taiwan, Korea, Singapore

There were a total of 973 patients screened for Study 304.

Table 6. Number of Screened Patients, by country for Study 304

Country	Number of Patients Screened	Percent
Argentina	7	0.7%
Australia	9	0.9%
Belgium	22	2.3%
Brazil	82	8.4%
Canada	36	3.7%
Chile	12	1.2%
Czech Republic	111	11.4%
Denmark	11	1.1%
France	8	0.8%
Germany	5	0.5%
Hungary	56	5.8%
India	191	19.6%
Korea	37	3.8%
Mexico	22	2.3%
New Zealand	7	0.7%
Peru	15	1.5%
Poland	65	6.7%
Romania	23	2.4%
Russia	109	11.2%
Singapore	10	1.0%
South Africa	40	4.1%
Spain	8	0.8%
Sweden	5	0.5%
Taiwan	3	0.3%
The Netherlands	1	0.1%
United Kingdom	18	1.9%
United States of America	60	6.2%
Total	973	

Study Period

08 April 2005 to 07 September 2009

Study Objective

The primary study objective was to compare the percentage of subjects in endoscopic remission (maintenance of mucosal healing) at 6 months between LIALDA (2.4g/day QD) and ASACOL (1.6g/day divided BID).

The secondary study objectives were:

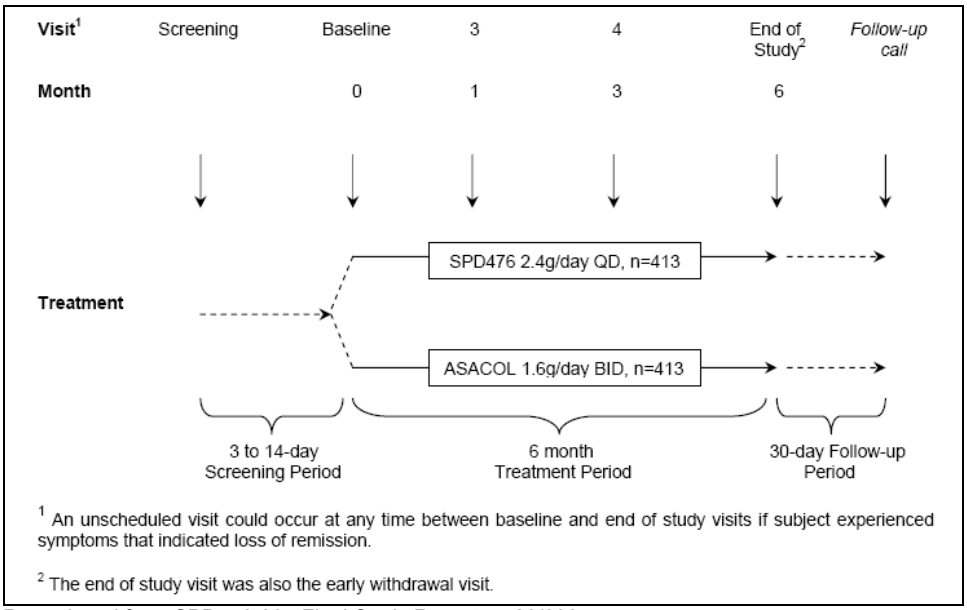
- To compare the percentage of subjects in endoscopic remission (maintenance of mucosal healing) with no or mild symptoms at 6 months between the 2 treatment groups
- To compare time to relapse between the 2 treatment groups
- To compare the modified UC-DAI score and its components (stool frequency, rectal bleeding, mucosal appearance, and Physician's Global Assessment [PGA]) between the 2 treatment groups
- To compare the quality of life (QoL) assessment of a subset of subjects between the 2 treatment groups
- To assess the safety and tolerability of Lialda compared to Asacol

Study Design

The pivotal study, SPD476-304 (Study 304), was a Phase 3, randomized, double-blind, parallel-group, active comparator study conducted at multiple centers in 27 countries worldwide. The study was designed to show that LIALDA 2.4g/day given once daily is non-inferior to ASACOL 1.6g/day given twice daily in maintaining endoscopic remission of UC (mucosal healing).

Adult patients with UC were seen for a screening visit up to two weeks prior to randomization. Patients who met the inclusion criteria and were in remission for at least 30 days were randomized to receive treatment with Lialda or Asacol. Patients were treated for six months. During the study, patients were seen for a study visit at Month 1, Month 3, and Month 6 (end of study). Patients could also be seen for unscheduled study visits at any time during the study if they experienced worsening of UC symptoms. Patients had monthly telephone visits for safety assessments and also had a telephone visit 30 days after the end of the study.

Figure 1. Overall Study Design



Reproduced from SPD476-304 Final Study Report, p. 23/893.

5.3.2 Key Inclusion Criteria

For inclusion in the study, patients had to meet all of the following criteria at screening and at baseline:

1. Male or non-pregnant females aged 18 years or older.
2. Satisfactory medical assessment with no clinically significant and relevant abnormalities (of medical history, physical examination, clinical, or laboratory evaluation).
3. Previous diagnosis of UC confirmed by histology that was considered in remission for ≥30 days, with an endoscopy score of ≤1; and had a combined symptom score (stool frequency and rectal bleeding) of ≤1.
4. On a stable dose of 5-ASA of ≤2.4g/day (or ≤6.2g/day sulfasalazine), for at least
5. 30 days prior to baseline
6. Have had ≥1 acute episode of UC (a documented episode of increased bowel frequency with rectal blood loss for which UC therapy was intensified) in the 12 months prior to screening, and ≥2 acute episodes in their medical history.

5.3.3 Key Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria at screening or at baseline:

1. Documented acute UC flare (increased bowel frequency with rectal blood for which UC therapy was intensified) within 30 days of screening.

2. History of proctitis only at the most recent relapse (extent of inflammation ≤15cm from the anus), previous resective colonic surgery, or Crohn's disease.
3. Current or recurrent disease other than UC, that could have affected the colon, the action, absorption, or disposition of the study medication, or clinical or laboratory assessments.
4. Current pregnancy or lactation.
5. History of current moderate or severe renal impairment (defined as a creatinine level of >2mg/dL) or moderate to severe hepatic impairment.
6. History of asthma with known sensitivity to 5-ASA.
7. Any predisposition to the development of myocarditis or pericarditis.
8. Use of maintenance therapy of 5-ASA doses of >2.4g/day prior to their most recent episode of acute UC.
9. Previous enrollment in Study 304 (with subsequent withdrawal).
10. Current or relevant previous history of serious, severe, or unstable (acute or progressive) physical or psychiatric illness, any medical disorder that may have required treatment or made the subject unlikely to fully complete the study, or any condition that presented undue risk from the investigational product or procedures.
11. History of sensitivity or allergic reaction to salicylates/aspirin or sulfasalazine.
12. History of alcohol or other substance abuse within the last year.
13. Use of any other investigational product or participation in any clinical trial within 30 days prior to treatment initiation in Study SPD476-304.

MO Comment: The inclusion and exclusion criteria appear appropriate for the study.

5.3.4 Treatment

Once eligible for the study, patients were randomized to either the Lialda treatment arm or Asacol treatment arm. Each tablet of Lialda was a red-brown, ellipsoidal, film-coated tablet containing 1.2g mesalamine (5-ASA). Each tablet of Asacol was a red, delayed-release tablet, over-encapsulated in a hard capsule shell containing 0.4 g mesalamine. Matched placebos of both Lialda and Asacol were used during the study to maintain blinding.

Table 7. Study 304, Treatment Arms

Treatment Arm	2x 1.2g Lialda tablets (once daily)	2x Lialda matched placebo (once daily)	2x 0.4 g Asacol (twice daily)	2x Asacol matched placebo (twice daily)
Lialda	X			X
Asacol		X	X	

Patients were instructed to take the study medication with food and swallow the tablets or capsules whole with water. Patients were also instructed not to crush or chew the study medication.

The dose of Lialda for Study 304 was based on previous Lialda clinical trials--specifically Study SPD476-303 (Study 303). This study was a long-term extension study of the pivotal Lialda induction studies (SPD476-301 and -302) and was used to inform the dose used during Study 304. Patients in Study 303 were given a dose of 2.4 g Lialda per day. During the study, only 44 patients (9.6%) of the 459 patients that were enrolled withdrew due to relapse. Based on that efficacy information along with the safety profile, the Applicant chose 2.4g/day as the most appropriate dose for the maintenance study (Study 304).

The dose of the active comparator, ASACOL, for Study 304 was 1.6 g/day. This dose was chosen by the Applicant because it is the dose currently approved for the maintenance of remission of UC in the US.

During the study, patients were instructed that any concomitant medication should be kept at a stable dose during the study. Patients were also instructed not to take medications for indigestion at the same time of day as the study medication. Non-steroidal anti-inflammatory drugs (NSAIDs), anti-diarrheals, laxatives, antibiotics, and drugs that cause constipation were to be avoided; however, prophylactic use of a stable dose of aspirin of up to 325mg/day for cardiac disease was permitted throughout the study. Patients were advised to use acetaminophen for pain during the study.

The dose, duration, and indication for all concomitant medications were recorded in each patient's file and CRF. Medications considered necessary for the patient's safety and well-being were allowed at the discretion of the investigator.

Prohibited concomitant medications were as follows:

- Rectal 5-ASA
- Systemic or rectal corticosteroids
- Other medication containing 5-ASA (eg, sulfasalazine or mesalazine) except during the screening period and except for cardiac disease as described above)
- Immunosuppressive agents
- Anti-tumor necrosis factor (anti-TNF) antibody therapy
- Coumarin-type anticoagulants (these were not prohibited prior to Amendment 4)

Treatment compliance was assessed at each visit. Parents were instructed to return any unused, previously dispensed medication. The number of capsules and/or tablets returned was verified against the number dispensed. Patients who took 80% to 120% were regarded as being compliant.

5.3.5 Study Visits and Procedures

All study visits occurred in an outpatient setting. The study visits and related safety assessments are summarized in Table 4 below.

Table 8. Schedule of Study Assessments

	Screening	Baseline				
	Visit 1	Visit 2	Visit 3	Visit 4	End of Study	Follow-up call
	Day -14 to -3	Day 0 ±7	Month 1±7 days	Month 3±7 days	Month 6±7 days	+ 30 days
Assessment/procedure						
Informed Consent	X					
In/Excl criteria	X	X				
Medical History	X					
Demographics	X					
Physical examination	X				X	
Vital signs	X	X	X	X	X	
Biochemistry & hematology	X			X^	X	
Urinalysis (dipstick)	X			X^	X	
Pregnancy test (urine)	X				X	
Endoscopy		X			X	
Telephone diary details issued	X					
Diary symptoms review	X	X	X	X	X	
PGA		X			X	
UCDAI assessment		X			X	
Randomization		X				
Study drug dispensed		X				
Adverse Event collection	X	X	X	X	X	X
Prior and concomitant medications	X	X			X	
Quality of Lilfe		X		X	X	
Drug Compliance					X	

^ Canada only
Adapted from SPD476-304 Final Study Report, Table 7 (p 33/893)

The study consisted of a 14-day screening period (Visit 1: Day -14 to Day -3). During this screening period, patients underwent physical examination, laboratory testing, and other procedures as outlined in Study Procedures table above.

Visit 2 occurred at randomization (Day 0). During this visit, patients underwent endoscopy (sigmoidoscopy or colonoscopy) to assess mucosal appearance.
For one week prior to each visit (excluding the screening visit) patients were instructed to call into an Interactive Voice Response System (IVRS) daily. Patients were instructed to call within an hour of bedtime. During this call, stool frequency and rectal bleeding symptoms were assessed. Additionally, patients were to call the IVRS daily if they experienced symptoms of relapse.

The scores for rectal bleeding and stool frequency for the last 3 days in each call-in period immediately prior to a study visit were recorded in the CRF. See Table 9 (below) for detail about the symptom assessment scores. The average of the last 3 scores prior to Visit 2 (Day 0) and Visit 5 (last visit/end of study) was calculated and used for calculation of the UC-DAI. If less than 3 scores were available, the mean of all available scores was used. However, no scores older than 5 days were to be used for score calculations.

Table 9. IVRS Symptom Assessment Scores

Parameter	Assessment	Score
Stool Frequency	Normal	0
	1-2 more than normal/day	1
	3-4 more than normal /day	2
	>4 more than normal /day	3
Rectal bleeding	No rectal bleeding	0
	Streaks of blood	1
	Obvious blood	2
	Mostly blood	3

During Study Visit 3 (Month 1 ± 7 days), patients had vital signs assessed and diary symptom scores reviewed.

Study Visit 4 (Month 3 ± 7 days) occurred midway through the study. During this visit, patients had vital signs assessed and diary symptom scores reviewed. Additionally, patients underwent laboratory testing and completed quality of life assessments.

Study Visit 5 (Month 6 ± 7 days) occurred at the end of the study. During this visit, patients underwent physical examination and laboratory evaluation. Additionally, patients underwent endoscopy for assessment of mucosal appearance.

During the study, if a patient experienced symptoms of relapse an unscheduled visit was planned within 14 days and endoscopy was conducted at this visit. If the endoscopy confirmed relapse (endoscopy score >1), patients were withdrawn from the study and this visit was counted as the end of study visit.

During endoscopy, mucosal appearance was scored on a scale from 0 to 3. A score of 0 was assigned for normal mucosa (intact vascular patter without friability or granulation). A score of 3 was assigned for a severely damaged mucosal appearance (ulceration and spontaneous bleeding).

See

Table 10 below for mucosal appearance scoring. All study endoscopies were to be performed by the same investigator to reduce inter-investigator variability in scores for a single patient.

Table 10. Mucosal Appearance Scoring

Score	Disease Severity	Characteristics
0	Normal	Intact Vascular Pattern No Friability or Granulation
1	Mild	Erythema Decreased Vascular Pattern Minimal Granularity
2	Moderate	Marked Erythema Granularity Friability Absent Vascular Pattern
3	Severe	Ulceration Spontaneous Bleeding

During Study 304, patients also completed quality of life assessments. These assessments were to be completed at screening, Month 3, and Month 6/EOS. However, not all patients participated in these assessments. Assessments were only conducted in countries where the Short Irritable Bowel Disease Questionnaire (SIBDQ) had been translated into the appropriate language and where the SIBDQ had been properly licensed. Quality of Life assessments occurred in the following countries: UK, USA, Canada (Dr. Bailey only), Belgium, Germany, France, Czech Republic, Poland, Hungary, Netherlands, Portugal, Denmark, Sweden, Romania, Australia, New Zealand, South Africa, and Singapore (for patients who spoke English). Overall, a total of 400 patients (48.4%) in the ITT population completed quality of life assessments. See Appendix B for the full SIBDQ.

At each visit, adverse events and prior and concomitant medications were assessed and recorded in each patient's CRF. IVRS responses were also reviewed at each visit as were adverse event data

A post-study follow-up safety assessment occurred via telephone two weeks after the last dose of study drug for each patient. During this assessment, concomitant medication and adverse event data were collected.

5.3.6 Control Procedures

Randomization

Patients were randomized by center in a 1:1 ratio to receive Lialda or Asacol. Initially, treatment group numbers were assigned sequentially in blocks of four based on the

lowest numbered treatment group pack available at each site. The randomization schedule was generated by computer software and the final randomization schedule was prepared by Quintiles. Following Protocol Amendment 2 (20 March 2007) randomization was done sequentially using an interactive voice response system (IVRS) prior to the treatment pack being dispensed.

Active Control
Asacol and matching placebo capsules were provided as red, delayed-release tablets, over-encapsulated in hard gelatin capsule shells. Lialda and matched placebo was provided in red-brown, ellipsoidal, film-coated tablets.

Blinding
In this double-blind study, all study site personnel were blinded to the patient treatment assignment. In the case that a blind needed to be broken, a concealed section of the study drug label could be removed revealing the patient's treatment assignment. A concealed section of the study drug label, attached to a detachable portion of the label contained the product identification. This detachable portion was affixed to the label page in the CRF.

Patients were dispensed blinded study drug at each study visit in an adequate amount to allow proper dosing until the next scheduled study visit.

The treatment code was not broken for any patient during the study.

Data Management
Pre-printed CRFs were used to collect information. After Protocol Amendment 2, the IVRS was used to provided randomization and allocation of patients to treatment. Additionally, the IVRS was used by patients to record daily symptoms.

For the analysis of clinical laboratory data, one central laboratory per geographical area was used.

5.3.7 Primary Efficacy Endpoint

The primary efficacy variable for this study was the maintenance of mucosal healing. Mucosal healing, remission, for this study was defined as an endoscopy score of ≤1 at Month 6. All patients who entered the study were to have a previous diagnosis of UC confirmed by histology that was considered in remission for ≥30 days. Specifically, on admission to the study, patients had to have both an endoscopy score of ≤1 and a combined symptom score (stool frequency and rectal bleeding) of ≤1.

The UCDAI is comprised of four indices of disease: stool frequency, rectal bleeding, mucosal appearance, and a physician's rating of disease severity. Each index is evaluated on a scale of 0 to 3, with a maximum total score of 12. To improve the clarity

of the UCDAI, the scale was amended such that an endoscopy score of 1 (mild disease) did not include the term friability. Instead, friability was scored 2 (moderate disease). This modified UCDAI was used for Study 304. See Table 10, above.

5.3.8 Secondary Efficacy Endpoint(s)

1. Proportion of patients in endoscopic remission in the ITT population
2. Supportive analysis investigating country effect
3. Analysis of the primary efficacy variable by the following covariates:
    a. Gender
    b. Age (<55 vs. 55+)
    c. Race (Caucasian vs. Non-Caucasian)
    d. Smoking status (Smokes/Previous vs. Never Smoked)
    e. Disease Classification (Left-Sided vs. Other)
    f. Time since most recent acute episode at baseline (≤12 weeks, >12-≤24 weeks, >24- ≤36 weeks, >36 weeks)
    g. Number of acute episodes of UC (≤2 episodes, >2-≤4 episodes, >4-≤10 episodes, >10 episodes)
4. Proportion of subjects in endoscopic remission (maintenance of mucosal healing) with no or mild symptoms at Month 6
5. Time to relapse
6. Change from baseline in the modified UC-DAI Score by treatment
7. Rectal bleeding and stool frequency change from baseline
8. Endoscopy score and PGA change from baseline
9. Quality of Life assessment

5.3.9 Statistical Information

The primary efficacy variable was the proportion of subjects in endoscopic remission (maintenance of mucosal healing) at Month 6 in each treatment group as defined by an endoscopy score of ≤1. Study 304 was planned as a non-inferiority study and the SAP specified that the per protocol (PP) population was to be used for the primary analysis.

The per protocol population excluded all patients who withdrew for reasons other than lack of efficacy or adverse events and/or had missing endoscopy data at Month 6. Patients who withdrew early for other reasons were considered treatment failures (i.e. not in remission). Additionally, PP patients could not have had any major protocol deviations.

According to the Applicant, the study was designed to test the null hypothesis that the difference in proportion of patients in remission between the Lialda and Asacol groups was less than or equal to -10%. The proportion of patients in remission at Month 6 and the 2-sided 95% confidence interval (CI) was to be calculated using a normal

approximation to the binomial distribution. Non-inferiority was to be concluded if the lower limit of the 95% CI was above the non-inferiority margin of -10%. Superiority was to be concluded if the 95% CI was above -10 and above 0.

Clinical Reviewer Comment:
The Applicant's non-inferiority margin was changed during the current review cycle to a more conservative -4.3%. This change is descried in detail in Section 6.1.4.

The original, planned sample size for Study 304 was 410 randomized patients. According to the Applicant this number was based on a predicted remission rate of 65% in per protocol patients taking Asacol 1.6 g/day based on the results of the Mesalamine Study Group.[1] Once the study had begun, the Applicant decided to double the sample size to allow for a predicted remission rate of 70% in both the Asacol and Lialda groups. The Applicant justifies this change stating that the Mesalamine Study Group study showed a true remission rate of 70% in the ITT group; therefore, this number is more representative of the treatment effect expected in Study 304.

No adjustments for multiplicity were made in the analysis of the secondary endpoints.

Because there was only one controlled clinical study submitted for this Application, all efficacy results are presented in Section 6, Review of Efficacy, below.

5.3.10 Protocol Amendments

The protocol was finalized 14 September 2009.

Amendment 1 was finalized before the study began. The change was introduced to include an additional blood test at Month 3 including liver function tests and creatinine for patient's in Canada only.

Amendment 2 was finalized 20 March 2007. The change was introduced for the following primary reasons:

1. To update the emergency contact list.
2. To change the clinical assumption of the 1.6 g/day Asacol response rate from 65% to 70% based on the results of the ITT population of the Mesalamine Study Group. This changed increased the study size from 416 to 832 patients and increased the number of study centers from 65 to 130 and increase the number of countries by 5.
3. To change the planned study recruitment end date from September 2006 to February 2009 and change the study enrollment period from 12 to 37 months.
4. To clarify that a baseline endoscopy is not required if one has been performed within the previous 10 days.

5. IVR system will be used to randomize patients and dispense and track medications.

Amendment 3 was introduced for the following primary reasons:

1. (b) (4)
2. Patients with moderate/severe hepatic impairment were excluded from the study due to updated class labeling revealing a risk for hepatic failure and death with mesalamine use in this sub-population.

Amendment 4 was finalized to change the Contract Research Organization for from PPD Development to ICON Clinical Research Limited.

The changes included as Amendments 5 and 6 contained mainly administrative in nature and will not be described.

6 Review of Efficacy

Efficacy Summary

Study 304 is compromised by a series of design and implementation flaws that bring into question whether any statistically valid conclusions can be made based on the study results alone. However, when combined with other information (historical control information, pharmacological similarity to an approved product, and the appropriateness of a more liberal NI margin) there is sufficient evidence from the clinical standpoint to support the approval of Lialda for the maintenance of UC indication.

Study 304 was designed as a non-inferiority study using Asacol as the comparator drug. For Study 304, this reviewer has chosen to use both the intent-to-treat and per protocol populations of those patients enrolled in Study 304 prior to the unplanned increase in the sample size (phase 1) and those enrolled after the sample size increase (phase 2). For this review, no weight was given to the larger population of phase 1 and 2 combined.

The NI margin of 10% pre-specified in the SAP was changed during the current review cycle by the Applicant to a more conservative margin of 4.3% based on a recent FDA Guidance. However, in the opinion of this reviewer, an appropriate margin for this drug and indication is 6% to 7% (see Section 6.1.4 for a full discussion of the proposed margin).

Using the margin of 6% to 7%, the primary statistical analysis patient population pre-specified by the Applicant meets the margin and provides statistical evidence that Lialda is non-inferior to Asacol for the maintenance of remission of ulcerative colitis.

Corroborating evidence of efficacy comes from examining the results of other populations in Study 304 along with the results of other studies using mesalamines versus placebo for the same indication. Published studies (described in Section 6.1.4) of mesalamines versus placebo for the maintenance of remission of UC indication provide substantiation of a valid treatment effect for Lialda for the maintenance indication. In these studies (see Table 17, below), estimates of the rates of remission for placebo ranged from approximately 40 to 59%. This range is different from the rates of remission for Lialda seen in Study 304 which were approximately 78% to 84%. The disparity seen between the placebo remission rates and Lialda remission rates further support the conclusion that Lialda is efficacious for the indication.

6.1 Indication

The Applicant is proposing that Lialda receive an indication for maintenance of remission, [redacted] UC.

6.1.1 Methods

A single Phase 3 controlled study was submitted to evaluate the efficacy and safety of Lialda 2.4 g daily for the maintenance of remission, [redacted] UC. Study 304 was designed to show that Lialda was non-inferior to Asacol 1.6 g/day [redacted] The primary efficacy endpoint was the proportion of patients in remission in Month 6 in each of the treatment groups.

Section 5.3 contains a discussion of the study; Section 6 contains the study results.

6.1.2 Demographics

Baseline demographic characteristics are summarized below in Table 11. Overall, in both Phases, randomization produced demographic sub-groups which were well-balanced between the two treatments—Lialda and Asacol.

The proportion of Caucasian and Asian race patients was disparate between the two phases with more Asians being enrolled in Phase 2. In phase 1, 74.5% of patients were Caucasian and 19.7% were Asian. However, in phase 2, only 53.9% of patients were Caucasian and 31.0% of patients were Asian. After protocol Amendment 2 (phase 2), additional study centers were included in the study which might explain the differences in racial proportions between the phases of the study.

Table 11. Demographics, Study 304

Demographic Subgroup	PHASE 1 N=416			PHASE 2		
	Lialda N= 208	Asacol N= 208	Phase 1 (All) N=416	Lialda N= 207	Asacol N= 203	Phase 2 (All) N=410
Sex (n,%)						
Male	101 (48.6%)	114 (54.8%)	215 (51.7%)	111 (53.6)	100 (49.3)	211 (51.5%)
Female	107 (51.4%)	94 (45.2%)	201 (48.3%)	96 (46.4%)	103 (50.7%)	199 (48.5%)
Age (years) (n,%)						
Mean (SD)	44.2 (13.5)	45.5 (13.4)	44.9 (13.5)	45.9 (14.5)	44.8 (13.5)	45.3 (14.0)
Median	44.0	45.5	45.0	46.0	45.0	45.0
min,max	18, 80	18, 85	18, 85	18, 85	19, 76	18, 85
Race* (n,%)						
Caucasian	154 (74.0%)	156 (75.0%)	310 (74.5%)	118 (57.0%)	103 (50.7%)	221 (53.9%)
Black	4 (1.9%)	1 (0.5%)	5 (1.2%)	5 (2.4%)	3 (1.5%)	8 (2.0%)
Hispanic	5 (2.4%)	6 (2.9%)	11 (2.6%)	14 (16.8%)	17 (8.4%)	31 (7.6%)
Asian/ PI*	42 (20.2%)	40 (19.2%)	82 (19.7%)	61 (29.5%)	66 (32.5%)	127 (31.0%)
Other	3 (1.4%)	5 (2.4%)	8 (1.9%)	9 (4.3%)	14 (6.9%)	23 (5.6%)

Adapted from Table 2 (p. 13/464), Table 12 (p. 36/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

MO Comment:
The patient populations of phase 1 and phase 2 differed in racial and country of origin makeup. The ITT population of phase 2 contained approximately 11% more Asian patients than phase 1. Initially, this difference raised a red flag given that recent epidemiologic research has shown that, "the clinical course of IBD seems to be less severe in the Asia-Pacific region than in Western countries".[2] However, a review of intra-phase randomization between treatment groups reveals that Asian patients in both phases were split nearly equally between treatment groups. Therefore, there is little potential for these differences to influence the overall efficacy results.

Disparities also existed in enrollment from countries and regions between the ITT population of phase 1 and 2. For example, phase 2 contained no patients from Russia. In contrast, phase 1 contained 100 (25%) patients from Russia. Additionally, phase 1 contained no patients from Australia/New Zealand or South Africa. In contrast, phase 2 contained 13 (3%) patients from Australia/New Zealand and 35 (8.5%) patients from South Africa. Patients from India were included in the ITT population for both phases. However, in phase 1, 63 (15%) of patients were from India; while in phase 2, 101 (25%) of patients were from India. Patients from the US were included in both phases of Study 304 in roughly equal percents—5.0% (phase 1), 5.1% (phase 2). However, US patients represented a small amount of patients for a single study in support of marketing Lialda in the US for maintenance of remission of UC. Increasing the proportion of patients from the US for US marketing studies remains an opportunity for improvement for future studies.

6.1.3 Subject Disposition

In Study 304, 977 patients were screened for participation. Of these patients, 829 were randomized. Of these patients, three (one randomized to Lialda and two randomized to Asacol) did not receive study medication. The remaining 826 patients were included in the intent-to-treat (ITT) and safety populations. These populations were defined as all randomized patients who received at least one dose of study drug.

Table 12. Populations Used for Evaluation, Study 304

POPULATION	PHASE 1		PHASE 2		COMBINED	
	Lialda	Asacol	Lialda	Asacol	Lialda	Asacol
Randomized	209	209	207	204	416	413
ITT/Safety	208	208	207	203	415	411
Per Protocol	178	179	165	157	343	336

Adapted from Table 1.1 (pages 97-104/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

The per protocol (PP) population included all patients in the ITT population who either completed the study or withdrew for reasons related to lack of efficacy or adverse events (AEs) and were considered protocol-compliant.

Table 13. Patient Disposition Study 304

	Phase 1			Phase 2			Combined		
	Lialda	Asacol	Total	Lialda	Asacol	Total	Lialda	Asacol	Total
	n (%)								
Randomized[a]	209	209	418	207	204	411	416	413	829
Completed Study	170 (81.3)	173 (82.8)	343 (82.1)	170 (82.1)	157 (77.1)	327 (79.6)	340 (81.7)	330 (79.9)	670 (80.8)
Discontinued Early	39 (81.3)	36 (17.2)	75 (17.9)	37 (17.9)	47 (14.7)	84 (12.2)	76 (18.3)	83 (20.1)	159 (19.2)
Lack of efficacy	30 (14.4)	27 (12.9)	57 (13.6)	20 (9.7)	30 (14.7)	50 (12.2)	50 (12.0)	57 (13.8)	107 (12.9)
AE/SAE	3 (1.4)	3 (1.4)	6 (1.4)	3 (1.4)	0	3 (0.7)	6 (1.4)	3 (0.7)	9 (1.1)
Non-Compliance	0	0	0	0	1 (0.5)	1 (0.2)	0	1 (0.2)	1 (0.1)
Patient request	2 (1.0)	3 (1.4)	5 (1.2)	8 (3.9)	3 (1.5)	11 (2.7)	10 (2.4)	6 (1.5)	16 (1.9)
Lost to follow-up	3 (1.4)	2 (1.0)	5 (1.2)	2 (1.0)	8 (3.9)	10 (2.4)	5 (1.2)	10 (2.4)	15 (1.8)
Protocol violation	1 (0.5)	0	1 (0.2)	2 (1.0)	3 (1.5)	5 (1.2)	3 (0.7)	3 (0.7)	6 (0.7)
Pregnancy	0	1 (0.5)	1 (0.2)	0	0	0	0	1 (0.2)	1 (0.1)
Other*	0	0	0	2 (1.0)	2 (1.0)	4 (1.0)	2 (0.5)	2 (0.5)	4 (0.2)

Adapted from Table 1 (p. 11/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request
[a] Three randomized patients did not receive a dose of study medication (1 Lialda, 2 Asacol) and are therefore not included in the ITT population.
* Patient 20414 did not return for a subsequent visit, Patient 62601 used prohibited corticosteroid, Patient 19619 was discontinued due to lack of investigation product at center, and Patient 50002 withdrew consent

Of the patients randomized to treatment in Study 304, 80.8% (607 patients) completed the 6 month study. The percentage of patients who completed the study was similar between those patients taking Lialda and those taking Asacol, 81.7% and 79.9%, respectively. Similarly, the percentage of patients who completed the study was similar between phase 1 and phase 2, 82.1% and 79.6%, respectively. The most common reason for early discontinuation was lack of efficacy. See Table 13 for additional patient disposition information.

A number of patients in the ITT population had major protocol violations, as defined by the SAP. Of those patients randomized, 147(17.8%) were excluded from the PP population for major protocol violations. There were more major protocol violations during phase 2 than during phase 1, 102 and 68, respectively. The proportion of patients treated with Lialda (across both phases) with protocol violations was similar to the proportion of Asacol-treated patients with protocol violations, 17.3% and 18.2% respectively. See Table 14, below.

Table 14. Major Protocol Deviations, ITT Population

	PHASE 1			PHASE 2			COMBINED		
	Lialda	Asacol	Total	Lialda	Asacol	Total	Lialda	Asacol	Total
Total ITT patients	208	208	416	207	203	410	415	411	826
Total pts with major protocol deviations	n (%)						72 (17.3%)	75 (18.2%)	147 (17.8%)
Failed inclusion criteria	17 (8.2)	15 (7.2)	32 (7.7)	14 (6.8)	22 (10.8)	36 (8.8)	31 (7.5)	37 (9.0)	68 (8.2)
Failed exclusion criteria	3 (1.4)	4 (1.9)	7 (1.7)	2 (1.0)	5 (2.5)	7 (1.7)	5 (1.2)	9 (2.2)	14 (1.7)
Compliance <80%	4 (1.9)	6 (2.9)	10 (2.4)	3 (1.4)	4 (2.0)	7 (1.7)	7 (1.7)	10 (2.4)	17 (2.1)
Early Withdrawal	5 (2.4)	6 (2.9)	11 (2.6)	14 (6.8)	16 (7.9)	30 (7.3)	19 (4.6)	22 (5.4)	41 (5.0)
Prohibited Concomitant medication	3 (1.4)	1 (0.5)	4 (1.0)	13 (6.3)	2 (1.0)	15 (3.7)	16 (3.9)	3 (0.7)	19 (2.3)
Sigmoidoscopy >7 days after last dose	1 (0.5)	3 (1.4)	4 (1.0)	0	0	0	1 (0.2)	3 (0.7)	4 (0.5)
Missing sigmoidoscopy at Month 6	0	0	0	2 (1.0)	1 (0.5)	3 (0.7)	2 (0.5)	1 (0.2)	3 (0.4)
Misrandomization	0	0	0	1 (0.5)	3 (1.5)	4 (1.0)	1 (0.2)	3 (0.7)	4 (0.5)
Total major protocol deviations	33 (15.9)	35 (16.8)	68 (16.3)	49 (23.7)	53 (26.1)	102 (24.9)	82 (19.8)	88 (21.4)	170 (20.6)

Adapted from Table 6 (p. 25/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request and Table 14 (p. 59/893), CSR SPD476-304, Final.

Events categorized as major protocol violations were defined in the Statistical Analysis Plan and agreed upon prior to data lock and unblinding, according to the Applicant. The most common protocol violation was failure to meet all inclusion criteria. Of the inclusion criteria, the one most frequently not met was the requirement to be on a stable dose of 5-ASA of ≤2.4 g/day (or sulfasalazine ≤6.2 g/day) for 30 days prior to baseline evaluation for study enrollment. See Table 15, below.

Table 15. Failed Inclusion Criteria, by Phase

	PHASE 1			PHASE 2			COMBINED		
	Lialda	Asacol	Total	Lialda	Asacol	Total	Lialda	Asacol	Total
Total ITT patients	208	208	416	207	203	410	415	411	826
Failed Inclusion Criteria	n (%)								
Satisfactory medical assessment	2 (1.0)	0	2 (0.5)	0	0	0	2 (0.5)	0	2 (0.2)
Histology-confirmed dx of UC	0	0	0	3 (1.4)	7 (3.,4)	10 (2.4)	3 (0.7)	7 (1.7)	10 (1.2)
UC in remission for ≤30 days	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	4 (0.5)
Baseline endoscopy score ≥1	0	0	0	0	1 (0.5)	1 (0.2)	0	1 (0.2)	1 (0.1)
Baseline line combined sx score of ≥1	3 (1.4)	2 (1.0)	5 (1.2)	1 (0.5)	4 (2.0)	5 (1.2)	4 (0.1)	6 (1.5)	10 (1.2)
Stable dose of 5-ASA for ≥30 days prior to baseline	11 (5.3)	11 (5.3)	22 (5.3)	10 (4.8)	11 (5.4)	21 (5.1)	21 (5.1)	22 (5.6)	43 (5.2)
≥1 acute episode of UC in past 12 months	1 (0.5)	2 (1.0)	3 (0.7)	0	0	0	1 (0.2)	2 (0.5)	3 (0.4)

Adapted from Table 1.8 (p. 266/464), SPD476-304 by Enrollment,, CSR SPD476-304, Final.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for Study 304 was the proportion of patients in each treatment group who remained in endoscopic remission from mild to moderate UC at Month 6. Patients were to enter the study in remission and were randomized to receive either Lialda 2.4 g once daily or Asacol 800 mg twice daily (1.6 g/day).

Study 304 was designed as a non-inferiority (NI) study. The NI study "is dependent on knowing something that is not measured in the study, namely, that the active control had its expected effect in the NI study."[3] In this case, the ability to correctly interpret the study results was dependent upon Asacol having the expected magnitude of effect in study patients. In clinical studies used for registration of Asacol for the maintenance of remission of UC, 70.1% of Asacol 1.6 g/day patients, compared with 48.3% of placebo patients (p=0.005) maintained remission at Month 6.[4]

Table 16. Proportion of Patients in Endoscopic Remission at Month 6, Study 304

		PHASE 1	PHASE 2	COMBINED
Intent-to-Treat Population	Lialda 2.4 g/day	78.4% (163/208)	77.3% (160/207)	77.8% (323/415)
	Asacol 1.6 g/day	79.3% (165/208)	74.4% (151/203)	76.9% (316/411)
	Difference (Lialda-Asacol)	-1.0%	2.9%	0.9%
	95% Confidence Interval	-9.3%, 7.4%	-5.9%, 7.0%	-5.0%, 7.0%
Per Protocol Population	Lialda 2.4 g/day	83.1% (148/178)	84.2% (139/165)	83.7% (287/343)
	Asacol 1.6 g/day	81.0% (145/179)	82.2% (129/157)	81.5% (274/336)
	Difference (Lialda-Asacol)	2.1%	2.1%	2.1%
	95% Confidence Interval	-6.4%, 10.7%	-6.7%, 10.9%	-4.0%, 8.0%

Adapted from Table 7 (p. 28/464) and Table 8 (p 30/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

The first question to answer in a statistical evaluation of the primary endpoint is whether Asacol (the active comparator) demonstrated its expected effect in Study 304. The answer is yes. In all phases (1 and 2) and all populations (ITT and PP), the remission rate for patients taking Asacol was 70% or greater.

The next question to answer is whether the lower limit of the confidence interval around the observed difference in effectiveness between Lialda and Asacol is within the non-inferiority (NI) margin. For the answer to this question, we must first define a clinically acceptable NI margin and determine which population (ITT or PP) to use for analysis.

For the primary statistical analysis, the Applicant pre-specified a NI margin of -10%. Specifically, the statistical analysis plan (SAP) specified that non-inferiority of Lialda to Asacol would be concluded if the lower limit of the 95% CI was above the non-inferiority margin of -10%.

However, in an information request from the FDA, the Applicant was asked to re-evaluate the margin according to the recommendations of the FDA draft *Guidance for Industry, Non-Inferiority Clinical Trials* (March 2010). The Applicant's re-evaluation of the NI margin used a published article of a trial using mesalamine 1.6 g/day vs. placebo for the maintenance of remission of UC. In the Mesalamine Study Group Trial the difference in remission rate between patients taking Asacol 1.6g/day and placebo was 25.8% (95% CI 8.6% to 43.0%) for the PP population and 21.8% (95% CI 7.6% to 36.1%).[5] The Applicant then used the fixed margin approach to calculate an appropriate margin. For this method, the lower bound of the confidence interval of the active control effect size in past placebo-controlled studies is selected as a conservative choice for the active comparator effect size, M_1. Next, the Applicant calculated M_2 (the

largest clinically acceptable degree of inferiority of the test drug compared to the active control). The Applicant assumed that maintaining at least 50% of M_1 would be clinically meaningful (this is a common assumption). Therefore, the Applicant calculated M_2 as 4.3% (Mesalamine Study Group) because of their plan to use the per protocol population.

MO Comment:
M_2 for the ITT population (using a 50% discount of M_1) is 3.8% and this is the margin advocated by the statistical reviewer, Dr. Milton Fan. Please see the statistical review for further details.

The NI margin should express the clinically acceptable extent to which Lialda can be less effective than Asacol. The recently published *Guidance for Industry: Non-Inferiority Clinical Trials* states that in situations where the test drug is pharmacologically similar to the active control, "the expectation of similar performance (but still requiring confirmation in a trial) might make it possible to accept a single trial and perhaps could also allow less conservative choices in choosing the non-inferiority margin." One way to make the NI margin less conservative is to be flexible in choosing the clinical margin, M2. This flexibility in choosing M_2 is supported by the NI Guidance which states that flexibility in choosing a less conservative is appropriate when "the primary endpoint does not involve an irreversible outcome such as death".

In the fixed margin approach to choosing the NI margin, M_2 is often chosen as 50% of M_1 (i.e. it would be clinically important to maintain at least 50% of the difference of M_1). However, a less conservative approach would be to choose M_2 such that 20% to 30% of M_1 is maintained. In that case, M_2 would be 70% to 80% of M_1.

MO Comment:
In the case of Lialda, the active comparator, Asacol, is pharmacologically similar and it is expected that the two drugs will have similar performance. Additionally, the endpoint of Study 304 does not involve an irreversible outcome such as death making the use of a less conservative M_2 appropriate. This reviewer believes that an appropriate M_2 for this study would maintain only 20% to 30% of M_1 which is less conservative than 50%. Even this is somewhat conservative but may be necessary given potential sources of uncertainty regarding the similarity of the patient populations in the Mesalamine group Study and in Study 304 and to reduce the risk of making an incorrect decision regarding the non-inferiority hypothesis.

To calculate an appropriate M_2, the lower bound of the 95% confidence interval (8.6%) of the active control from the Mesalamine Group Study should be chosen as the conservative choice for the active comparator effect size, M_1. Next, the largest clinically acceptable degree of inferiority of 20% to 30% is used to discount M_1 which leads to an M_2 of 6% to 7%.

The final question to be answered in evaluating a NI study is "which population (ITT or PP) should be used for evaluation? It is difficult to answer that question "the conservatism or anticonservatism of the PP or ITT analysis depends on many factors, including the type of protocol deviation and missingness, the treatment trajectory (for longitudinal study) and the method of handling missing data in ITT population." [6] For that reason, the NI Guidance states that "it is therefore important to conduct both ITT and as-treated analyses in NI studies."[7]

MO Comment:
Given the uncertainty in the statistical community as to which population should be used (ITT vs. PP), the results for both populations were examined.

Evaluation of the primary endpoint results of Study 304 in light of a 6% to 7% margin using the fixed margin approach reveals the following:

1. In phase 1, only the per protocol population results meet the NI margin.
2. In phase 2, results for both the ITT and PP populations are within the NI margin.

MO Comment:
No weight is being given to the results of the combined population of phase 1 and phase 2 given the unplanned doubling of the patient population.

Supportive Primary Endpoint Analyses

The efficacy of Lialda for the maintenance of remission of UC is further supported by the results of previously-published, randomized, placebo-controlled studies which show a statistically significant difference between placebo and mesalamines for the maintenance of remission of UC. Two of the referenced studies of mesalamine products (Asacol and Apriso) were used in support of approval for the maintenance of UC indication. These studies had definitions of remission comparable to that used for Study 304 with similar study durations. Placebo remission rate for similar trials ranged from 40% to 68%. The remission rates for Lialda in Study 304 ranged from 77% to 84% depending on which phase and population is analyzed.

MO Comment:
In a broad sense, the placebo and Lialda response ranges appear to be quite different. While not statistically persuasive, these results provide some evidence that Lialda has some effect on the maintenance of remission.

Table 17 outlines several studies of maintenance of remission of UC studies using mesalamine and placebo.

Table 17. Cross-Study Comparison of Mesalamine Maintenance of Remission Rates

Study Drug	Definition of Remission	Time of Analysis	Maintenance of Remission Rate	
			Active Drug	Placebo
Lialda registration trial* NDA 22-000 S-005 (mesalamine) 2.4 g/day	endoscopy score ≤1 (intact vascular pattern, no friability or granulation; or erythema, decreased vascular pattern, minimal granularity)	6 months	ITT Ph1- 78.4% Ph2- 84.2%	n/a
			PP Ph1- 83.1% Ph2- 84.2%	
Mesalamine Study Group[8] Mesalamine 1.6 g/day	endoscopy score =0 (normal or mild granularity, edema, hyperemia, or erythema; mildly diminished vascular markings)	6 months	ITT 70.1%	ITT 48.2%
			Evaluable 65.5%	Evaluable 39.7%
Hawkey, et al.[9] Mesalamine 1.6 g/day	endoscopy score=0 (not specifically defined in article) *and* <3 consecutive days of rectal bleeding *and* <1 week of liquid stools	6 months	Evaluable 62.8%	Evaluable 42.9%
Apriso registration trials[10] (encapsulated mesalamine granules) 1.5 g/day	endoscopy score ≤1 (intact mucosa with preserved or distorted vessels; or erythema, decreased vascular pattern, granularity, and no mucosal hemorrhage) *and* rectal bleeding score =0 (absence of bleeding)	12 months	ITT Study 1- 78.9% Study 2- 79.9%	ITT Study 1- 58.3% Study 2- 67.7%
			PP Study 1- 78.5% Study 2- 80.1%	PP Study 1- 59.1% Study 2- 67.4%

6.1.5 Analysis of Secondary Endpoints(s)

There was no ranking of secondary endpoints to account for multiplicity. The proportion of patients in endoscopic remission at Month 6 in the ITT population was a secondary endpoint. Those results are presented in section 6.1.4 along with the proportion of patients in endoscopic remission at Month 6 in the PP population.

MO Comment:
The secondary endpoints are reviewed for descriptive purposes only. In addition to a lack of a pre-defined plan for dealing with multiplicity, Study 304 is did not meet the pre-defined margin and the conclusion regarding the efficacy of Lialda in maintaining endoscopic remission is based on the preponderance of evidence from various sources. Therefore, no statistically valid conclusions can be reached regarding any of the secondary endpoints.

(b) (4)

Clinical remission was defined as a score of 0 for both rectal bleeding and stool frequency. The proportion of patients taking Lialda in clinical remission at baseline in phase 1 ranged from 77.9 (ITT) to 79.8% (PP). This number is not 100% because patient did not have to enter the study in clinical remission. For inclusion, patients only had to have a study a combined symptom score (stool frequency and rectal bleeding) of ≤1.

Table 18. Clinical Remission+ in Patients Taking Lialda, Study 304

Phase 1	ITT		PP	
	Lialda	Asacol	Lialda	Asacol
Number of Patients	208	208	178	179
Clinical Remission, Baseline	77.9%	76.9%	79.8%	77.7%
Clinical Remission, Month 6	67.8%	67.3%	73.0%	69.3%
Difference (Lialda-Asacol)	5.0%		0.038	
95% CI for difference	-9.0%, 10.0%		-6.2%, 13.7%	
Phase 2	**ITT**		**PP**	
Number of Patients	207	203	165	157
Clinical Remission, Baseline	77.3%	73.4%	78.2%	75.8%
Clinical Remission, Month 6	63.3%	62.6%	66.1%	69.4%
Difference (Lialda-Asacol)	0.7%		-3.4	
95% CI for difference	-6.1%, 13.3%		-14.2%, 7.4%	

Clinical remission defined as scores of 0 for rectal bleeding and stool frequency
Adapted from Table 2.8.1 (p. 385-390/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

In phase 1, 67.8% of patients taking Lialda in the ITT population were in clinical remission compared with 67.3% of patients taking Asacol at Month 6. In the PP population 73.0% of Lialda patients were in clinical remission at Month 6 compared with 69.3% of patients taking Asacol.

MO Comment:
On the surface, the results of the clinical remission evaluation support the conclusion that Lialda is effective in the maintenance of clinical remission. However, because patients did not have to enter the study in clinical remission, the Month 6 results in Table 18 do differentiate those patients who maintained clinical remission from baseline to Month 6 from those patients who attained clinical remission from baseline to Month 6.

Another important secondary endpoint is the proportion of patients with a UCDAI score ≤1 in clinical remission (rectal bleeding and stool frequency scores = 0) at Month 6. This endpoint reveals which patients were in both endoscopic remission and clinical remission at Month 6. The proportion of patients who met these criteria at Month 6 in the phase 1, ITT population was comparable between treatment groups (61.5% Lialda, 59.6% Asacol). Results were similar between treatment groups for all phases (1 and 2) and analysis populations (ITT and PP).

MO Comment:
The results presented in Table 19 (those in endoscopic and clinical remission) reveal that the percentage of Lialda patients in endoscopic remission at Month 6 is greater than the percentage of patients in endoscopic and clinical remission by approximately 15% in the ITT and PP populations of both phases.

Table 19. Percentage of Patients with UCDAI ≤1 in Clinical Remission[+] at Month 6, Study 304

Phase 1	ITT		PP	
	Lialda	Asacol	Lialda	Asacol
Number of Patients	208	208	178	179
UCDAI ≤1 and clinical remission, Month 6	61.5% (128)	59.6% (124)	66.3% (118)	62.0% (111)
Difference (Lialda-Asacol)	1.9%		4.3%	
95% CI for difference	-7.9%, 11.8%		-6.2%, 14.8%	
Phase 2	**ITT**		**PP**	
Number of Patients	207	203	165	157
UCDAI ≤1 and clinical remission, Month 6	51.7% (107)	53.7% (109)	55.2% (91)	58.6% (92)
Difference (Lialda-Asacol)	-2.0%		-3.4%	
95% CI for difference	-12.2%, 8.1%		-14.9%, 8.0%	

[+] Clinical remission defined as scores of 0 for rectal bleeding and stool frequency
Adapted from Table 2.9.1 (p. 391-396/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

Other Secondary endpoints are described below.

Phase of Enrollment Effect

To determine if there was an effect on the rate of remission by phase of enrollment, the Applicant used the Cochran-Mantel-Haenszel (CMH) test to compare the proportion of patients in remission at Month 6 by phase of enrollment. The calculated odds ratio was 1.16 (95% CI 0.78, 1.72) for the PP population and the Breslow-Day test p-value was 0.9939. The calculated odds ratio was 1.06 (95% CI 0.76, 1.46) for the ITT population and the Breslow-Day test p-value was 0.5155. These results indicate that there was no significant phase of enrollment difference in the rates of remission. These results also indicate that no phase was driving the overall study results.

Country Effect

Analysis of country effect on the proportion of patients in remission showed some variability seen in the between-treatment group differences across countries/regions. The differences in remission rates (Lialda-Asacol) varied widely and favored Lialda in Australia/New Zealand with a difference of -40%. Remission rates in Asia favored Lialda with a difference of 33%. In these countries/regions there were relatively small numbers of patients and no conclusions can be reached about the regional variations in remission rates. Statistically, there were no significant country/region differences in the odds ratios of patients in remission.

See Table 20, below. Results were similar for the ITT population and between phase 1 and phase 2.

Table 20. Country Effect on Remission Rates, PP Population

Analysis of Country Effect on the Proportion of Subjects in Endoscopic Remission (Maintenance of Mucosal Healing) at Month 6 (Per Protocol Population)

	SPD476 2.4g/day QD N=343		ASACOL 1.6g/day divided BID N=336		Difference (%)
Number of subjects in endoscopic remission/Number of subjects (%)					
Asia	13/19	(68.4)	6/17	(35.3)	33.13
Australia/NZ	3/5	(60.0)	3/3	(100.0)	-40.00
Canada	5/11	(45.5)	8/10	(80.0)	-34.55
Central and South America	32/38	(84.2)	24/32	(75.0)	9.21
Eastern Europe	86/101	(85.1)	89/107	(83.2)	1.97
India	55/57	(96.5)	55/62	(88.7)	7.78
Russia	44/48	(91.7)	43/46	(93.5)	-1.81
South Africa	13/15	(86.7)	11/15	(73.3)	13.33
USA	16/21	(76.2)	16/17	(94.1)	-17.93
Western Europe	20/28	(71.4)	19/27	(70.4)	1.06
Odds Ratio (SPD476 – ASACOL)	1.21				
95% CI (SPD476 – ASACOL)	(0.80, 1.82)				
P-value (Breslow Day Test)	0.1154				

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Note: Subjects with missing data at Month 6 were assumed to be failures.

Covariate Analyses

Analysis of the primary efficacy variable by the following covariates was performed (See Table 21, below):

a. Gender
b. Age (<55 vs. 55+)
c. Race (Caucasian vs. Non-Caucasian)
d. Smoking status (Smokes/Previous vs. Never Smoked)
e. Disease Classification (Left-Sided vs. Other)
f. Time since most recent acute episode at baseline (≤12 weeks, >12-≤24 weeks, >24- ≤36 weeks, >36 weeks)
g. Number of acute episodes of UC (≤2 episodes, >2-≤4 episodes, >4-≤10 episodes, >10 episodes).

Breslow Day results indicated no statistically significant differences in the odds ratios of remission rates by the above covariates. However, looking at the difference in remission rates for patients taking Lialda, some imbalances are seen. See Table 21 for results of subgroup analyses of the ITT population. The remission rate for Caucasian

patients taking Lialda was higher in phase 1 than for non-Caucasian patients (80.5% vs. 72.2%, respectively). However, in phase 2, remission rates for non-Caucasians taking Lialda was her than the remission rate for Caucasians (83.1% vs. 72.9%, respectively).

In phase 2, there were differences seen between remission rates based on smoking history. For current/previous smokers the difference (Lialda-Asacol) was -9.7%. For patients who had never smoked, the difference was 2.8%.

There was also an apparent difference in the rate of remission for patients taking Lialda based on the time since the most recent UC attack. In phase 1, the rate of maintenance of remission at Month 6 was 68.8% with ≤12 weeks since the last attack and 87.7% in patients with 12-24 weeks since the last attack. This differential in efficacy at 12 weeks is not seen in phase 2.

In phase 2, patients with left-sided disease taking Lialda had lower efficacy than patients with disease in other locations, 73.3% vs. 89.3%, respectively. This trend is not replicated in phase 1 where the rate of remission is nearly equal for those with left-sided disease and disease in other locations, 78.3% and 78.7%, respectively.

Table 21. Subgroup Analyses of Proportion of Subjects in Endoscopic Remission at Month 6 by Phase, ITT Population

Variable Subgroup	Phase 1				Phase 2			
	Lialda	Asacol	(Lialda-Asacol)	95% CI	Lialda	Asacol	(Lialda-Asacol)	95% CI
Gender								
Male	80/101 (79.2%)	94/114 (82.5%)	-3.3%	(-13.8%, 7.3%)	86/111 (77.5%)	74/100 (74.0%)	3.5%	(-8.1%, 15.1%)
Female	83/107 (77.6%)	71/94 (75.5%)	2.0%	(9.7%, 13.8%)	74/96 (77.1%)	77/103 (74.8%)	2.3%	(-9.6%, 14.2%)
Age								
<55 yrs	123/158 (77.8%)	122/155 (78.7%)	-0.9%	(-10.0%, 8.3%)	112/143 (78.3%)	109/151 (72.2%)	6.1%	(-3.7%, 16.0%)
≥55 yrs	40/50 (80.0%)	43/53 (81.1%)	-1.1%	(-16.4%,14.2%)	48/64 (75.0%)	42/52 (80.8%)	-5.8%	(-20.8%, 9.3%)
Race								
Caucasian	124/154 (80.5%)	126/156 (80.8%)	-0.3%	(-9.0%, 8.5%)	86/118 (72.9%)	83/103 (80.6%)	-7.7%	(-18.8%, 3.4%)
Non-Caucasian	39/54 (72.2%)	39/52 (75.0%)	-2.8%	(-19.6%, 14.0%)	74/89 (83.1%)	68/100 (68.0%)	15.2%	(3.1%, 27.2%)
Smoking								
Current/Previous	44/60 (73.3%)	54/65 (83.1%)	-9.7%	(24.2%, 4.7%)	51/66 (77.3%)	37/49 (75.5%)	1.8%	(-14.0%, 17.5%)
Never	119/148 (80.4%)	111/143 (77.6%)	2.8%	(-6.6%, 12.1%)	109/141 (77.3%)	114/154 (74.0%)	3.3%	(-6.5%, 13.1%)
Disease								
Left-side	123/157 (78.3%)	126/154 (81.8%)	-3.5%	(-12.3%, 5.4%)	110/150 (73.3%)	115/154 (74.7%)	-1.3%	(-11.2%, 8.5%)
Other	37/47 (78.7%)	37/52 (71.2%)	7.6%	(-9.4%, 24.6%)	50/56 (89.3%)	34/43 (79.1%)	10.22%	(-4.4%, 24.8%)
Time since recent episode								
≤12 weeks	55/80 (68.8%)	61/78 (78.2%)	-9.5%	(-23.1%, 4.2%)	58/77 (75.3%)	52/78 (66.7%)	8.7%	(-5.6%, 22.9%)
12-24 weeks	57/65 (87.7%)	46/59 (78.0%)	9.7%	(-3.5%, 23.0%)	44/58 (75.9%)	51/60 (85.0%)	-9.1%	(-23.4%, 5.1%)
24-36 weeks	36/45 (80.0%)	31/39 (79.5%)	0.5%	(-16.7%, 17.8%)	34/42 (81.0%)	31/42 (73.8%)	7.1%	(-10.7%, 25.0%)
>36 weeks	15/18 (83.3%)	26/31 (83.9%)	-0.5%	(-22.1%, 21.0%)	24/30 (80.0%)	17/23 (73.9%)	6.1%	(-16.9%, 29.0%)
Acute episodes								
≤2	57/74 (77.0%)	60/71 (84.5%)	-7.5%	(-20.2%, 5.3%)	47/58 (81.0%)	43/63 (68.3%)	12.8%	(-2.5%, 29.1%)
2-4	59/70 (84.3%)	54/70 (77.1%)	7.1%	(-5.9%, 20.2%)	73/90 (81.1%)	53/73 (72.6%)	8.5%	(-4.5%, 21.5%)
4-10	28/40 (70.0%)	34/46 (73.9%)	-3.9%	(-23.0%, 15.1%)	27/39 (69.2%)	40/47 (85.1%)	-15.9%	(-33.6%, 1.8%)
>10	16/21 (76.2%)	13/15 (86.7%)	-10.5%	(-35.5%, 14.6%)	10/16 (62.5%)	13/17 (76.5%)	-14.0%	(-45.1%, 17.2%)

Table Created by Dr. Milton Fan, Statistical Reviewer

Proportion of subjects in endoscopic remission (maintenance of mucosal healing) with no or mild symptoms at Month 6

Maintenance of mucosal healing with no or mild symptoms was defined as an endoscopy score of ≤1 and a combined symptom score (stool frequency plus rectal bleeding) of ≤1. Patients with a symptoms score of ≤1 taking Lialda had a remission rate of 80% (PP) and 74% (ITT) in phase 1 and 77% (PP) and 72%(ITT) in phase 2 .

MO Comment:
Understanding which of the patients in remission also had a combined symptoms score (stool frequency plus rectal bleeding) of ≤1 is very important. This evaluation acts as a sensitivity analysis for the primary endpoint. Mucosal healing (the primary endpoint) is only important if it leads to symptom improvement. Further, symptoms are more important to patients than mucosal healing.

Results of this analysis show that most patients in endoscopic remission had no or mild symptoms at Month 6. If we examine the difference between all patients in endoscopic remission (the primary endpoint) and those patients in endoscopic remission with no or mild symptoms, we can see that only about 3-6% of patients in remission continued to have moderate to severe symptoms. Phase 2 PP had the largest disparity between patients in endoscopic remission and those in endoscopic remission with no or mild symptoms, 6%.

Overall, these results tend to suggest that Lialda efficacy in maintaining endoscopic remission results in patients maintaining no or mild clinical symptom scores.

Table 22. Maintenance of Remission for patients taking Lialda, All patients vs. patients with combined symptoms° score ≤1

	Phase 1		Phase 2	
	ITT	PP	ITT	PP
All patients in endoscopic remission	78%	83%	77%	84%
Patients in endoscopic remission with combined symptoms score of ≤1	74%	80%	72%	78%
Difference (all patients-patients with combined symptoms score ≤1)	4%	3%	5%	6%

° Stool frequency plus rectal bleeding score of ≤1

Time to relapse

For this analysis, the Applicant defined relapse as early withdrawal from the study due to lack of efficacy. Patients who withdrew for other reasons were censored at the date of withdrawal. For the ITT patients, 14.9% of Lialda patients relapsed compared with

13% of Asacol patients in phase 1. Time to relapse, by population and phase of enrollment, is presented in Kaplan-Meier curves below.

Figure 2. Kaplan-Meier Curve for Time to Relapse (ITT-Phase 1)

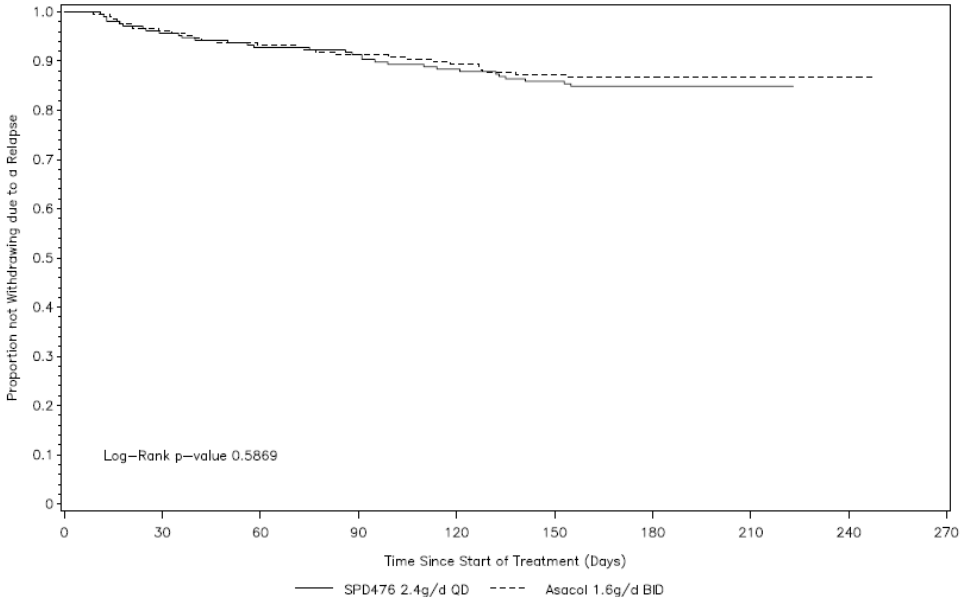


Figure 3. Kaplan-Meier Curve for Time to Relapse (ITT-Phase 2)

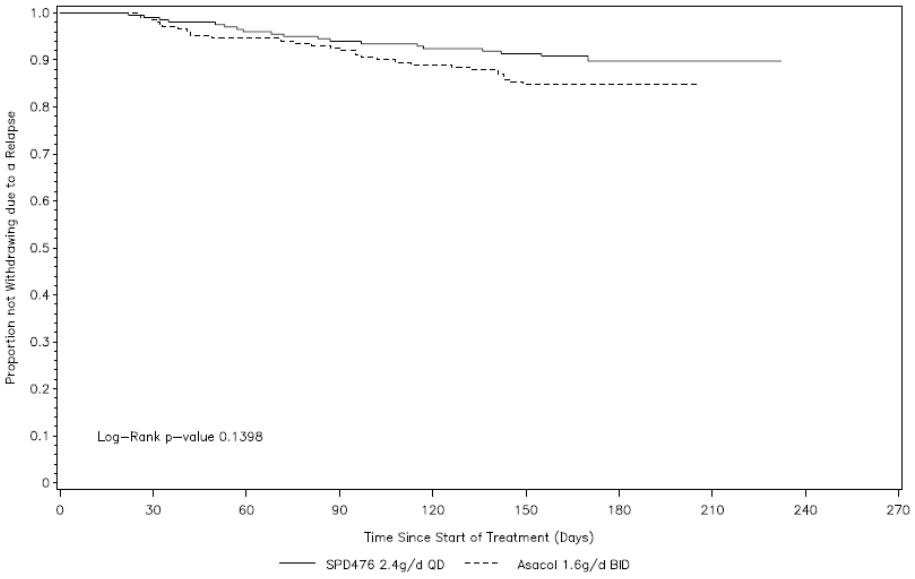


Figure 4. Kaplan-Meier Curve for Time to Relapse (PP-Phase 1)

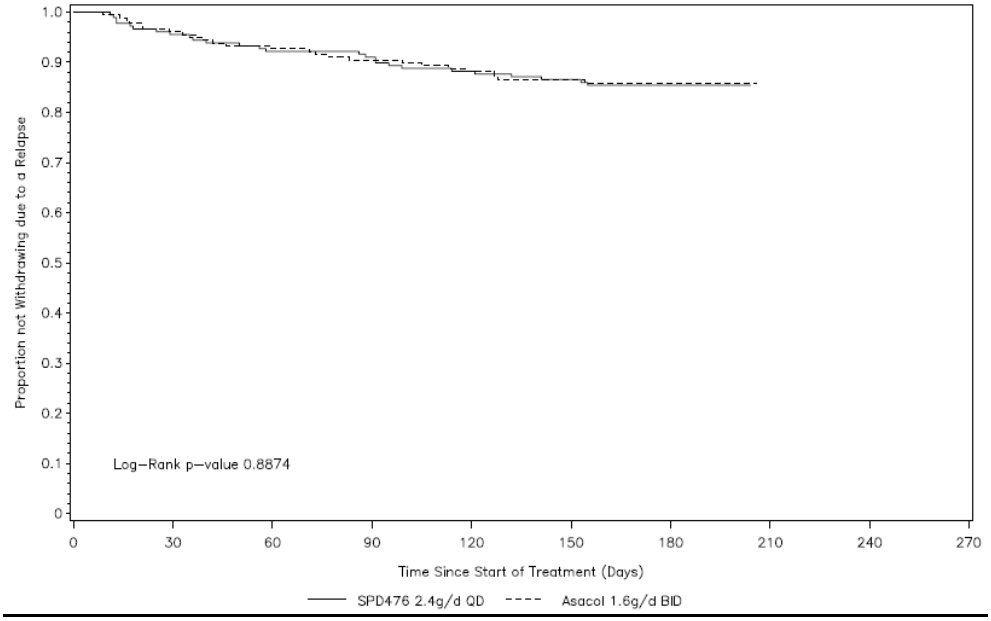
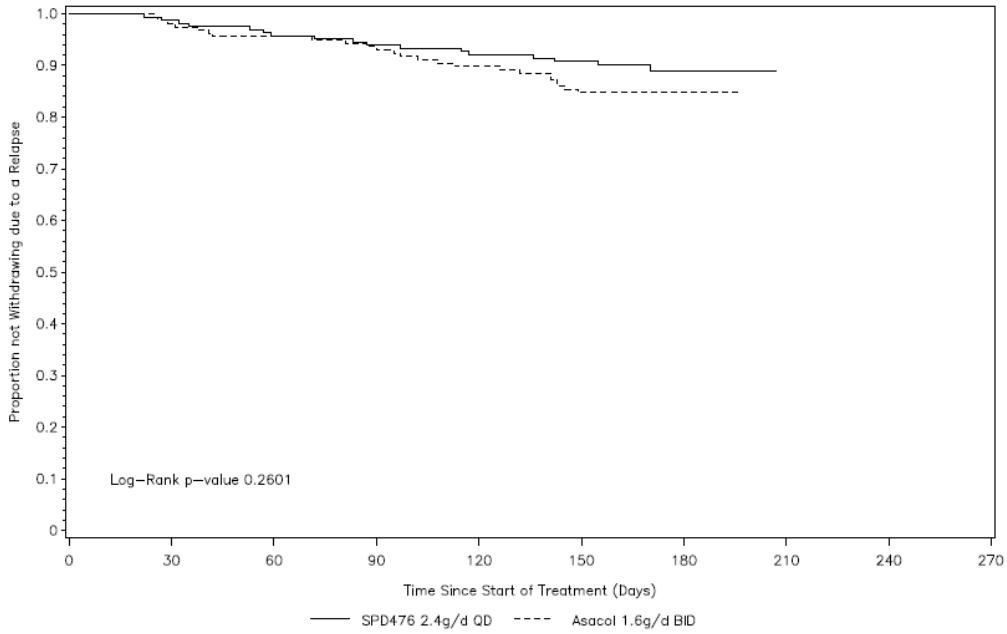


Figure 5. Kaplan-Meier Curve for Time to Relapse (PP-Phase 2)



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Change from baseline in the modified UC-DAI Score by treatment

The primary endpoint for Study 304 examined only the change in endoscopy subscore of the UCDAI from baseline to Month 6. However, the Applicant also examined the change from baseline in the composite UCDAI score. See Section 5.3.6 for a detailed explanation of the UCDAI and its components. In general, a higher score represents more severe disease and the maximum total UCDAI score is 12.

During Study 304 the mean change in UCDAI was small from baseline to Month 6. For phase 1 ITT patients taking Lialda the mean change was 0.080 (SD 1.0485). The mean change in UCDAI for phase 2 ITT patients was 0.089 (SD 1.4147). Changes for all populations (ITT and PP) and phases (1 and 2) were less than ±0.2.

Rectal bleeding and stool frequency change from baseline

At baseline the mean stool frequency (SF) score for patients in all phases, populations, and treatment groups was approximately zero. Stool frequency is scored as zero if patients report having a normal (individual to each patient) number of stools per day (see Table 23 below). This supports the fact that patients were in remission at baseline. At Month 6, the mean score for all patients remained approximately zero.

Table 23. Stool Frequency Scoring System and Mean Score, ITT

Score	Disease Severity	Stools per day	Mean SF score for patients taking Lialda	
0	Normal	Normal number	**ITT Phase 1 Baseline**	**ITT Phase 1 Month 6**
1	Mild	1-2 more than normal/ day	0.089	0.085
2	Moderate	3-4 more than normal/ day	**ITT Phase 2 Baseline**	**ITT Phase 2 Month 6**
3	Severe	>4 more than normal/ day	0.107	0.147

Adapted from Table 2.7.2 (p. 358-366/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

The mean rectal bleeding (RB) score for patients in all phases, populations, and treatment groups was approximately zero. For a rectal bleeding score of zero, patients could have no rectal bleeding (see Table 24 below). By the end of the study, Month 6, the mean rectal bleeding score continued to be approximately zero.

Table 24. Rectal Bleeding Scoring System and Mean Score, ITT

Score	Disease Severity	Characteristics	Mean RB score for patients taking Lialda	
0	Normal	No rectal bleeding	**ITT Phase 1 Baseline**	**ITT Phase 1 Month 6**
1	Mild	Streaks of blood	0.035	0.062
2	Moderate	Obvious Blood	**ITT Phase 2 Baseline**	**ITT Phase 2 Month 6**
3	Severe	Mostly blood	0.028	0.086

Adapted from Table 2.7.4 (p. 376-384/464), SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

MO Comment:
A small study published in 2005 sought to address the question of whether endoscopy is necessary for the assessment of ulcerative colitis disease activity. The study measured the correlation between invasive and noninvasive indices using a regression analysis. The study found that endoscopy items correlated with stool frequency and stool blood items and that endoscopy actually contributes little additional information.[11]

If stool frequency and rectal bleeding actually predict remission and are highly correlated to endoscopy score then the above analyses can serve as a sort of sensitivity analysis of primary endpoint for Study 304. The normal rectal bleeding and stool frequency results confirm that patients started the study in remission and the Month 6 results suggest that Lialda is efficacious in the maintenance of remission of ulcerative colitis.

Endoscopy score and PGA change from baseline

For Study 304, remission was defined as having an endoscopy score ≤1. See Table 10 for endoscopy scoring system sub-score descriptions. The proportion of patients in endoscopic remission at Month 6 was the primary endpoint. Additionally, the Applicant explored the secondary endpoint of the change in endoscopy score from baseline. For entry into Study 304, patients had to have a baseline endoscopy score of 0 or 1. At Month 6 (phase 1, ITT) endoscopy scores for Lialda patients improved in 11.1% of patients, stayed the same in 61.5%, and worsened in 9.1%. For ITT phase 2 patients endoscopy scores for Lialda patients improved in 13.5% of patients, stayed the same in 59.4%, and worsened in 8.2%. See Table 25, below. Overall, endoscopy scores remained the same or improved for approximately 70% of patients in all phases and treatment groups.

Table 25. Change in Endoscopy Score, ITT

	Phase 1		Phase 2		Combined	
Δ Endoscopy Score	Lialda	Asacol	Lialda	Asacol	Lialda	Asacol
Improved	11.1%	12.0%	13.5%	14.3%	12.3%	13.1%
Same	61.5%	59.6%	59.4%	57.6%	62.2%	59.6%
Worsened	9.1%	11.5%	8.2%	4.9%	20.0%	20.4%
Unknown	18.3%	16.8%	18.8%	23.2%	5.1%	6.8%

Adapted from Table 2.10.2 (p. 403-408/464),
SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

At baseline and Month 6 patients were assigned a physician global assessment (PGA) score. The PGA was scored on a scale from 0 to 3 (0 = no active disease, 3 = severe disease). Most patients in both phases and treatment groups maintained the same PGA score from baseline to Month 6.

Table 26. Change in PGA Score, ITT

	Phase 1		Phase 2		Combined	
Δ PGA Score	Lialda	Asacol	Lialda	Asacol	Lialda	Asacol
Improved	3.4%	6.3%	6.8%	6.4%	5.1%	6.3%
Same	70.7%	67.3%	65.2%	63.1%	68.0%	65.2%
Worsened	7.7%	9.6%	9.2%	7.4%	8.4%	8.5%
Unknown	18.3%	16.8%	18.8%	23.2%	18.6%	20.0%

Adapted from Table 2.11.2 (p. 415-419/464),
SPD476-304 by Enrollment, submitted 16 Feb 2011 in response to FDA Information Request

MO Comment: The change in endoscopy and PGA score provided little additional information in the efficacy evaluation of Lialda. No substantial differences in the changes in these scores were seen between phases or between treatment groups.

Quality of Life assessment

At baseline, Month 3, and Month 6/end of study, patients were to complete the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) quality of life tool. Patients only completed the tool if the SIBDQ had been licensed and translated in their country. Only 49% of Lialda patients and 48% of Asacol patients completed the SIBDQ. The SIBDQ is comprised of 10 questions. Scores range from 10-70 with higher scores represented a better quality of life. If answers to 3 or less questions were missing, the mean of the non-missing scores was imputed for these values. If answers to more than 3 questions were missing, the SIBDQ score was counted as missing.

At Month 6, patients in the Lialda group had a mean increase of 1.837 in the SIBDQ total score compared with a mean increase of 0.872 among patients in the Asacol group.

MO Comment: Change in the SIBDQ quality of life scores did not provide any additional information in the efficacy evaluation of Lialda.

6.1.6 Other Endpoints

No other endpoints were assessed.

6.1.7 Subpopulations

For primary efficacy analyses by subpopulations see Section 6.1.5 and Table 20.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No additional clinical information was reviewed relevant to dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Studies were of sufficient duration and no issues were seen with persistence of efficacy or tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses that have not been described in other parts of this review.

7 Review of Safety

Safety Summary

7.1 Methods

Lialda was evaluated in 1,082 patients whose UC was in remission in controlled and open-label trials. During the single controlled trial, Study 304, a total of 415 patients were exposed to Lialda. During two 12-month, open-label, maintenance of UC trials, an additional 667 patients were exposed to Lialda.

Study SPD476-404 (Study 404) was a Phase 4, open-label, 12-14 month study in patients using Lialda. In addition to the maintenance of remission phase, the study also had an 8-week acute phase. Only results from the maintenance phase are included in

the safety summary. Study SPD476-303 (Study 303) was a Phase 3, open-label, 12-14 month study in patients using Lialda. During this study, patients were randomized to once daily or twice treatment. Study 303 was an extension of two acute UC trials. The total planned daily dose for all 3 studies in the safety analyses was 2.4 g/day.

Two analysis populations were used for all analyses in the integrated safety summary: the RCT population and the All Lialda population. These sub-populations were taken from the larger Safety Population, which included all patients who received at least one dose of the study drug (Lialda or Asacol) and provided at least one post-baseline safety assessment. The primary study, SPD476-304, was used as the RCT population to allow for a safety comparison between Lialda and Asacol. Study 304 was 6 months in duration while Studies 404 and 303 were 12 months in duration.

Across all three studies, a total of 380 (35.1%) patients in the All Lialda population were exposed to Lialda 2.4 g/day for at least 24 weeks. For patients in the 12 month studies (404 and 303), the mean duration of exposure was 53.9 weeks. For patients in the 6 month study (304), the mean duration of exposure was 23.5 weeks.

In the RCT population, the proportion of patients reporting a treatment-emergent adverse event (TEAE) was approximately equal in the Lialda and Asacol groups (37.1% versus 36.0%, respectively). Recurrence of UC and headache were the most frequently reported TEAEs in both treatment groups. In this population 12.3% of Lialda patients and 10.9% of Asacol patients reported at least one TEAE which investigators characterized as possibly related to the study medication. In Study 304, 6 Lialda patients reported 7 serious adverse events (SAEs) and 3 Asacol patients reported 4 SAEs.

In the All Lialda population, 59.1% of patients reported at least one TEAE. A recurrence of ulcerative colitis was the most commonly reported TEAE, 63 patients (5.8%). In this population, 122 patients (11.3%) reported a TEAE which investigators characterized as possibly related to the study medication. Serious adverse events occurred in 122 patients (11.3%).

The majority of AEs in both the RCT and All Lialda populations were mild or moderate in severity.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from Study 304. This study was the only controlled study submitted in support of this Application. Additional safety information was obtained from open label Studies 404 and 303 and combined with safety information from patients taking Lialda in Study 304 to form the All Lialda Population.

7.1.2 Categorization of Adverse Events

Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, Version 12.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event incidence data were included from three studies: Study 304, Study 303, and Study 404. See Section 7.1 for a description of how pooled data is presented in this review.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis population.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The doses and durations of Lialda studied were adequate to assess safety and to support the proposed indication of "maintenance of remission". Study 304 had a six month treatment period. Open-label Studies 303 and 404 had durations of at least 12 months.

Across the studies (304, 303, and 404), 1,082 patients received Lialda of 2.4 g/day (once daily or twice daily) for a mean duration of exposure of approximately 41 weeks. See Table 27, below.

Table 27. Extent of Exposure (Weeks)

Weeks of Exposure	RCT Lialda n=415	Asacol N=411	All Lialda n=1082
0-<12	42 (10.1%)	41 (10.0%)	72 (6.7%)
12-<24	28 (6.7%)	30 (7.3%)	62 (5.7%)
≥24	340 (81.9%)	329 (80.0%)	
24-<48			413 (38.2%)
≥48			527 (48.7%)
Mean (SD)	23.5 (6.8)	23.5 (6.7)	40.7 (18.9)
Median	26.1	26.0	45.5
Range	0, 29	0, 30	1, 80

Adapted from Table 1 (p 14/57) 2.7.4 Summary of Clinical Efficacy and Table 3.1 (p 28/893) Clinical Study Report SPD476-304

The demographic make-up of the pooled safety population was adequate. Most patients were white race and male. For further information regarding Study 304 patient demographics, see Section 6.1.2.

7.2.2 Explorations for Dose Response

In the current Application, all patients receiving Lialda received the same dose—2.4 g per day. There was no exploration for dose response.

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this NDA.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the three submitted studies. See Section 5.3.5 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see the clinical pharmacology review by Dr. Kristin Estes.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The studies were adequately designed to allow for safety analyses. The submitted studies also adequately monitored for possible renal, pancreatic, and hepatic adverse events—events known to be associated with 5-ASA. The studies did not reveal any new safety signals. The three key Studies (304, 303, and 404) showed Lialda 2.4g once daily to be relatively safe and well-tolerated.

7.3 Major Safety Results

RCT Population
During Study 304, approximately 37% of patients taking Lialda experienced at least one treatment-emergent AE, compared with 36% of patients taking Asacol. Compared with those who experienced an AE, a smaller percentage of patients in both treatment groups experienced an AE that was classified as related by the investigator, 13% Lialda, 11% Asacol. In both treatment groups, most events were mild or moderate in severity and only 2% and 4% of patients (Lialda and Asacol, respectively) discontinued from Study 304 due to an AE. See Table 28. Summary of Safety Results, below.

All Lialda Population

In the All Lialda population, the incidence of AEs was higher than in those patients taking Lialda in Study 304, 59% vs. 37%, respectively. This difference may be due to the difference in the length of duration of the studies. For the All Lialda population, the majority of patients were in 12-month studies. In contrast, Study 304 was only 6 months in duration. For other safety results, see Table 28, below.

Table 28. Summary of Safety Results

	Study 304		All Lialda N=1082
	RCT Lialda N=415	Asacol N=411	
	n (%)	n (%)	n(%)
Any Adverse Event	155 (37.4)	148(36.0)	123 (59.1)
Any treatment-related AE	52 (12.6)	45 (10.9)	24 (11.5)
Any Severe AE	11 (2.7)	12 (2.9)	15 (7.2)
Serious Adverse Event (SAE)	6 (1.4)	3 (0.7)	9 (0.4)
Discontinuation due to Adverse Event (DAE)	8 (2.0)	4 (1.0)	15 (7.2)
Deaths	0	0	1 (0.0)

Adapted from Tables 6 and 7 (p 20/57) Section 2.7.4 Summary of Clinical Efficacy

7.3.1 Deaths

No patient died during Study 304, the single controlled study in this Application. Similarly, no patient died during Study 404, a 12-month uncontrolled study.

There was one death reported in Study 303, a 12-month uncontrolled study. The patient (56210) was a 25 year old Caucasian female randomized to Lialda 1.2 g twice daily. The patient took Lialda for 284 days. The patient experienced an accidental electric shock while cleaning her car with an electric vacuum cleaner. The patient was seen for an in-patient visit 6 days prior to her death. At that time her UC was in remission and the patient was reportedly clinically stable and in good mental health. The patient had a history of mitral insufficiency (grade 1-2), mitral valve prolapse, nephrolithiasis, and erythema nodosum.

7.3.2 Nonfatal Serious Adverse Events

RCT Population

Study 304 was six months in duration. The safety population included patients. During this Study, 6 patients in the Lialda group and 3 patients in the Asacol group experienced SAEs. Details of these serious adverse events are described below.

Patient 14804 (Asacol 1.6g/day)
This 70 year old Caucasian male began experiencing severe right sciatica pain and was found to have an intervertebral disc protrusion. The patient was hospitalized and underwent surgery. The patient completed the study medication, but was not seen at the Month 6 visit due to hospitalization. The patient recovered from surgery without sequelae.

Patient 14804 (Lialda 2.4g/day)
This 35 year old Asaian-Pacific Islander female began experiencing worsening of UC symptoms on Day 69 of study treatment. The patient required hospitalization and withdrew due to lack of efficacy on Study Day 72. The patient spent 2 days in the hospital after which the event was considered resolved.

Patient 33102 (Lialda 2.4g/day)
This 48 year old Caucasian female began experiencing right lower quadrant abdominal pain on Study Day 89. The patient was admitted to the hospital with appendicitis on Study Day 90 and subsequently underwent emergency laparoscopic appendectomy. The patient was off Lialda for one day and subsequently completed the study.

Patient 34110 (Asacol 1.6g/day)
This 35 year old Black female was hospitalized on Study Day 34 for ruptured right fallopian tube due to an ectopic pregnancy. The patient underwent right salipingectomy and the event was considered severe and resolved on Study Day 35. The patient did not take study drug for approximately one month. One month after re-starting the drug, the patient withdrew from the study (patient request).

Patient 52201 (Lialda 2.4g/day)
This 57 year old Hispanic male completed the entire six months of study treatment. During his end of study colonoscopy, a polypectomy was performed on 2 elevated lesions that had grown in size since a previous colonoscopy. After the procedure, the patient developed a lower GI bleed requiring hospitalization for 2 days. During hospitalization, the patient had a clip placed on the bleeding lesion (15 cm above the anal verge). The patient was discharged from the hospital and the event was considered resolved.

Patient 55102 (Lialda 2.4g/day)
This 37 year old Caucasian female began experiencing symptom of severe pancolitis on Study day 170. The study drug was permanently discontinued on this day and the patient was withdrawn from the study for lack of efficacy. Approximately one month after discontinuing study medication the patient underwent a laparoscopic colectomy with ileostomy. The patient was discharged from the hospital 3 days after surgery. The investigator considered the pancolitis to be severe.

Patient 57102 (Asacol 1.6g/day)
This 44 year old Caucasian female began experiencing symptoms of a flare of UC. The subject was withdrawn from the study on Study Day 141 and was hospitalized for UC symptoms.

Patient 60301 (Lialda 2.4g/day)
This 59 year old Caucasian male began experiencing right arm weakness and was hospitalized on Study Day 105. The patient was diagnosed with brachial neuritis and treated with aspirin on Study Days 108 to 110 and prednisone from Study Day 110 to 118. No action was taken regarding study medication and the patient completed the study. Approximately six months after the study, the patient reported that the event had resolved completely.

Patient 62601 (Lialda 2.4g/day)
This 61 year old Caucasian male with a past medical history of asthma began experiencing an asthma exacerbation on Study Day 81. The patient was treated with Combivent 2.5 mg unit dose vials three times daily. On Study Day 117 the patient was admitted to the hospital and diagnosed with an asthma attack precipitated by bronchitis. The patient was discharged on Study Day 120 and these events were considered resolved. The patient was withdrawn from the study for use of prohibited concomitant corticosteroids while hospitalized on Study Day 127.

Table 29. Serious Adverse Events, Study 304

	SPD476 2.4g/day QD N=415		ASACOL 1.6g/day divided BID N=411	
MedDRA System Organ Class/Preferred Term	N	(%)	N	(%)
Gastrointestinal Disorders	2	(0.5)	1	(0.2)
Colitis	1	(0.2)	0	
Colitis ulcerative	1	(0.2)	1	(0.2)
Infections and Infestations	2	(0.5)	0	
Appendicitis	1	(0.2)	0	
Bronchitis	1	(0.2)	0	
Injury, Poisoning, and Procedural Complications	1	(0.2)	1	(0.2)
Fallopian tube perforation	0		1	(0.2)
Post procedural haemorrhage	1	(0.2)	0	
Musculoskeletal and Connective Tissue Disorders	0		1	(0.2)
Intervertebral disc protrusion	0		1	(0.2)
Nervous System Disorders	1	(0.2)	0	
Radiculitis brachial	1	(0.2)	0	
Pregnancy, Puerperium, and Perinatal Conditions	0		1	(0.2)
Ectopic pregnancy	0		1	(0.2)
Respiratory, Thoracic, and Mediastinal Disorders	1	(0.2)	0	
Asthma	1	(0.2)	0	
Subjects With ≥1 Treatment-emergent SAE	6	(1.4)	3	(0.7)

Electronically copied and reproduced from Table 40, CSR SPD476-304, p 92/893.

All Lialda Population

In the All Lialda population the incidence of SAEs was 3.0%. In this population, 33 patients had a total of 39 SAEs. The only SAEs that occurred in more than one patient were ulcerative colitis (10 patients) and pneumonia (2 patients). Two SAEs were considered by investigators to be related to study treatment—pancreatitis (Study 404) and liver function test abnormality (Study 303).

Table 30. Serious Adverse Events, All Lialda Population

Number of Subjects Included in the Safety Population	1082	
Number of Subjects With ≥1 SAE	33	(3.0)
Number of Events	39	
Gastrointestinal Disorders	14	(1.3)
Colitis ulcerative	10	(0.9)
Colitis	1	(0.1)
Haematochezia	1	(0.1)
Ileus	1	(0.1)
Pancreatitis	1	(0.1)
Infections and Infestations	5	(0.5)
Pneumonia	2	(0.2)
Appendicitis	1	(0.1)
Bronchitis	1	(0.1)
Cellulitis	1	(0.1)
Lung abscess	1	(0.1)
Reproductive System and Breast Disorders	3	(0.3)
Endometriosis	1	(0.1)
Menometrorrhagia	1	(0.1)
Ovarian cyst	1	(0.1)
Respiratory, Thoracic, and Mediastinal Disorders	3	(0.3)
Asthma	1	(0.1)
Chronic obstructive pulmonary disease	1	(0.1)
Pulmonary oedema	1	(0.1)
Cardiac Disorders	2	(0.2)
Angina pectoris	1	(0.1)
Angina unstable	1	(0.1)
Hepatobiliary Disorders	2	(0.2)
Cholecystitis acute	1	(0.1)
Chronic hepatitis	1	(0.1)
Injury, Poisoning, and Procedural Complications	2	(0.2)
Electric shock	1	(0.1)
Post procedural haemorrhage	1	(0.1)
Nervous System Disorders	2	(0.2)
Cerebral infarction	1	(0.1)
Radiculitis brachial	1	(0.1)
Psychiatric Disorders	2	(0.2)
Depression	1	(0.1)
Schizophrenia	1	(0.1)
Investigations	1	(0.1)
Liver function test abnormal	1	(0.1)
Musculoskeletal and Connective Tissue Disorders	1	(0.1)
Back pain	1	(0.1)
Vascular Disorders	1	(0.1)
Hypertension[a]	1	(0.1)

Electronically copied and reproduced from Section 2.7.4 Summary of Clinical Safety, Table 10 (p 24/57).
[a] Patient 11706, Study 404 had an AE of benign prostatic hypertrophy (BPH) which was miscoded as Hypertension.

7.3.3 Dropouts and/or Discontinuations

RCT Population

During Study 304, 12 patients had TEAEs that led to withdrawal (9 events in the Lialda group, 4 events in the Asacol group). Most TEAEs that led to withdrawal were categorized as possibly related by the investigator. The only TEAE that led to withdrawal in more than one patient was worsening of ulcerative colitis. See Table 31, below.

Table 31. TEAEs Leading to Withdrawal, Study 304

Subject ID	Preferred Term	Severity	Causal Relationship
SPD476 2.4g/day QD			
10010	Abdominal pain upper	Moderate	Possibly related
	Colitis ulcerative	Mild	Unrelated
12107	Colitis ulcerative	Moderate	Possibly related
18203	Asthenia	Mild	Possibly related
19947	Disturbance in attention	Mild	Probably related
	Hearing impaired	Mild	Probably related
	Memory impairment	Mild	Probably related
33301	Colitis ulcerative	Moderate	Unrelated
34105	Anxiety[a]	Moderate	Possibly related
34124	Abdominal distension	Moderate	Possibly related
	Decreased appetite	Moderate	Possibly related
59103	Cholecystitis	Severe	Unrelated
ASACOL 1.6g/day divided BID			
19930	Discomfort	Mild	Possibly related
	Restlessness	Mild	Possibly related
20114	Dysentery	Severe	Possibly related
24503	Pregnancy	Severe	Unrelated
32905	Nausea	Moderate	Possibly related

Electronically copied and reproduced from Table 41, CSR SPD476-304, p 93/893.

All Lialda Population

In the All Lialda Population, 43 patients had TEAEs that led to withdrawal. The most common SOC leading to withdrawal was Gastrointestinal Disorders. See Table 32, below.

Table 32. Adverse Events Leading to Study Withdrawal, All Lialda Population

	All SPD476	
	n	%
Number of Subjects Included in the Safety Population	1082	
Number of Subjects Withdrawn Due to TEAE	43	(4.0)
Number of Events	49	
Gastrointestinal Disorders	30	(2.8)
Colitis ulcerative	23	(2.1)
Abdominal pain	2	(0.2)
Abdominal pain upper	2	(0.2)
Abdominal distension	1	(0.1)
Colitis	1	(0.1)
Pancreatitis	1	(0.1)
Rectal haemorrhage	1	(0.1)
Infections and Infestations	3	(0.3)
Pneumonia	2	(0.2)
Cellulitis	1	(0.1)
Lung abscess	1	(0.1)
Hepatobiliary Disorders	2	(0.2)
Cholecystitis	1	(0.1)
Chronic hepatitis	1	(0.1)
Nervous System Disorders	2	(0.2)
Disturbance in attention	1	(0.1)
Headache	1	(0.1)
Memory Impairment	1	(0.1)
Ear and Labyrinth Disorders	1	(0.1)
Hearing impaired	1	(0.1)
General Disorders and Administration Site Conditions	1	(0.1)
Asthenia	1	(0.1)
Injury, Poisoning, and Procedural Complications	1	(0.1)
Electric shock	1	(0.1)
Investigations	1	(0.1)
Liver function test abnormal	1	(0.1)
Metabolism and Nutrition Disorders	1	(0.1)
Decreased appetite	1	(0.1)
Musculoskeletal and Connective Tissue Disorders	1	(0.1)
Arthralgia	1	(0.1)
Psychiatric Disorders	1	(0.1)
Schizophrenia	1	(0.1)
Reproductive System and Breast Disorders	1	(0.1)
Endometriosis	1	(0.1)

Copied and electronically reproduced from Section 2.7.4 Summary of Clinical Safety, Table 11 (p 26-24)
Note: This table does not include 1 subject (SPD476-304-34105) who had a TEAE of anxiety that was possibly related to study drug and led to withdrawal, as the event was inadvertently not entered into the database. This subject is discussed within CSR SPD476-304, Section 14 (Data Errata).

7.3.4 Significant Adverse Events

In the All Lialda population of the Studies 303, 304, and 404, there was one patient pregnancy and one partner pregnancy in patients treated with Lialda.

SPD476-404-11315 (Lialda 2.4g/day)
This 42 year old Caucasian female had a positive pregnancy test on Study Day 299. The patient was withdrawn from the Study approximately one month after learning about the pregnancy. The patient gave birth to a full-term, healthy baby girl

SPD476-304-51203 (Lialda 2.4g/day)
This 29 year old Hispanic male and his wife did not use contraception during Study 304. At 7 weeks gestation, the wife learned about her pregnancy. At this time the patient was withdrawn from the study due to lack of efficacy. The patient's wife gave birth to a full-term, healthy baby boy.

Other significant AEs are those categorized as "related" or "possibly related" to the study drug. In Study 304, 12.6% of patients taking Lialda and 10.9% of patients taking Asacol reported an adverse event that was categorized by the investigator as being "related" or "possibly related" to study treatment. The only treatment-related adverse events occurring in ≥1% of patients taking Lialda were ulcerative colitis, asthenia, and increased gamma-glutamyltransferase (GGT).

Table 33. Treatment-related AEs in ≥1% of patients taking Lialda

	Study 304		All Lialda N=1082
	RCT Lialda N=415	Asacol N=411	
Number of Patients	415	411	1,082
	n (%)	n (%)	n(%)
Patients with ≥1 Related TEAE	52 (12.6)	45 (10.9)	122 (11.3)
Total Number of Events	75	63	187
System Order Class Preferred Term			
Gastrointestinal Disorders			
Ulcerative Colitis	10 (2.4)	9 (2.2)	17 (1.6)
General Disorders and Administration Site Conditions			
Asthenia	4 (1.0)	0	5 (0.5)
Investigations			
GGT Increased	4 (1.0)	0	1 (0.1)

Adapted from 2.7.4 Summary of Clinical Safety, Table 3.2.6 (p 202-207) and CSR SPD4760304 Table 3.2.6 (p 320-324)

Other than AEs associated with study discontinuation (Section 7.3.3), AEs classified as SAEs (section 7.3.2), and those that occurred in patients who became pregnant

(described above) there were no other significant AEs in patients taking Lialda in any of the clinical trials included in this safety review.

7.3.5 Submission Specific Primary Safety Concerns

A review of safety information from clinical trial and post-marketing use of Lialda in adults has not prompted any submission-specific safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

RCT Population

RCT and All Lialda Populations
The most common adverse events were ulcerative colitis, headache, and (b) (4) Each of these adverse events is currently included in Lialda labeling.

Table 34. TEAEs Occurring in at Least 1% of the RCT or All Lialda Populations

MedDRA System Organ Class Preferred Terms	**RCT**		**All Lialda**
	Lialda 2.4 g/day N=415 (%)	**Asacol 1.6 g/day N=411 (%)**	**N=1082 (%)**
Gastrointestinal Disorders			
Colitis Ulcerative	10 (2.4)	9 (2.2)	63 (5.8)
Abdominal Pain	9 (2.2)	7 (1.7)	24 (2.2)
Diarrhea	6 (1.4)	9 (2.2)	18 (1.7)
Abdominal Distention	5 (1.2)	2 (0.5)	14 (1.3)
Abdominal Pain Upper	3 (0.7)	7 91.7)	13 (1.2)
Dyspepsia	5 (1.2)	5 (1.2)	13 (1.2)
Rectal hemorrhage	5 (1.2)	6 (1.4)	11 (1.0)
*Total UC-Related TEAEs**	*30 (7.2)*	*31 (7.5)*	*(10.7)*
General Disorders and Administration Site Conditions			
Fatigue	6 (1.4)	3 (0.7)	11 (1.0)
Infections and Infestations			
Nasopharyngitis	12 (2.9)	10 (2.4)	30 (2.8)
Sinusitis	0	1(0.2)	13 (1.2)
Upper Respiratory Infection	9 (2.2)	6 (1.5)	24 (2.2)
Influenza	5 (1.2)	3 (0.7)	13 (1.2)
Bronchitis	5 (1.2)	2 (0.5)	16 (1.5)
Gastroenteritis	4 (1.0)	1 (0.2)	11 (1.0)
Musculoskeletal And Connective Tissue Disorders			
Back pain	2 (0.5)	4 (1.0)	13 (1.2)
Arthralgia	5 (1.2)	5 (1.2)	12 (1.1)
Nervous System Disorders			
Headache	16 (3.9)	19 (4.6)	31 (2.9)
Skin and Subcutaneous Tissue Disorders			
Rash	2 (0.5)	0	13 (1.2)
Vascular Disorders			
Hypertension	3 (0.7)	4 (1.0)	11 (1.0)
Investigations			
Gamma-glutamyltransferase (GGT) Increased	4 (1.0)	0	4 (0.4)
Alanine Aminotransferase (ALT) Increased	3 (0.7)	4 (1.0)	6 (0.6)
Blood and Lymphatic System Disorders			
Anemia	3 (0.7)	4 (1.0)	14 (1.3)

Source: Summary of Clinical Safety (2.7.4) Table 9 (p 22/57) and CSR SPD476-304 Table 36 (p 86/893).
* UC-Related Terms were ulcerative colitis, abdominal pain, diarrhea, and rectal hemorrage

7.4.2 Laboratory Findings

Clinical laboratory trends, individually clinical significant abnormalities, and changes over time were reviewed for clinical chemistry, hematology, and urinalysis parameters. No clinically important findings were seen.

The most common laboratory abnormalities reported in Study 304 were increased GGT (1%) and increased ALT (1%). These abnormalities are related to hepatic injury. Current Lialda labeling contains a section in the Warnings and precautions regarding hepatic impairment.

7.4.3 Vital Signs

Vital sign trends, individually clinical significant abnormalities, and changes over time were reviewed. No clinically important findings were seen.

7.4.4 Electrocardiograms (ECGs)

No ECG data were collected as part of any of the studies submitted in the Application.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted in support of this application.

7.4.6 Immunogenicity

Not applicable. The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this application.

7.5 Other Safety Explorations

No other safety explorations were performed. No new non-clinical safety studies were conducted in support of this application.

7.5.1 Dose Dependency for Adverse Events

Not Applicable. All patients were treated with 2.4 g/day Lialda.

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

Subgroup analyses of AE data for sex

7.5.4 Drug-Disease Interactions

No particular explorations for drug-disease interactions were conducted.

7.5.5 Drug-Drug Interactions

The following have been identified as potential interactions based upon reports of interaction between other products containing mesalamine.

1. The concomitant use of mesalamine with known nephrotoxic agents, including nonsteroidal anti-inflammatory drugs and azathioprine may increase the risk of renal reactions.
2. In patients receiving azathioprine or 6-mercaptopurine, concurrent use of mesalamine can increase the potential for blood dyscrasias.

A sufficient number of patients on these concomitant medications were not included in Study 304 to allow for a review of these interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. Results from preclinical carcinogenicity studies have been previously reviewed and are reflected in the current Lialda product label.

7.6.2 Human Reproduction and Pregnancy Data

There is no new information on pregnancy, use in labor and delivery, or lactation. Current labeling addresses these areas.

7.6.3 Pediatrics and Assessment of Effects on Growth

Lialda is currently indicated only for adults.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No case of overdose has been reported during any of the clinical trials submitted in support of this NDA.

A case of possible intentional overdose with Pentasa® (mesalmine) was reported in the US in 2007. The spontaneous case report from a medical examiner (forensic pathologist, M.D.) describes a completed suicide in a 17-year-old female who may have taken 14 of her brother's Pentasa (mesalamine) pills. According to the medical examiner, there was no evidence of disease or injury on autopsy and all toxicology (blood, urine and vitreous fluid) evaluations came back negative for everything except trace amounts of salicylates. It should be noted that a small amount of white powdery substance found near the patient tested positive for cocaine. No concomitant medications were reported. The medical examiner listed the cause of death as "undetermined."

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-day Safety Update on 04 October 2010 which included a Summary of Clinical Safety. The safety cut-off date for this submission was 13 September 2010. The update presented information from the Lialda clinical program and SAE data from ongoing studies SPD476-112 and -409.

No SAEs were reported. However, a single pregnancy was reported in a 29 year old black female treated with Lialda 4.8g/day. The patient was discontinued from Study 409 one month after a positive urine pregnancy test. The outcome of the pregnancy was not reported (likely because it was not known at the time of this submission).

Renal manifestations are a well-known possible adverse event associated with the use of mesalamine products. A recently published literature review reports that nephrotoxicity, in patient's taking 5-ASA, occurs at a mean rate of 0.26% per patient-year. Nephrotoxicity is most often reported within the first year and the most common form is interstitial nephritis with nonspecific signs and symptoms.[12] In an attempt to capture possible nephrotoxicity, the Applicant included an analysis of TEAEs involving the renal system using appropriate Standardized MedDRA Query (SMQ). No TEAEs were identified for patients in Study 304, the 6-month controlled study. In Study 303 and 404, the 12-month open-label studies, a total of 4 (0.65%) of patients experienced 5 AEs—increased blood creatinine (2 patients), increased blood urea (2 patients), and abnormal renal function test (1 patient).

Current mesalamine labeling contains a warning of hepatic failure in patients with pre-existing liver disease taking mesalamine. The Applicant included an analysis of TEAEs

involving the hepatic system using the appropriate Standardized MedDRA Query (SMQ). No cases of liver failure were seen. And 9 patients in the Lialda group and 6 (1.5%) patients in the Asacol group experienced hepatic TEAEs. None of the hepatic events was considered severe in intensity.

Table 35. Hepatic TEAEs in Study 304, Safety Population

	SPD476 2.4g/day QD N=415		ASACOL 1.6g/day divided BID N=411	
	n	(%)	n	(%)
Subjects With Hepatic TEAEs	9	(2.2)	6	(1.5)
Gamma-glutamyltransferase increased	4	(1.0)	0	
Alanine aminotransferase increased	3	(0.7)	2	(0.5)
Aspartate aminotransferase increased	1	(0.2)	1	(0.2)
Blood alkaline phosphatase increased	1	(0.2)	1	(0.2)
Hepatic enzyme increased	1	(0.2)	0	
Hyperbilirubinaemia	1	(0.2)	0	
Liver function test abnormal	1	(0.2)	1	(0.2)
Blood bilirubin increased	0		2	(0.5)

Electronically copied and reproduced from 2.7.4 Summary of Clinical Safety, Table 14 (p. 34/57)

Based on this information, mechanism of action of 5-ASA and the incidence of AEs related to the pancreatic and hepatic systems seen in association with the use of other mesalamine products, TEAEs of these systems were also analyzed.

Additionally, pericarditis and myocarditis are mentioned in current mesalamine labeling as possible adverse reactions. None of these adverse events were reported by any of the patients in the Study MPUC30034, MPUC3004, or MPUC3005.

8 Postmarket Experience

The most recent annual report covered the period of 16 January 2010 to 15 January 2011. During this time, there were no unpublished clinical trials, reports, or summaries of published reports of new toxicological findings. In addition, there were no unpublished clinical trials in pediatric patients reported during the reporting period. A review of the distribution data for the reporting period reveals that the quantity of the Lialda drug product distributed was (b) (4) in the United States and (b) (4) outside the US.

Currently, Shire's Lialda pediatric study requirements under PREA are "delayed" with a due date of December 31, 2010.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

The Applicant is proposing an indication statement that includes "maintenance of remission (b) (4) ulcerative colitis." The relevant indication for the active comparator, Asacol, is "maintenance of remission of ulcerative colitis."

(b) (4)

MO Comment:
I recommend that the maintenance indication for Lialda include only "maintenance of remission of ulcerative colitis."

9.3 Advisory Committee Meeting

An advisory committee meeting was not held regarding this Application.

However, on June 24, 2011, Milton Fan, statistical reviewer, presented this Application during a session of the Office of Biostatics Statistical Rounds. The Rounds included discussion of some of the key statistical questions concerning this Application.

The questions and discussion directly related to this Application are very briefly summarized below and no attempt is made to capture the complete discussion.

Question 1
Which analysis population, phase 1, phase 2, or pooled analysis (ITT or PP) should be considered as the primary analysis population from a statistical perspective? Are the results sufficient to show non-inferiority from a statistical perspective?

Question 2
For this Application, the test drug and active control are in the same drug class, are pharmacologically similar, and both have similar safety profiles. How much of a discount factor should be applied to M_1 for determining the non-inferiority margin M_2 ? Is a 50% discount overly conservative?

Brief Meeting Discussion
The audience asked questions to understand the Applicant's rationale for doubling the patient population. The concept of "overpowering" a study was discussed and Dr. Thomas Permutt expressed his thought that including more patients in a study gives a more precise confidence interval which is always a positive thing.

There was no consensus from the audience regarding which population should be used for analysis (ITT vs. PP).

Dr. Bob O'Neill addressed the question of M_2 in detail. He clarified that the M_1 and M_2 should be approached separately. M_1 is derived historically and is the treatment difference between the active comparator and placebo. While M2 is derived clinically and should reflect what degree of the treatment difference between placebo and the active comparator needs to be preserved. Dr. O'Neill specifically stated that in certain situations no discount of M_1 is needed.

Appendix A. Modified Ulcerative Colitis Disease Activity Index (UCDAI)

Subscore	Score	Disease Severity	Characteristics
Rectal Bleeding	0	Normal	No rectal bleeding
	1	Mild	Streaks of blood
	2	Moderate	Obvious Blood
	3	Severe	Mostly blood
Stool Frequency	0	Normal	Normal number of stools per day
	1	Mild	1-2 more than normal/ day
	2	Moderate	3-4 more than normal/ day
	3	Severe	>4 more than normal/ Day
Mucosal Appearance	0	Normal	Intact Vascular Pattern No Friability or Granulation
	1	Mild	Erythema Decreased Vascular Pattern Minimal Granularity
	2	Moderate	Marked Erythema Granularity Friability Absent Vascular Pattern
	3	Severe	Ulceration Spontaneous Bleeding
Physician Global Assessment	0	Normal	
	1	Mild	
	2	Moderate	
	3	Severe	

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References

[1] The Mesalamine Study Group. An Oral Preparation of Mesalamine as Long Term Maintenance therapy for Ulcerative Colitis. Ann Intern Med, 1996;124:204-211.
[2] Ouyang Q, Tandon R, Goh KL *et al* . Management consensus of inflammatory bowel disease for the Asia–Pacific region. *J Gastroenterol Hepatol* 2006; 21: 1772–82. [Review].
[3] Guidance for Industry, Non-Inferiority Clinical Trials, March 2010
[4] Asacol PI
[5] Response to FDA Information Request for NDA 22000S-005, March 11, 2010.
[6] M M Sanchez, X Chen. Choosing the analysis population in non-inferiority studies: Per protocol or intent-to-treat. *Statist. Med*, 2006; 25:1169–1181.
[7] Guidance for Industry, Non-Inferiority Clinical Trials, March 2010
[8] The Mesalamine Study Group. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis: a randomized, placebo-controlled trial. *Ann Intern Med*. 1996; 124:204-11. [PubMed 8533995]
[9] C J Hawkey, L M Dube, L V Rountree, P J Linnen, J F Lancaster, A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. The European Zileuton Study Group For Ulcerative Colitis, *Gastroenterology*, 1997; 112: 718-724.
[10] Apriso PI
[11] Higgins PDR et al, Is Endoscopy Necessary for the Measurement of Disease Activity in Ulcerative Colitis? *Am J Gastroenterol* 2005;100:355-361.

[12] Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. Inflamm Bowel Dis. 2007;13:629-638.

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/s/

AISHA E PETERSON JOHNSON
07/11/2011

ANIL K RAJPAL
07/11/2011
I concur with Dr. Peterson-Johnson.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22000-005 **Applicant: Shire** **Stamp Date: June 14, 2010**

Drug Name: Lialda 1.2 g tablet **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing: **Fileable**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			Section 5.3.5.3 had technical and formatting issues and correction was requested on June 23, 2010.
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)2 with Asacol as reference drug
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	This was a non-inferiority trial of one dose Lialda compared to reference drug with approved maintenance indication. Dosage based on extensive historical data on mesalamines.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Single pivotal maintenance trial

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1= A phase 3, randomized, multi-center, double-blind, parallel-group, active comparator study to compare the efficacy and safety of SPD476 2.4g/day QD with Asacol 1.6 g/day BID in maintenance of remission in patients with ulcerative colitis (UC) Indication: Maintenance of Remission of UC				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Deferral request for the pediatric trial as well as a pediatric protocol has been submitted for patients ages 5 to 17 yrs. A waiver has been previously granted for UC patients ages 0 to 5 yrs.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES__

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ii-Lun Chen, MD	July 29, 2010
Reviewing Medical Officer	Date
Anil Rajpal, MD	July 29, 2010
Clinical Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

II-LUN CHEN
07/29/2010

ANIL K RAJPAL
07/29/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div II, Branch VI and HFD-180	NDA 22-000 S-005

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Applicant name: Shire Address: 725 Chesterbrook Blvd. Wayne PA 19087-5637	Letter date: 14-June-10 Stamp date: 14-June 10 Received by reviewer: 15-June-10 PDUFA due date: 14-July 11

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Lialda®	Mesalamine	

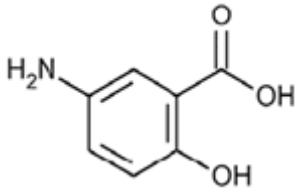
8. COMMUNICATION PROVIDES FOR:

The purpose of this submission is to request revisions to the US Prescribing Information (USPI) based on three maintenance clinical studies (SPD476-303, SPD476-304, and SPD474-04).

9. PHARMACOLOGICAL CATEGORY:	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
For treatment of colitis	Rx	
12. DOSAGE FORM	**13. POTENCY**	
Delayed Release Tablets	1.2g	

14. CHEMICAL NAME AND STRUCTURE

Compendia Names:
Mesalamine (USAN)
Mesalazine (INN and BAN)
Chemical Name: (1) Benzoic acid, 5-amino-2-hydroxy-; (2) 5-Aminosalicylic acid
Chemical Formula: $C_7H_7NO_3$
Molecular Weight: 153.14
CAS Number: CAS-89-57-6
Chemical Structure:



15. COMMENTS

The proposed PI is acceptable from the CMC perspective.

16. CONCLUSION AND RECOMMENDATION

APPROVAL

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Yong Wang	See appended electronic signature sheet	05-15-2011

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/s/

YONG WANG
07/11/2011

THOMAS F OLIVER
07/11/2011

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 22-000	**Supplement Number and Type: S005/Efficacy**	**Established/Proper Name: Lialda (mesalamine)**
Applicant: Shire Development Inc.	**Letter Date:02 June 2010**	**Stamp Date: 02 June 2010**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			Not applicable

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			Not applicable

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	√		The Sponsor requests categorical exclusion for an environmental assessment in accordance with 21 CFR 25.3 1 (a) and (b).

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?			Not required (same drug substance and drug product already approved under NDA 22-000)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Not required (same drug substance and drug product already approved under NDA 22-000)
14.	Does the section contain information regarding the characterization of the DS?			Not required (same drug substance and drug product already approved under NDA 22-000)
15.	Does the section contain controls for the DS?			Not required (same drug substance and drug product already approved under NDA 22-000)
16.	Has stability data and analysis been provided for the drug substance?			Not required (same drug substance and drug product already approved under NDA 22-000)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Not required

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?			Not required (same drug substance and drug product already approved under NDA 22-000)
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?			Not required (same drug substance and drug product already approved under NDA 22-000)
21.	Is there a batch production record and a proposed master batch record?			Not required (same drug substance and drug product already approved under NDA 22-000)
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			Not required (same drug substance and drug product already approved under NDA 22-000)
23.	Have any biowaivers been requested?			Not required (same drug substance and drug product already approved under NDA 22-000)
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?			Not required (same drug substance and drug product already approved under NDA 22-000)
25.	Does the section contain controls of the final drug product?			Not required (same drug substance and drug product already approved under NDA 22-000)
26.	Has stability data and analysis been provided to support the requested expiration date?			Not required (same drug substance and drug product already approved under NDA 22-000)
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			Not required (same drug substance and drug product already approved under NDA 22-000)
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			Not required (same drug substance and drug product already approved under NDA 22-000)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?			Not required (same drug substance and drug product already approved under NDA 22-000)

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Not required (same drug substance and drug product already approved under NDA 22-000)

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?			Not required (same drug substance and drug product already approved under NDA 22-000)

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	Yes		
33.	Have the immediate container and carton labels been provided?	No		Not applicable to the revision of the US Prescribing Information (USPI) for a preapproved drug product

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		√	

{See appended electronic signature page}

Name of
Marie Kowblansky, Ph.D.
CMC Lead
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Terrance Ocheltree, Ph.D.
Director
Division of New Drug Quality Assessment # 2
Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

MARIE KOWBLANSKY
07/30/2010

TERRANCE W OCHELTREE
07/30/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22000**
SERIAL NUMBER:	**0031**
DATE RECEIVED BY CENTER:	**06/14/2010**
PRODUCT:	**Lialda® (mesalamine) Delayed Release Tablet**
INTENDED CLINICAL POPULATION:	**Patients with active, mild to moderate ulcerative colitis.**
SPONSOR:	**Shire US Inc.**
DOCUMENTS REVIEWED:	**NDA Efficacy Supplement**
REVIEW DIVISION:	**Division of Gastroenterology and Inborn Errors Products (DGIEP)**
PHARM/TOX REVIEWER:	**Sushanta Chakder, Ph.D.**
PHARM/TOX SUPERVISOR:	**Sushanta Chakder, Ph.D.**
DIVISION DIRECTOR:	**Donna Griebel, M.D.**
PROJECT MANAGER:	**Kevin Bugin.**

Date of review submission to Division File System (DFS): June 02, 2011

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: From a nonclinical standpoint, the Prior Approval Efficacy Supplement is recommended for approval.

B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling:

No changes in the nonclinical sections (sections 8.1 Pregnancy, 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility, 13.2 Animal Toxicology) of the current labeling of Lialda were proposed. Thus, the sponsor's proposed label is acceptable, and no changes are recommended.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings:

No nonclinical studies were submitted in the current efficacy supplement. The nonclinical safety of mesalamine has been established in studies reviewed under the initial NDA submission.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

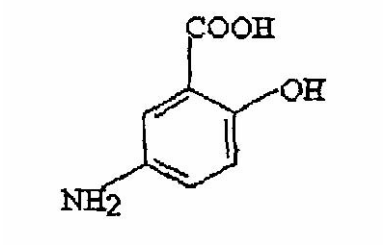
NDA number: 22-000
Review number: 01
Sequence number/date/type of submission: 0031/June 14, 2010/Efficacy Supplement
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Shire US Inc.
Reviewer name: Sushanta Chakder, Ph.D.
Division name: Division of Gastroenterology and Inborn Errors Products (DGIEP)

HFD #: 180
Review completion date: June 09, 2011

Drug:

Trade name: Lialda® Tablets
Generic name: Mesalamine
Code name: N/A
Chemical name: 5-Aminosalicylic acid; 5-Amino-2-hydroxybenzoic acid
CAS registry number: 61513-32-4
Molecular formula/molecular weight: 153.135

Structure:



Relevant INDs/NDAs/DMFs: IND 66,193/NDA 19-651 (Asacol delayed release Tablets), Procter and Gamble, Inc.

Drug class: Anti-inflammatory agent

Intended clinical population: Adult patients with active, mild to moderate ulcerative colitis.

Clinical formulation: Each Delayed Release Tablet contains 1200 mg mesalamine, and the following excipients: sodium carboxymethylcellulose, carnuba wax, stearic acid, colloidal hydrated silica, sodium starch glycolate, talc, magnesium stearate, methacrylic acid co-polymer type A and type B, triethyl citrate, titanium dioxide, red ferric oxide and polyethylene glycol 6000.

Route of administration: Oral

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-000, Supplement 005 are owned by Shire US Inc. or are data for which Shire has obtained a written right of reference. Any information or data necessary for approval of NDA 22-000, Supplement 005 that Shire does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Shire does not own or from FDA reviews or summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22-000, Supplement 005.

Studies reviewed within this submission: No nonclinical studies were submitted under the current Prior Approval Efficacy Supplement

Studies <u>not</u> reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

No studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

The sponsor did not provide any Pharmacokinetics/Toxicokinetics study report under the current submission.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

2.6.6 TOXICOLOGY

No toxicology study reports were submitted.

2.6.6.4 Genetic toxicology

No genotoxicity study reports were submitted.

2.6.6.5 Carcinogenicity

No study reports were submitted.

2.6.6.6 Reproductive and developmental toxicology

No reproductive and developmental toxicity studies were submitted.

2.6.6.7 Local tolerance

No studies were submitted.

2.6.6.8 Special toxicology studies: None

2.6.6.8 Discussion and Conclusions

Lialda (mesalamine) Delayed Release Tablet was approved on January 16, 2007 for the induction of remission in patients with active, mild to moderate ulcerative colitis. The current submission is a Prior Approval Efficacy Supplement for an additional indication (maintenance of remission, (b) (4) of ulcerative colitis). Based on three maintenance clinical trials (SPD476-303, SPD476-304, and SPD476-404), the sponsor is requesting revisions to the US Prescribing Information of Lialda Tablets. No nonclinical studies were submitted in the current Prior Approval Efficacy Supplement. Nonclinical safety of mesalamine has been established previously, and the nonclinical studies were reviewed under the original NDA. Nonclinical toxicology studies with mesalamine identified the kidney and the GI tract as the target organs of toxicity. Renal lesions including tubular degeneration, tubular dilatation, renal infarct, interstitial nephritis, tubular necrosis, and papillary necrosis were observed in rodents and/or cynomolgus monkeys. Mesalamine was not genotoxic, and in reproduction studies in rats and rabbits, no adverse effects were observed. Carcinogenicity studies in rats and mice did not reveal any carcinogenic potential. The sponsor did not propose any changes in the nonclinical sections of the labeling, and no labeling changes are recommended.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

In the current Prior Approval Efficacy Supplement, the sponsor is seeking an additional indication (maintenance of remission, (b) (4) of ulcerative colitis) for Lialda Delayed Release Tablets, and is requesting revisions to the US Prescribing Information of Lialda Tablets. No new nonclinical studies were submitted

in the current Efficacy Supplement. In addition, no changes in the nonclinical sections of the existing labeling were proposed.

Unresolved toxicology issues (if any): None

Recommendations: From a nonclinical standpoint, approval of the Supplemental NDA application is recommended.

Suggested labeling: None

APPENDIX/ATTACHMENTS: N/A

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/s/

SUSHANTA K CHAKDER
06/09/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22000 **Applicant: Shire** **Stamp Date: 06/14/2010**

Drug Name: Lialda **NDA/BLA Type: Supplement**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A. No Pharmacology/Toxicology studies were submitted
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		X	
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?		X	
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Sushanta K. Chakder, Ph.D.	7/29/10
Reviewing Pharmacologist	Date
Sushanta K. Chakder	7/29/10
Team Leader/Supervisor	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

SUSHANTA K CHAKDER
08/03/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

STATISTICAL REVIEW(S)

Statistical Team Leader Memorandum

Submission: NDA 22000/S005
Product: Lialda, mesalamine, 1.2g tablet
Sponsor: Shire Pharmaceuticals
Indication: Maintenance of remission of ulcerative colitis
Medical Div: DGIEP

The purpose of this memorandum is to discuss some alternative interpretations of the statistical issues discussed in the primary review. The reviewer has raised, and correctly so, two critical issues affecting the level of statistical evidence presented by the sponsor's maintenance of remission study: the unplanned sample size adjustment and the interpretation of the non-inferiority comparisons.

Sample size adjustment

As noted in the primary review, the study was initiated on April 8, 2005 to enroll 410 subjects, and a protocol amendment was made, late in study, on March 20, 2007 to revise the assumed magnitude of the treatment group response rates used in the original sample size calculations; this resulted in an additional 416 subjects after a long enrollment delay. The reviewer's position was that since this increase in sample was not pre-specified, and (presumably) one could not rule out some interim examination of the data by the sponsor, statistical inference based on all the data might not be reliable, and separate analyses of each "phase" of the trial was necessary with more statistical credibility attached to the phase 1 analysis.

The sponsor maintained that the adjustment reflected a more realistic consideration of potential treatment effect in a non-inferiority setting, specifically, assuming equal treatment effect under the alternative hypothesis as opposed to assuming a small treatment benefit of the test drug. The sponsor stated that the blinding of the study data was maintained throughout the transition from phase 1 through phase 2 and that lack of enrollment continuity was a consequence of logistical delays.

It is important that the study blind was maintained, and this is a critical concern. It is common in clinical trials for sponsors to examine blinded data to see if assumed event rates are on target. Pre-planned sample size adjustments based on blinded analyses do not require an alpha penalty. In this case, the sample increase was not pre-planned (nor can be considered an adaptive feature of the study) but occurred during study through a protocol amendment. There is no formal way to impose a penalty in this situation; however, there appears to be no evidence that the integrity of the data were compromised.

In my view, the proper analysis population for this study is represented by the combined data from the entire trial – based both on the ITT and the PP populations. The separate analyses based on phase 1 and phase 2 should be considered sensitivity analyses, and it should not be expected that they individually meet the (more rigid) non-inferiority criteria. The overall sample size should also not be an issue of concern as a larger sample

size leads to better precision in a non-inferiority study, as opposed to over-powering for a clinically non-significant effect size as might be the case for a superiority study.

Differences in efficacy between the phase 1 and phase 2 results would not be unexpected. In general, homogeneity of study subjects would not be constant factor over time during the conduct of a large multinational trial The observation that the regional makeup of the study was changed from phase 1 to phase 2 and resulted in more favorable point estimates does not support the contention that the phase 2 results themselves are statistically unreliable. Differences between the ITT and PP results might also be expected to be different in early versus late periods of the trial. One could also argue that the latter phase results might be more informative since trial experience would tend to reduce trial noise.

Non-inferiority comparisons

The sponsor's originally proposed 10% non-inferiority (NI) margin was not based on the rationale as put forth in the Agency's guidance document, and it seems clear that a 10% margin has not been adequately justified for the control product (Asacol). As requested by the primary reviewer, the sponsor applied the principles of the guidance, using the 1996 Mesalamine Study Group trial, to conclude that 8.6% represents the M1 margin.

Acceptance of M1 is critical to a conclusion of treatment efficacy. As stated in the guidance, the conclusion that the active control has at least that much of an effect (has assay sensitivity) is based on three considerations: historical evidence of active control effect; applicability of the historical trials to the current study; and the presence of good trial quality and conduct, the latter including a sufficiently objective endpoint not compromised by misclassification error. It is not the intention to measure these characteristics here although there does not appear to be evidence that the assay sensitivity assumption has been compromised. Thus M1 assumes these positive characteristics and a study which rules out the M1 margin can be considered to have shown efficacy, that is, the study drug would have been statistically superior to a placebo control had one been used. A conclusion of NI however is based on the margin M2.

The treatment difference confidence interval ruling out M1 in a NI study is analogous to the situation in a superiority study where the interval rules out zero. The notion of preserving efficacy can be applied to either situation where a stronger result is required and the objective is to have the interval rule out some (clinically undesirable) range of effect. For the NI study, the part of M1 to be maintained should be largely a clinical judgment. For this study, M2 was chosen (by the statistician) to be 50% of M1, thus "preserving" half of the effect measure by M1. This choice of M2 was thus based perhaps more on arbitrary convention than on clinical reasoning. Clearly, the choice of M2 should take into consideration that two mesalamine products with no significant risk factors are being compared, and the need for 50% preservation is debatable.

In my view, the choice of M2 is largely moot and should not be decided at the analysis stage. Given the study results (with no prior agreement on NI margin) the focus should

be more on what the data show rather than a formal test of a (post hoc) hypothesis. For the overall study, the point estimates and the lower confidence bounds of the treatment differences are 0.9% (-5%) and 2.1% (-4%) for the ITT and PP populations, respectively. The important features of these results are that the lower bounds not only rule out M1, but (1 – 5/8.6) = 42% of M1 is preserved. The central tendency shown by the point estimates to slightly favor the new treatment is a desirable result but does not support any degree of NI in a formal way.

Since the assumption of M1 rests upon the notion that the trial has assay sensitivity, it seems natural to place more confidence in the results based on the PP population, although it is necessary to analyze both the PP and ITT populations. As indicated above, there is no practical difference in the two results. Arguments against using the ITT population in a NI analysis, is supported by the notion that poor study conduct, non-compliance, and misclassification can falsely drive results toward the hypothesis of no difference; however, this also leads to increased variability which would also make it more difficult to meet the NI margin. When comparing the PP treatment groups, there is potential compromise of randomization, and the reviewer raised the concern that bias might have been introduced in the construction of the PP population, particularly between the trial phases. This concern would be difficult to justify. There does not appear to be any clear data supporting a differential bias in PP classified subjects.

The reviewer commented briefly that the fact that this was a single study possibly further detracted from the supportable evidence shown by this study or perhaps required some stricter interpretation. In the past, the medical division has advised sponsors that having showed substantial evidence of efficacy in the induction phase for this indication a well controlled single maintenance study could be sufficient. In this situation, the statistical goal would be to meet the usual study requirements based on a .05 level of significance.

Conclusion

In my view, the sponsor's maintenance study has demonstrated adequate evidence of efficacy. I would conclude that a non-inferiority conclusion of the new product against the comparator has not been rigorously justified, (b) (4) In the clinical trials section of the label, a descriptive summary of complete trial data would be more appropriate, with presentation of confidence intervals for both the ITT and PP populations.

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/s/

MICHAEL E WELCH
07/14/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-000-005
Drug Name:	Lialda (mesalamine) delay release tablet, 1.2 g
Indication(s):	Maintenance of remission, (b) (4) of ulcerative colitis
Applicant:	Shire Pharmaceuticals, Inc.
Date(s):	Received June 14, 2010 PUFA: July 14, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Milton C. Fan, Ph.D. , DB III
Concurring Reviewers:	Mike Welch, Ph.D. , Deputy Dir., DB III
Medical Division:	Gastroenterology and Inborn Errors Products (DGIEP)
Clinical Team:	Aisha Peterson Johnson, M.D., Anil Rajpal, M.D. (TL) (DGIEP)
Project Manager:	Kevin Bugin (DGIEP)

Keywords: clinical studies, NDA review, non-inferiority, non-inferiority margin, ITT

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor submitted a single non-inferiority study (SPD476-304), comparing SPD476 2.4 g/day QD vs. Asacol 1.6 g/day BID for the claim of maintenance of remission, (b) (4) of ulcerative colitis.

The study was initiated on April 8, 2005 to enroll 410 subjects. Amendment 2 was made on March 20, 2007 to revise the clinical assumption of the treatment group response rates based on ITT population instead of PP population and to enroll additional 416 patients.

A protocol amendment was submitted to FDA on April 23, 2007. The study was completed on September 7, 2009, and the protocol was finalized a week later on September 14, 2009. The Statistical Analysis Plan (SAP) was finalized a few days later on September 17, 2009.

However, this adjustment to sample size was not planned prior to the start of the study, and should not be considered an adaptive study design change but a post hoc adjustment of study size. Any traditional analysis might not be trusted. In this reviewer's opinion, the confidence interval of the traditional analysis cannot be interpreted properly. Without a pre-specified plan for adjustment, there is no proper way to correct for a valid adjustment.

Since study population enrolled after the amendment (phase 2) was different from the pre-amendment population (phase 1), and the overall results were driven by phase 2, only the results from the phase 1 can be interpreted statistically.

The sponsor's non-inferiority margin of 10% obtained from the meta analysis did not incorporate a 50% discount for assay sensitivity. The margin of 10% seems to be too large and might not be acceptable.

As requested from this reviewer, the sponsor applied the principles of the FDA non-inferiority guidance, using the Mesalamine Study Group trial (1996) to conclude that marginal M_1 would be defined as -8.6%. Assuming that at least 50% of M_1 should be maintained, M_2 would be defined as -4.3% as the non-inferiority margin preferred by this reviewer.

For the pre-specified primary efficacy endpoint, proportion of subjects in endoscopic remission at Month 6, both phase 1 and phase 2 failed to meet the non-inferiority criteria M_2 (-4.3%) for both ITT and PP analyses. Furthermore, the phase 1 ITT analysis also failed to meet non-inferiority criteria M_1 (-8.6%).

For the overall study population, the non-inferiority criterion (M_2) was just met for the PP analysis, but not for the ITT analysis .

Based on this reviewer's "true" ITT analysis including all randomized subjects, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 (-4.3%) but met non-inferiority criteria M_1 (-8.6%). However, for the overall population, the "true" ITT analysis was close to meeting the non-inferiority criterion M_2 (-4.3%).

The reviewer's meta analysis was also used to combine phase 1 and phase 2 for the "true" ITT population, it resulted in a 95% C.I. of the treatment group difference (SPD476 – Asacol) of (-4.6%, 6.8%), which was also close to meet non-inferiority criterion M_2 (-4.3%).

The differences (SPD476- Asacol) for US subject were -16.4% and 1.3% for phase 1 and phase 2, respectively, for the ITT analysis. But, due to small sample size (38 subjects), the US results are not interpretable.

In conclusion, this study has shown that non-inferiority was inconclusive based on results from the phase 1 for non-inferiority margin (M_2). However, if the non-inferiority margin (M_1) would be considered "acceptable" as a clinical non-inferiority margin, this study just would meet (albeit marginally) that non-inferiority criterion. However, even these results may not be statistical persuasive given the unplanned increase in sample size. There is the additional issue of this being a single study that requires a higher level of statistical evidence; however, single maintenance trials at nominal significance levels have been utilized previously for this indication.

1.2 Brief Overview of Clinical Studies

1.2.1 Study SPD476-304

This was a phase 3, randomized, double-blind, parallel-group, active comparator study, conducted globally in subjects with ulcerative colitis (UC) in endoscopic remission.

Subjects were randomized in a 1:1 ratio to receive either SPD476 2.4g/day administered QD or ASACOL 1.6g/day divided dose, administered as 0.8g BID.

The primary objective was to compare the percentage of subjects in endoscopic remission (maintenance of mucosal healing) at 6 months between SPD476 (2.4g/day QD) and ASACOL (1.6g/day divided BID).

1.3 Statistical Issues and Finding

The statistical issues listed below were identified at the NDA filing meeting:

- Sample Size increased from 410 to 826 during the trial due to change to clinical assumptions
    - 410, original sample size based on Per Protocol results
    - Protocol amended when only 39 patients were still ongoing. Sample size based on ITT results

  - Sample size doubled without clear justification
- Non-inferiority margin of 10%
  - obtained from meta analysis without 50% discount for assay sensitivity
  - 10% seems to be too large.
  - Not agreed to by the Agency
  - Should be in the range of 3.8% to 4.6% (according to this reviewer's analysis)
- Enrolled only 38 US patients (5.6%)
  - The results for US was -6% for ITT
  - The results for US was -18% for PP
  - Due to small sample size, US results might not be interpreted

Study was initiated on April 8, 2005 to enroll 410 subjects. Amendment 2 was made on March 20, 2007 to revise clinical assumption based on ITT population instead of PP population and to enroll additional 416 patients.

Protocol amendment was submitted to FDA on April 23, 2007. Study was completed on September 7, 2009. Protocol was finalized a week later on September 14, 2009. Statistical Analysis Plan (SAP) was finalized a few days later on September 17, 2009.

However, this adjustment to sample size was unplanned. This was not a proper adaptation but a post hoc adjustment of study size. Any traditional analysis might not be trusted. The confidence interval of the traditional analysis cannot be interpreted properly. Without the specific plan for adjustment, it cannot be known what the valid adjustment is.

Since the phase 2 population was different from the phase 1 population; overall results were driven by phase 2, and, only results from the phase 1 could be interpreted statistically.

The sponsor's non-inferiority margin of 10% obtained from a meta analysis without 50% discount for assay sensitivity. Margin of 10% seems to be too large and might not be acceptable.

As per request from this reviewer, the sponsor applied the new FDA non-inferiority guidance, and based on the Mesalamine Study Group trial (1996) argued that M_1 would be defined as -8.6%. Assuming that maintained at least 50% of M_1, M_2 would be defined as -4.3%, the desired non-inferiority margin. .

For pre-specified primary efficacy endpoint, proportion of subjects in endoscopic remission at Month 6, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 (-4.3%) for both ITT and PP analyses. Furthermore, phase 1 ITT analysis also failed to meet non-inferiority criteria M_1 (--8.6%).

For overall, PP analysis just barely met the non-inferiority criterion (M_2), but ITT analysis failed to meet the non-inferiority criterion.

Based on this reviewer's "true" ITT analysis including all randomized subjects, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 (-4.3%) but met non-inferiority criteria M_1 (-8.6%). Furthermore, for overall, "true" ITT analysis was close to meeting non-inferiority criterion M_2 (-4.3%).

Meta analysis was used to combine phase 1 and phase 2 for the "true" ITT population, it resulted 95% C.I. of (-4.6%, 6.8%), which was also close to meeting non-inferiority criterion M_2 (-4.3%).

The differences (SPD476- Asacol) for US were -16.4% and 1.3% for phase 1 and phase 2, respectively, for ITT analysis. But, due to small sample size, the US results could not be interpretaed.

2. INTRODUCTION

2.1 Overview

Lialda was approved on 16 January 2007, indicated for the induction of remission in patients with active, mild to moderate colitis.

The sponsor seeks for the additional of new indication (maintenance of remission, (b) (4) of ulcerative colitis).

The sponsor had submitted an adequate and well-controlled studies trial (SPD476-304) and an open-label study to assess clinical recurrence (SPD476-404), and an open-label extension study to evaluate safety and tolerability (SPD476-303) for the claim.

Protocol SPD476-303: A phase III, Randomized, 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.

Protocol SPD476-304: MATRx Maintenance: A Phase 3, Randomized, Multi-center, Double-blind, Parallel Group, Active Comparator Study to Compare the Efficacy and Safety of SPD476 (Mesalazine) 2.4 g/day Once Daily (QD) with Asacol 1.6g/day Twice Daily (BID) in the Maintenance of Remission in Patient with Ulcerative Colitis.

Protocol SPD476-404: **S**trategies **i**n **M**aintenance for **P**atients Receiving **L**ong-term Th**e**rapy" (S.I.M.P.L.E.): A Phase IV, Multi-center, Open-label Study to Assess Clinical Recurrence Related to Compliance With Treatment With MMX® Mesalamine 2.4g/day Given Once Daily for the Maintenance of Quiescent Ulcerative Colitis (UC)

However, it was found that there was a huge time gap between dates of first dose of study medication from July 20, 2006 to Nov 22, 2007. No patients were enrolled for more than 16 months. There were 419 patients enrolled before 7/20/2006 and were randomized, 3 of them did not take drug. There were 410 patients were enrolled and randomized after

7/20/2006. This study should be divided two parts: part 1 first 419 patients; part 2 remaining 410 patients.

Per this reviewer's request, the sponsor submitted response to request dated February 22, 2010. It included complete efficacy sections (containing all primary and secondary endpoints, broken out by phase) for the ITT population.

Only study (SPD476-304) will be statistically reviewed.

2.2 Data Sources

The sponsor had submitted an adequate and well-controlled studies trial (SPD476-304) and an open-label study to assess clinical recurrence (SPD476-404), and an open-label extension study to evaluate safety and tolerability (SPD476-303) for the claim.

Protocol SPD476-303: A phase III, Randomized, 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.

Protocol SPD476-304: MATRx Maintenance: A Phase 3, Randomized, Multi-center, Double-blind, Parallel Group, Active Comparator Study to Compare the Efficacy and Safety of SPD476 (Mesalazine) 2.4 g/day Once Daily (QD) with Asacol 1.6g/day Twice Daily (BID) in the Maintenance of Remission in Patient with Ulcerative Colitis.

Protocol SPD476-404: **S**trategies **i**n **M**aintenance for **P**atients Receiving **L**ong-term Th**e**rapy" (S.I.M.P.L.E.): A Phase IV, Multi-center, Open-label Study to Assess Clinical Recurrence Related to Compliance With Treatment With MMX® Mesalamine 2.4g/day Given Once Daily for the Maintenance of Quiescent Ulcerative Colitis (UC)

The electronic submission was located at *\\Cdsesub1\evsprod\NDA022000.*

The sponsor submitted response to request for information S/N: 0043 dated September 20, 2010, for the Information Request by this reviewer dated August 27, 2010.

The sponsor submitted response to request for information S/N: 0045 dated September 24, 2010, for the Information Request by this reviewer dated August 27, 2010.

The sponsor submitted response to request for information S/N: 0054 dated February 22, 2010, for the Information Request by this reviewer dated December 8, 2010.

The sponsor submitted response to request for information S/N: 0057 dated April 6. 2011, for the Information Request by this reviewer dated March 4, 2011.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study SPD476-304

3.1.1.1 Study Design

This was a phase 3, randomized, double-blind, parallel-group, active comparator study, conducted globally in subjects with ulcerative colitis (UC) in endoscopic remission.

Subjects were randomized in a 1:1 ratio to receive either SPD476 2.4g/day administered QD or ASACOL 1.6g/day divided dose, administered as 0.8g BID.

The primary objective was to compare the percentage of subjects in endoscopic remission (maintenance of mucosal healing) at 6 months between SPD476 (2.4g/day QD) and ASACOL (1.6g/day divided BID).

The secondary objectives of the study were as follows:

- To compare the percentage of subjects in endoscopic remission (maintenance of mucosal healing) with no or mild symptoms at 6 months between the two treatment groups
- To compare time to relapse between the two treatment groups
- To compare the modified Ulcerative Colitis Disease Activity Index (UC-DAI) score and its components (stool frequency, rectal bleeding, mucosal appearance, and Physician's Global Assessment [PGA]) between the two treatment groups
- To compare the quality of life (QoL) assessment of a subset of subjects between the two treatment groups
- To assess the safety and tolerability of SPD476 compared to ASACOL.

The purpose of this study was to confirm the efficacy and safety of SPD476 administered QD compared to ASACOL administered BID in the maintenance treatment of UC in remission. ASACOL was selected as the comparator because it was the most commonly prescribed 5-aminosalicylic acid (mesalazine) (5-ASA) for UC in the United States (US), UK, and several other European countries when the study was designed.

ASACOL 1.6g/day is the approved dose in the US for the maintenance of remission of UC, and this dose has been shown to be efficacious in a blinded, placebo-controlled study. The approved dose range for the maintenance treatment of UC in remission in Europe is 1.2-2.4g/day. A 1.6g/day dose was therefore selected for the study since it falls midway between the approved dose range for Europe, while still allowing the study to be conducted in the US, and it is considered to be a clinically effective dose.

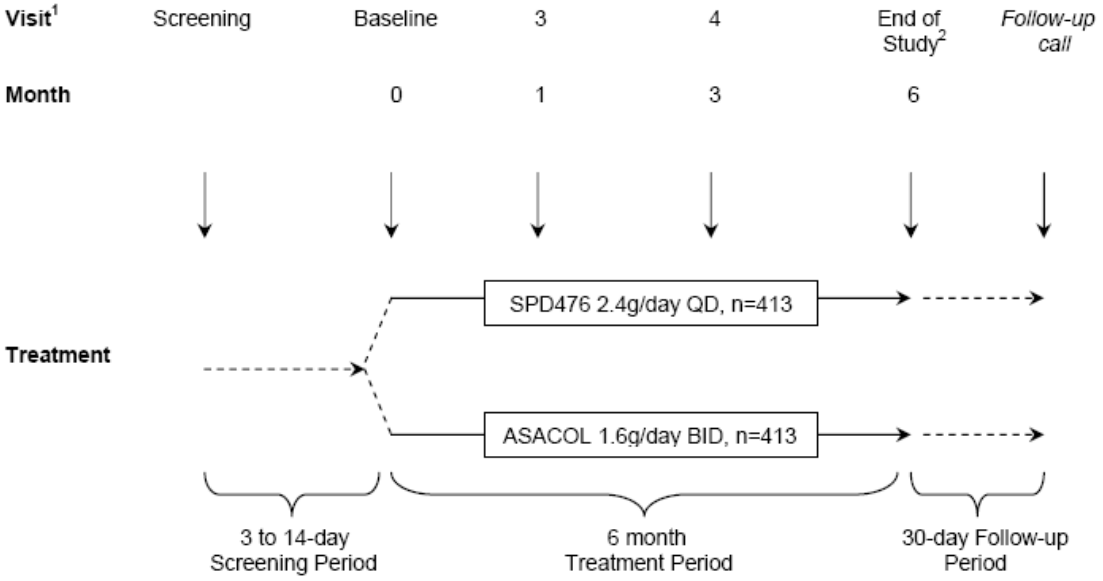
Eligible subjects were adult male and female subjects with a previous diagnosis of UC confirmed by histology that was considered in remission for ≥30 days, with an endoscopy score of ≤1 and a combined symptom score (stool frequency and rectal bleeding) of ≤1. Subjects had to have at least 1 acute episode of UC (a documented episode of increased

bowel frequency with rectal blood loss for which UC therapy was intensified) in the 12 months prior to enrollment, and at least 2 episodes in their overall medical history.

Additionally, eligible subjects' UC should have been controlled by a stable dose of no more than 2.4g/day 5-ASA for at least 30 days prior to baseline.

There were 5 study visits, starting with a screening visit up to 2 weeks prior to subject randomization onto study medication. The treatment period lasted for 6 months and involved 4 visits: baseline (Month 0), Month 1, Month 3, and Month 6 (end of study).

Figure 1: Study Design Flow Chart



[1] An unscheduled visit could occur at any time between baseline and end of study visits if subject experienced symptoms that indicated loss of remission.

[2] The end of study visit was also the early withdrawal visit.

Subjects may also have attended an unscheduled study visit at any time during the study if there was a return or worsening of UC symptoms. Subjects had a monthly telephone contact for safety assessments, and were contacted 30 days after the end-of-study visit for a safety follow-up call.

The choice of non-inferiority margin was based on clinical and statistical considerations (Committee for Proprietary Medicinal Products 2000; Committee for Proprietary Medicinal Products 2004).

In the Mesalamine Study Group trial (The Mesalamine Study Group 1996), the difference between the 1.6g/day and placebo was 25.8% for the per protocol population (95% CI [8.6% to 43.0%] based on the normal approximation to the binomial distribution) and 21.8% (95% CI [7.6% to 36.1%]) for the ITT population. Thus, a 10% margin would

maintain at least half of the superiority (ASACOL vs. placebo) suggested by the Mesalamine Study Group.

In addition to the Mesalamine Study Group trial, a meta-analysis (Sutherland et al 2003) of published, prospective, randomized, controlled trials with treatment durations of at least 6 months reported a Peto Odds Ratio (odds in favor of maintaining remission, placebo vs. 5-ASA) of 0.47 with 95% CI (0.36-0.62). There was no significant evidence of heterogeneity between studies. A non-inferiority margin of 10%, based on a true 70% remission rate in the ASACOL arm, is analogous to an odds ratio non-inferiority margin of 0.643 (odds in favor of remission SPD476 vs. ASACOL). Since under these remission rate assumptions the proposed odds ratio non-inferiority margin lies above the 95% CI for the placebo vs. 5-ASA odds ratio from the meta-analysis (95% [0.36 to 0.62]), the choice of a non-inferiority margin of 10% (based on the normal approximation to the binomial distribution) was justified (Committee for Proprietary Medicinal Products 2004).

As it is difficult to translate the Peto odds ratio into differences in proportions, an additional meta-analysis was performed by the sponsor on the same studies included in the meta-analysis using a weighted variance and difference approach (Babbs 2003). This analysis produced a 95% CI for the difference in proportions of (11.5%, 24.3%). Therefore, the non-inferiority margin of 10% in this study (SPD476-304) maintains at least half of the superiority (ASACOL vs. placebo) suggested by The Mesalamine Study Group, 1996 and is less than the lower limit of the 95% CI computed in the meta-analysis.

The primary efficacy variable for the study was endoscopic remission (maintenance of mucosal healing) at Month 6. Secondary variables included endoscopic remission (maintenance of mucosal healing) with no or mild symptoms, and a comparison of the modified UC-DAI score and its components.

For assessment of the primary objective, endoscopic remission (maintenance of mucosal healing) was defined as an endoscopy score of ≤1.

For assessment of the secondary objective of endoscopic remission (maintenance of mucosal healing) with no or mild symptoms, this was defined as an endoscopy score of ≤1, and a combined symptom score (rectal bleeding and stool frequency) of ≤1.

The time to relapse was defined as the time from randomization to the date of withdrawal due to lack of efficacy.

The UC-DAI is widely used to assess treatment efficacy in subjects with mild to moderate UC. The UC-DAI consisted of 4 individual parameters (stool frequency, rectal bleeding, endoscopy score [mucosal appearance], and PGA).

For the purpose of this study, the standard UC-DAI scale was amended so that an

endoscopy score of 1 (mild disease) did not include friability; instead friability was scored as 2 (moderate disease). All 4 parameters were assessed individually on a scale of 0 to 3. The modified UC-DAI score was calculated at the baseline visit, the end of study (Month 6/early withdrawal) visit, and at an unscheduled visit, by summing the individual scores for the 4 parameters. Subject's symptoms (rectal bleeding and stool frequency) were reported by the subjects to the IVRS every day for 1 week prior to each visit, within an hour before bedtime, and were retrieved by the investigator/designee on the day of the subject's visit. The score scales for stool frequency were as follows: 0 = normal, 1 = 1-2 more than normal per day, 2 = 3-4 more than normal per day, and 3 $\geq$ 4 more than normal per day. The score scales for rectal bleeding were as follows: 0 = no rectal bleeding, 1 = streaks of blood, 2 = obvious blood, and 3 = mostly blood. Rectal bleeding and stool frequency were assessed at each visit. The scores for these individual parameters for the last available 3 days in the 5-day period immediately prior to the study visit were recorded in the CRF, and the CRF data was used for all summaries of symptom data. The average of the scores of the last available 3 days was calculated for each parameter only at baseline and at the end of study (Month 6/early withdrawal) visit to determine the total modified UC-DAI score. No data older than 5 days prior to the study visit was used. If only 1 or 2 day's data were available, then the mean of the 1 or 2 days was used to calculate the mean (i.e., mean of available non-missing data). If there were no data available, then the mean score was missing for that component.

An endoscopy was performed at baseline and the end of study (Month 6/early withdrawal) visit, and mucosal appearance was scored on a scale from 0 to 3, with 0 = normal (intact vascular pattern; no friability or granulation), 1 = mild (erythema, decreased vascular pattern, minimal granularity), 2 = moderate (marked erythema, granularity, friability, absent vascular pattern, bleeding with minimal trauma, no ulcerations), and 3 = severe (ulceration, spontaneous bleeding). The endoscopy at baseline and at the end of study (Month 6/early withdrawal) visit was requested to be performed by the same investigator/endoscopist.

The PGA was performed at baseline and the end of study (Month 6/early withdrawal) visit and was scored on a scale from 0 to 3, with 0 = no active disease, 1 = mild disease, 2 = moderate disease, and 3 = severe disease. The PGA was requested to be performed by the same investigator that performed this assessment at the baseline visit.

Quality of life was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).

Subjects were asked to complete the SIBDQ at the baseline visit, Month 3, and the end of study (Month 6/early withdrawal) visit to assess their QoL. The SIBDQ was composed of 10 items, each scored from 1 to 7. The scores of each question were summed to give a total final score (minimum score 7, maximum score 70). A high total score denoted good QoL, and a low score denoted poor QoL.

The SIBDQ was not currently translated and approved in all of the languages required for

this study; therefore, only subjects for whom the questionnaire had been translated, and the license permitted its use, had their QoL assessed. The countries that used the SIBDQ were the UK, USA, Canada (Dr. Bailey only), Belgium, Germany, France, Czech Republic, Poland, Hungary, Netherlands, Portugal, Denmark, Sweden, Romania, Australia, New Zealand, South Africa, and Singapore (for subjects who spoke English).

Efficacy assessments included a minimum of 2 endoscopies to assess mucosal appearance as well as the modified UC-DAI score and its components.

Safety was assessed through the monitoring of AEs, clinical laboratory testing (hematology, biochemistry, and urinalysis), vital signs, physical examinations, and urine pregnancy tests for females of childbearing potential.

No formal hypothesis testing was performed on the demographic, baseline characteristic, and safety data for this study.

The primary efficacy variable was the proportion of subjects in endoscopic remission (maintenance of mucosal healing) at Month 6 in each treatment group as defined by an endoscopy score of ≤1. The primary analysis compared the primary efficacy variable between SPD476 and ASACOL using the per protocol population.

In the original protocol (Version 1.0, dated 23 Nov 2004), approximately 410 subjects were to be randomized in order to obtain a per protocol (evaluable) population of 165 subjects per treatment group. Following an amendment to the protocol on 20 Mar 2007, the number of subjects required in the study increased to approximately 826, in order to obtain a per protocol (evaluable) population of 330 subjects per treatment arm.

3.1.1.2 Sponsor's Analysis

The original sample size was to be approximately 410 randomized subjects. During routine study assessment in 2006, while data were still blinded, the sponsor re-evaluated the endoscopic remission rate for ASACOL. The original assumptions had been based on the results of the Mesalamine Study Group trial (The Mesalamine Study Group 1996). In that publication, for the ASACOL 0.8g/day group, the remission rate was 63.3% in the ITT population and 58.8% in the per protocol population; for the ASACOL 1.6g/day group, the remission rate was 70.1% in the ITT population and 65.5% per protocol population.

Based on those results, the sponsor initially assumed that the endoscopic remission rate of subjects treated with 1.6g/day ASACOL would be 65%. This assumption was based on the results of the per protocol population; however, there was a 70.1% remission rate in the ITT population. Also, the 95% CI for the remission rate in the per protocol population ranged from 53-78%. Given this uncertainty around the estimate of the ASACOL remission rate in the Mesalamine Study Group trial, it was deemed to be more prudent to change the clinical assumption for the remission rate for ASACOL to 70%, since this would provide a sample size estimate based on no expected difference between the 2

treatments. A remission rate of 70% for SPD476 remained unchanged. This change to the clinical assumptions was reflected in Protocol Version 3.0, dated 20 Mar 2007.

Throughout the conduct of the study, the data remained blinded. To allow additional enrollment into the study due to the 2007 amendment (Amendment 2), a new randomization scheme was produced by the same external group who produced the original randomization scheme in (b) (4)

A total of 829 subjects were randomized to treatment, 416 to SPD476 and 413 to ASACOL. Of the 829 randomized subjects, 3 subjects did not receive a dose of study medication. Therefore, a total of 826 subjects (415 in the SPD476 group and 411 in the ASACOL group) were included in the safety and intent-to-treat (ITT) populations, defined as all randomized subjects who received at least 1 dose of investigational product. A total of 670 subjects completed the study, 81.7% (340) of subjects treated with SPD476 and 79.9% (330) of subjects treated with ASACOL.

A total of 679 subjects (343 in the SPD476 group and 336 in the ASACOL group) were included in the per protocol population, defined as all subjects in the ITT population who either completed the study or withdrew for reasons related to a lack of efficacy or adverse events (AEs) and who were deemed to be protocol-compliant.

The most common reason for premature withdrawal from the study was lack of efficacy (12.0% of subjects treated with SPD476 and 13.8% of subjects treated with ASACOL).

The detailed subject disposition is given below.

Subject Disposition (All Subject)

	SPD476 2.4g/day QD		ASACOL 1.6g/day divided BID		Overall	
	N	(%)	N	(%)	N	(%)
Subjects Screened					977	
Subjects Randomized	416		413		829	
Subjects Completed	340	(81.7)	330	(79.9)	670	(80.8)
Subjects Who Discontinued Early	76	(18.3)	83	(20.1)	159	(19.2)
Lack of Efficacy	50	(12.0)	57	(13.8)	107	(12.9)
Patient Request	10	(2.4)	6	(1.5)	16	(1.9)
Lost to Follow-up	5	(1.2)	10	(2.4)	15	(1.8)
Adverse Event/SAE	6	(1.4)	3	(0.7)	9	(1.1)
Protocol Violation	3	(0.7)	3	(0.7)	6	(0.7)
Non-compliance	0		1	(0.2)	1	(0.1)
Pregnancy	0		1	(0.2)	1	(0.1)
Other[a]	2	(0.5)	2	(0.5)	4	(0.5)

[a] Other reasons for withdrawal included Subject 20414 (SPD476) who did not come back for a subsequent visit, Subject 62601 (SPD476) who used prohibited corticosteroids for an asthma attack while hospitalized, Subject 19619 (ASACOL) who was discontinued due to a lack of study medication at the center, and Subject 50002 (ASACOL) who withdrew consent.

The detailed major protocol deviation for ITT Population is given in Appendix Table 1.

As seen from Appendix Table 1, there was disproportionate of subjects who took prohibited concomitant medications (14 for SPD476vs. 3 for ASACOL).

3.1.1.2.1 Planned Analysis

For the per protocol population, all subjects who withdrew for reasons other than lack of efficacy or AE or who had missing endoscopy data at Month 6 were excluded. All other subjects that withdrew early (e.g., subjects who withdraw due to lack of efficacy or AE) were treated as not being in endoscopic remission (maintenance of mucosal healing) at Month 6. A 2-sided 95% confidence interval (CI) for the difference between the 2 treatment groups (SPD476- ASACOL) in the proportions of subjects in remission at 6 months was computed using the normal approximation to the binomial distribution. Non-inferiority of SPD476 to ASACOL was to be concluded if the lower limit of the 95% CI was above the non-inferiority margin of -10% (this was equivalent to performing a 1-sided hypothesis test at the 0.025 level of significance, based on the null hypothesis that SPD476 was inferior to ASACOL). If the 95% CI for the difference in proportions not only was above the non-inferiority margin, but also above 0, then it was to be concluded that there was evidence of superiority of SPD476 over ASACOL in terms of statistical significance at the 2-sided, 5% level ($p<0.05$).

Additional statistical analyses of the primary efficacy variable, and analyses of secondary efficacy variables, were considered supportive. Supportive analysis of the primary efficacy variable was performed on the ITT population, using the same methodology as

the primary analysis. For the analysis of secondary efficacy variables, a 2-sided 95% CI was presented where applicable. A supportive analysis of the primary efficacy variable investigated country effect by pooled countries. For the per protocol and ITT populations, a Cochran-Mantel-Haenszel test was used to compare the proportion of subjects in endoscopic remission (maintenance of mucosal healing) stratified by pooled country, and the odds ratio and 95% CI was presented. The p-value from the Breslow-Day test for homogeneity across the odds ratios was also presented.

Additionally, supportive analyses of the primary efficacy variable were conducted using the same methodology with the following baseline covariates: gender (male, female), age (<55 years, 55+ years), race (Caucasian, non-Caucasian), smoking status smokes/previous smoker, never smoked), disease classification (left-sided, other), time since most recent acute episode at baseline (≤12 weeks, >12-≤24 weeks, >24-≤36 weeks, >36 weeks), and number of acute episodes of UC (≤2 episodes, >2-≤4 episodes, >4-≤10 episodes, >10 episodes).

The proportion of subjects in each treatment group who were in endoscopic remission (maintenance of mucosal healing) with no or mild symptoms at Month 6 were compared using similar methodology to the primary analysis.

The time to relapse was compared between treatment groups using a Cox regression model, including a factor for treatment group only. Hazard ratios and the corresponding 95% CI were presented for both the ITT and per protocol populations. The time to relapse was also presented graphically using Kaplan-Meier methodology for the ITT and per protocol populations.

The change from baseline in the modified UC-DAI score was analyzed using analysis of covariance with treatment group as a factor and baseline modified UC-DAI score as a covariate. Least squares means were obtained for the change from baseline to Month 6 and endpoint and presented with the difference in least squares mean and 95% CI.

Summary statistics for the average stool frequency score and average rectal bleeding score were presented for all timepoints for both the ITT and per protocol populations.

Change from baseline was presented for all post baseline visits, and a summary of the proportion of subjects in the following categories was also included: 0, >0-<1, 1-<2, 2-<3, 3.

The proportion of subjects in clinical remission at each timepoint, as well as the change from baseline in endoscopy and PGA scores, were compared between treatment groups using similar methodology as the primary analysis.

Summary statistics for the total SIBDQ score and change from baseline were presented for each treatment group for the per protocol and ITT populations.

3.1.1.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for randomized patients is given in Appendix Table 2.

As seen from Appendix Table 2, demographic characteristics of the safety population were well-balanced between treatment groups. Overall, subjects in the safety population had a median age of 45.0 years; 51.6% were male, and the majority was Caucasian (64.3%) and never smoked (70.9%). For the safety population, the median duration since the time of UC diagnosis was 228.7 weeks (i.e., 4.4 years). Most subjects' UC was diagnosed through colonoscopy (80.9%) and 98.7% of subjects that had a diagnosis of suspected UC through endoscopy or barium enema had compatible histology to confirm the diagnosis. The classification of the most recent acute disease among subjects in the safety population was most commonly left-sided (75.6%).

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy variable was the proportion of subjects in endoscopic remission (maintenance of mucosal healing) at Month 6 in each treatment group as defined by an endoscopy score of ≤1. The primary analysis compared the primary efficacy variable between SPD476 and ASACOL using the per protocol population.

The result from analyses of the proportion of subjects in endoscopic remission at Month 6 is given below.

Analysis of the Proportion of Subjects in Endoscopic Remission at Month 6 (Maintenance of Mucosal Healing) (Per Protocol Population)

		SPD476 2.4g/day QD N=343	ASACOL 1.6g/day divided BID N=336
Month 6	Subjects in endoscopic remission (n, %)	287 (83.7)	274 (81.5)
	Difference in proportions (SPD476 – ASACOL)		0.02
	95% CI for difference in proportions[a]		(-0.04, 0.08)

[a] Calculated using the normal approximation to the binomial distribution.

Note: Subjects with missing data at Month 6 or endpoint were considered failures in that respective analysis.

Data Source: Table 2.1.1

As seen from tables above, for the per protocol population at Month 6, SPD476 met the primary endpoint of non-inferiority versus ASACOL with the 95% CI for the difference between SPD476 and ASACOL in the proportions of subjects in endoscopic remission (maintenance of mucosal healing) of -0.04 to 0.08 which met the non-inferiority margin of 10% (-0.10) .

The result from analyses of the proportion of subjects in endoscopic remission at Month 6 ITT population is given below.

Analysis of the Proportion of Subjects in Endoscopic Remission at Month 6 (Maintenance of Mucosal Healing) (Intent-to-Treat Population)

		SPD476 2.4g/day QD N=415	ASACOL 1.6g/day divided BID N=411
Month 6	Subjects in endoscopic remission (n, %)	323 (77.8)	316 (76.9)
	Difference in proportions (SPD476 – ASACOL)		0.01
	95% CI for difference in proportions[a]		(-0.05, 0.07)

Note: Subjects with missing data at Month 6 or endpoint were considered failures in that respective analysis.

[a] Calculated using the normal approximation to the binomial distribution.

Data Source: Table 2.1.2

As seen from Table above, for the ITT population at Month 6, SPD476 met the primary endpoint of non-inferiority versus ASACOL with the 95% CI for the difference between SPD476 and ASACOL in the proportions of subjects in endoscopic remission (maintenance of mucosal healing) of -0.05 to 0.07 which met the non-inferiority margin of 10% (-0.10) .

3.1.1.2.3.1 Subgroup Analyses

Supportive analyses on the primary efficacy endpoint were conducted to investigate any effect by country, gender, age, race, smoking status, disease classification, time since most recent acute episode, and number of acute UC episodes. Although not statistically significant, there was some non-homogeneity evident with regard to country, race, disease classification, and number of acute UC episodes. However, no discernable trends or conclusions could be identified based on these analyses.

Secondary efficacy analyses of SPD476 demonstrated that SPD476 achieved a similarly high proportion of subjects in endoscopic remission (maintenance of mucosal healing) with no or mild symptoms at 6 months as compared with ASACOL.

Results of analysis of country effect on the proportion of subjects in endoscopic remission (maintenance mucosal healing) at Month 6 for Per Protocol Population are given below.

Analysis of Country Effect on the Proportion of Subjects in Endoscopic Remission (Maintenance of Mucosal Healing) at Month 6 (Per Protocol Population)

	SPD476 2.4g/day QD N=343		ASACOL 1.6g/day divided BID N=336		Difference (%)
Number of subjects in endoscopic remission/Number of subjects (%)					
Asia	13/19	(68.4)	6/17	(35.3)	33.13
Australia/NZ	3/5	(60.0)	3/3	(100.0)	-40.00
Canada	5/11	(45.5)	8/10	(80.0)	-34.55
Central and South America	32/38	(84.2)	24/32	(75.0)	9.21
Eastern Europe	86/101	(85.1)	89/107	(83.2)	1.97
India	55/57	(96.5)	55/62	(88.7)	7.78
Russia	44/48	(91.7)	43/46	(93.5)	-1.81
South Africa	13/15	(86.7)	11/15	(73.3)	13.33
USA	16/21	(76.2)	16/17	(94.1)	-17.93
Western Europe	20/28	(71.4)	19/27	(70.4)	1.06
Odds Ratio (SPD476 – ASACOL)	1.21				
95% CI (SPD476 – ASACOL)	(0.80, 1.82)				
P-value (Breslow Day Test)	0.1154				

Note: Subjects with missing data at Month 6 were assumed to be failures.
Data Source: Table 2.2.1

As seen from Table above, the differences (SPD476- Asacol) for USA were -17.9% for PP analysis. For ITT analysis, the differences (SPD476- Asacol) for USA were -6.8% (See Appendix Table 3). However, due to small sample size, the USA results might not be interpretable.

3.1.1.2.4 Sponsor's Analysis of Secondary Efficacy Parameters

3.1.1.2.4.1 Time to Relapse

The time-to-relapse results were comparable between SPD476 and ASACOL. In the per protocol population, 12.8% of subjects in the SPD476 group withdrew due to relapse compared with 14.6% of subjects in the ASACOL group. There was no statistically significant difference between treatment groups in the time to relapse using the log-rank test for the per protocol population (hazard ratio=0.87; p=0.5116).

3.1.1.2.4.2 Change from Baseline in the Modified UC-DAI Score

There were small mean increases in the modified UC-DAI score from baseline to Month 6 for subjects across both treatment groups in the per protocol population, with somewhat larger mean increases observed from baseline to endpoint for both treatment groups. From baseline to Month 6, the difference in the least squares means between SPD476 and ASACOL was small (-0.01).

3.1.1.2.4.3 Change from Baseline in Stool Frequency and Rectal Bleeding Scores

The changes from baseline in stool frequency and rectal bleeding scores throughout the study were generally comparable between treatment groups, and the majority of subjects had scores of 0 at each timepoint recorded during the study. At baseline, 79.0% of subjects in the SPD476 group and 76.8% of subjects in the ASACOL group were in clinical remission according to the definition used in this study (scores of 0 for rectal bleeding and stool frequency). At Month 6, 69.7% of subjects in the SPD476 group were in clinical remission, which was comparable to those in the ASACOL group (69.3%); the difference in proportions was 0.003.

3.1.1.2.4.4 Endoscopy Score

From baseline to Month 6 for the per protocol population, the proportions of subjects with improvement, same scores, or worsening endoscopy scores were generally comparable between treatment groups. Improvements or same scores were achieved by a slightly higher proportion of subjects in the SPD476 group from baseline to Month 6 (78.7% SPD476 vs. 75.9% ASACOL; difference in the proportions was 0.028).

3.1.1.2.4.5 PGA Score

Similarly, from baseline to Month 6 for the per protocol population, improvements or same PGA scores were achieved by a slightly higher proportion of subjects in the SPD476 group from baseline to Month 6 (78.4% SPD476 vs. 75.3% ASACOL; difference in the proportions was 0.031)

3.1.1.2.4.6 Quality of Life Results

Subjects' QoL was maintained and the results of SPD476 were comparable to those of ASACOL.

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Sample Size Determination

In non-inferiority controlled clinical trials, the sample size will be quadruples, if the non-inferiority margin cuts in half.

Furthermore, if test drug is assumed to be slightly better than active control, sample size can be sharply reduced.

The sponsor initially assumed that the endoscopic remission rate of subjects treated with 1.6g/day ASACOL would be 65% and the endoscopic remission rate of subjects treated with SPD476 would be 70%. The sample size required for 80% power and 10% non-inferiority margin was 153 subjects per treatment group. If it was assumed that the endoscopic remission rates for both groups were 70%, the required sample size would be

330 subjects per group. The sample size would be cut by about 54%, if it was assumed that SPD476 was slight better than the control (1.6g/day ASACOL) (70% vs. 65%).

So, the sponsor made unrealistic assumption to reduce the required sample size without any planning of sample size re-estimation.

3.1.1.3.2 Non-inferiority Margin

The non-inferiority margin should be chosen to be smaller than demonstrated difference between active control and placebo.

The sponsor's pre-specified non-inferiority margin of 10% was obtained by 50% of treatment effect observed on Mesalamine Study without taking consideration of study-to-study variability of treatment effects and 50% discount for "constancy assumption."

Margin of 10% seemed to be too large and might not be acceptable. The internal review of historical studies revealed the margin should be about 4.0.

As per request from this reviewer, the sponsor applied the new FDA non-inferiority guidance, based on Mesalamine Study Group Trial (1996) to obtain that M_1 would be defined as -8.6%. Assuming that maintained at least 50% of M_1, M_2 would be defined -4.3% as the desired non-inferiority margin. .

Furthermore, this reviewer performed meta-analysis for two placebo-controlled studies (Hanauer et. al., Kawkey et. al..,) for Asacol 1.6 g/day. The 6-month maintenance of remission rates for similar dose of Asacol 1.6 g/day for two placebo controlled studies are given below.

6-month Maintenance of Remission Rates

Study	Analysis	Asacol 1.6 g/day	Placebo	Difference	95% CI
Hanauer et al.	ITT	61/87 (70.1%)	42/87 (48.2%)	21.8%	(7.6%, 36.1%)
	Evaluable	38/58 (65.5%)	25/63 (39.7%)	25.8%	(8.6%, 43.0%)
Hawkey et al.	ITT[a]	59/99 (59.6%)	45/111 (40.5%)	19.1%	(5.8%, 32.4%)
	Evaluable	59/94 (62.8%)	45/105 (42.9%)	19.9%	(6.3%, 33.5%)
Pooled	ITT	120/186 (64.5%)	87/198 (43.9%)	20.6%	(10.8%, 30.3%)
	Evaluable	97/152 (63.8%)	70/168 (41.7%)	22.1%	(11.5%, 32.8%)
Combined	ITT			20.4%	(10.6%, 30.1%)
	Evaluable			22.2%	(11.5%, 32.9%)

[a]Patients excluded in evaluable pop were considered to be non-responder.

For Hanauer's Study, primary efficacy endpoint was treatment outcome. Treatment outcome could be either success, defined as maintenance remission (as indicated by endoscopic evaluation) at the 6-month study visit, or failure, defined as endoscopy relapse at any time during the study or withdrawal due to an adverse event.

For Hawkey's Study, the primary efficacy endpoint was maintenance of remission. Patients were considered to have a relapse if they were found to have a sigmoidoscopic score of 1 or more or experienced 3 consecutive days of rectal bleeding caused by ulcerative colitis or liquid stools for 1 week.

The primary efficacy endpoint for Hawkey's study was not the same as that for Hanauer's study. Therefore, these two studies should not be combined. If only Hanauer's study was used to determine the non-inferiority margin, non-inferiority margin would be 7.6%/2 = 3.8% for ITT analysis which was less than (4.3%) for evaluable analysis.

So the desired non-inferiority marginal should be in range of 3.8% to 4.3%.

3.1.1.3.3 Intent-to-Treat and Per Protocol Populations

The advantages of Intent to Treat population are to ensure, on average, comparable treatment groups at baseline and to prevent bias by subjective removal of subjects.

To avoid various biases, the draft guidance "Guidance for Industry Non-inferiority Clinical Trails" suggests to conduct both ITT and as-treated analyses in non-inferiority trials.

PP analysis was prone to selection bias. So, it was deemed not a good alternative.

The sponsor pre-specified per protocol analysis as primary analysis for primary efficacy endpoint. However, for the non-inferiority analysis, the analysis of the primary efficacy endpoint should be conducted on both Intent-to-Treat and per-protocol analyses.

ICH E-9 recommends using both per protocol and ITT analyses. So, the non-inferiority criteria should be satisfied for both the ITT and PP datasets for the study to be considered successful. .

3.1.1.3.4 Timeline for Protocol Amendment

Per request from this reviewer, the sponsor provides the following timeline for protocol amendment.

- Study initiated on 4/8/2005 – 410 subjects, (March 2005 – September 2006)
- Amendment 2 on 3/20/07 – revised clinical assumption
- Study extended to enrolled additional 416 patients (March 2005 to February 2009)
- Protocol amendment submitted to FDA on 4/23/2007
- Study completed on 9/7/2009
- Protocol finalized on 9/14/2009
- SAP finalized on 9/17/2009

Study was initiated on April 8, 2005 to enroll 410 subjects. Amendment 2 was made on March 20, 2007 to revise clinical assumption based on ITT population instead of PP population and to enroll additional 416 patients.

Protocol amendment was submitted to FDA on April 23, 2007. Study was completed on September 7, 2009. Protocol was finalized a week later on September 14, 2009. Statistical Analysis Plan (SAP) was finalized a few days later on September 17, 2009.

It was found that there was a huge gap for date of first dose of study medication from July 20, 2006 to Nov 22, 2007. No patients were enrolled for more than 16 months. 419 patients enrolled before 7/20/2006 and were randomized, 3 of them did not take drug. 410 patients were enrolled and randomized after 7/20/2006. This study should be divided two phases: phase 1 first 419 patients; phase 2 remaining 410 patients.

As request, the sponsor submitted the response to information request to explain the reasons for the 16 month delay in enrollment. Appendix Table 4 provided reasons for the 16-month delay in enrollment included time to assess the availability of countries, study sites for participation in phase 2 of enrollment, the remanufacturing of placebo-match ASACOL tablets, study medication labeling activities, and a transition of study management to a new Contract Research Organization (CRO).

3.1.1.3.5 Increase of Sample Size

The increase of sample is not based on information from a study external source. It should be considered as unplanned sample size adjustment.

Addition of 416 patients was unjustified. If it was assumed the response rates were 70%, for both treatment groups, the sample size for each treatment should be 330. So, the increase of sample size should be 125 per group which was much less than 208 per group as planned. Furthermore, protocol was amended when only 39 patients were still going.

It was difficult to interpret results from a single non-inferiority study with sample size doubled from proposed sample size in origin study design.

Sample size increased from 410 to 826 during the trial due to change to clinical assumption. It is unclear when the sponsor re-evaluated the endoscopic remission rate and made protocol amendment to extend the study in terms of number of subjects enrolled. This adaptive sample size adjustment was unplanned and should be considered as post-hoc. The impact of adaptive sample size adjustment on the primary efficacy endpoint should be evaluated. Some statistical method used for adjusting for adaptive sample size adjustment might be needed.

3.1.1.3.6 Subject Disposition by Phase

Per this reviewer's request, the sponsor performed analysis of subject disposition by phase. The results are given below.

Subject Disposition by Phase of Enrollment (All Subjects)

	SPD476 2.4g/day QD		ASACOL 1.6g/day divided BID		Overall	
	n	(%)	n	(%)	n	(%)
Phase 1 of Enrollment						
Subjects Randomized	209		209		418	
Subjects Completed	170	(81.3)	173	(82.8)	343	(82.1)
Subjects Who Discontinued Early	39	(18.7)	36	(17.2)	75	(17.9)
Lack of Efficacy	30	(14.4)	27	(12.9)	57	(13.6)
Adverse Event/SAE	3	(1.4)	3	(1.4)	6	(1.4)
Patient Request	2	(1.0)	3	(1.4)	5	(1.2)
Lost to Follow-up	3	(1.4)	2	(1.0)	5	(1.2)
Protocol Violation	1	(0.5)	0		1	(0.2)
Pregnancy	0		1	(0.5)	1	(0.2)
Phase 2 of Enrollment						
Subjects Randomized	207		204		411	
Subjects Completed	170	(82.1)	157	(77.0)	327	(79.6)
Subjects Who Discontinued Early	37	(17.9)	47	(23.0)	84	(20.4)
Lack of Efficacy	20	(9.7)	30	(14.7)	50	(12.2)
Patient Request	8	(3.9)	3	(1.5)	11	(2.7)
Lost to Follow-up	2	(1.0)	8	(3.9)	10	(2.4)
Protocol Violation	2	(1.0)	3	(1.5)	5	(1.2)
Adverse Event/SAE	3	(1.4)	0		3	(0.7)
Non-compliance	0		1	(0.5)	1	(0.2)
Other[a]	2	(1.0)	2	(1.0)	4	(1.0)
Results of Study Overall						
Subjects Randomized	416		413		829	
Subjects Completed	340	(81.7)	330	(79.9)	670	(80.8)
Subjects Who Discontinued Early	76	(18.3)	83	(20.1)	159	(19.2)
Lack of Efficacy	50	(12.0)	57	(13.8)	107	(12.9)
Patient Request	10	(2.4)	6	(1.5)	16	(1.9)
Lost to Follow-up	5	(1.2)	10	(2.4)	15	(1.8)
Adverse Event/SAE	6	(1.4)	3	(0.7)	9	(1.1)
Protocol Violation	3	(0.7)	3	(0.7)	6	(0.7)
Non-compliance	0		1	(0.2)	1	(0.1)
Pregnancy	0		1	(0.2)	1	(0.1)
Other[a]	2	(0.5)	2	(0.5)	4	(0.5)

[a] Other reasons for withdrawal included Subject 20414 (SPD476) who did not come back for a subsequent visit, Subject 62601 (SPD476) who used prohibited corticosteroids for an asthma attack while hospitalized, Subject 19619 (ASACOL) who was discontinued due to a lack of investigational product at the center, and Subject 50002 (ASACOL) who withdrew consent.

BID=twice daily; QD=once daily; SAE=serious adverse event.

Data Source: Table 1.1

As seen from table above, more Asacol subjects who discontinued early as compared to SPD476 (47 vs. 37) in phase 2. It was also observed that more Asacol subjects who discontinued early due to lack of efficacy as compared to SPD476 (30 vs. 20) in phase 2.

3.1.1.3.7 Demographic Characteristics by Phase

Per this reviewer's request, the sponsor performed analysis of demographic characteristics by phase for safety population. The results are given below.

Demographic Characteristics by Phase of Enrollment (Safety Population)

	SPD476 2.4g/day QD		Asacol 1.6g/day divided BID		Overall	
	n	(%)	n	(%)	n	(%)
Phase 1 of Enrollment						
Number of Subjects	208		208		416	
Sex						
Male	101	(48.6)	114	(54.8)	215	(51.7)
Female	107	(51.4)	94	(45.2)	201	(48.3)
Ethnic Origin						
Caucasian	154	(74.0)	156	(75.0)	310	(74.5)
Asian/Pacific Islander	42	(20.2)	40	(19.2)	82	(19.7)
Hispanic	5	(2.4)	6	(2.9)	11	(2.6)
Black	4	(1.9)	1	(0.5)	5	(1.2)
Other	3	(1.4)	5	(2.4)	8	(1.9)
Age						
Mean (SD)	44.2	(13.52)	45.5	(13.44)	44.9	(13.48)
Median	44.0		45.5		45.0	
Min - Max	18–80		18–85		18–85	
Phase 2 of Enrollment						
Number of Subjects	207		203		410	
Sex						
Male	111	(53.6)	100	(49.3)	211	(51.5)
Female	96	(46.4)	103	(50.7)	199	(48.5)
Ethnic Origin						
Caucasian	118	(57.0)	103	(50.7)	221	(53.9)
Asian/Pacific Islander	61	(29.5)	66	(32.5)	127	(31.0)
Hispanic	14	(6.8)	17	(8.4)	31	(7.6)
Black	5	(2.4)	3	(1.5)	8	(2.0)
Other	9	(4.3)	14	(6.9)	23	(5.6)
Age						
Mean (SD)	45.9	(14.55)	44.8	(13.46)	45.3	(14.01)
Median	46.0		45.0		45.0	
Min-Max	18–85		19–76		18–85	

BID=twice daily; Max=maximum; Min=minimum; QD=once daily; SD=standard deviation.
Data Source: Table 1.2.1

As seen from table above, about 20% less Caucasian subjects were enrolled in phase 2 as compared to phase 1 (54% vs. 75%). More Asian and Hispanic subjects were enrolled in phase 2.

So, study population for phase 1 might be different from that for phase 2.

In the phase 2, it was also observed that more SPD476 subjects had prohibited concomitant medication as compared to Asacol subjects (13 vs. 2). More SPD476 had ≥7 number of acute episodes since diagnosis as compared to Asacol subjects (43 vs. 28).

3.1.1.3.8 Primary Analysis of Primary Efficacy Endpoint

Per this reviewer's request, the sponsor performed analysis of primary efficacy endpoint by phase of enrollment for ITT and Per Protocol populations.

The results for ITT and Per Protocol populations are given below.

Analysis of the Proportion of Subjects in Endoscopic Remission at Month 6
ITT Population

	SPD476	Asacol	Diff (SPD476 – Asacol)	95% C.I.
Phase 1	163/208 (78.4%)	165/208 (79.3%)	-1.0%	(-9.3%, 7.4%)
Phase 2	160/207 (77.3%)	151/203 (74.4%)	2.9%	(-5.9%, 11.7%)
Overall	323/415 (77.8%)	316/411 (76.9%)	0.9%	(-5.0%, 7.0%)

Compiled from Table 8
CI was calculated using the normal approximation to the binomial distribution

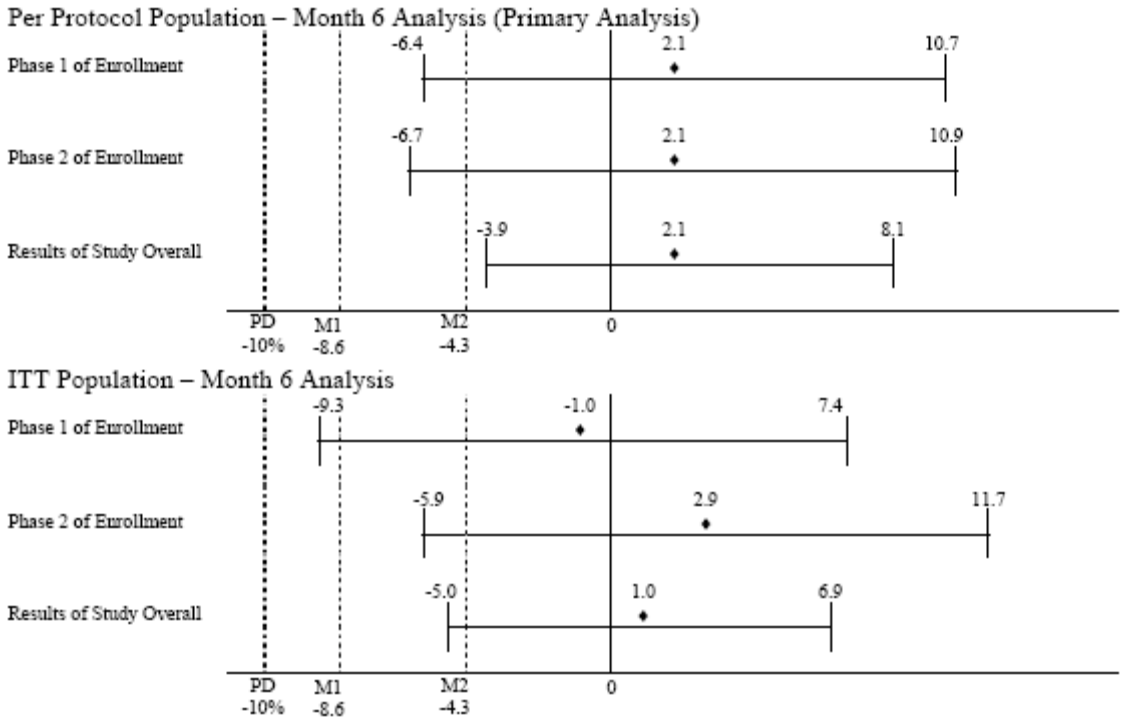
Analysis of the Proportion of Subjects in Endoscopic Remission at Month 6
Per Protocol Population

	SPD476	Asacol	Diff (SPD476 – Asacol)	95% C.I.
Phase 1	148/178 (83.1%)	145/179 (81.0%)	2.1%	(-6.4%, 10.7%)
Phase 2	139/165 (84.2%)	129/157 (82.2%)	2.1%	(-6.7%, 10.9%)
Overall	287/343 (83.7%)	274/336 (81.5%)	2.1%	(-4.0%, 8.0%)

Compiled from Table 7
CI was calculated using the normal approximation to the binomial distribution

The sponsor also provided plots for endoscopic remission by phase for Per Protocol and ITT populations. The detailed plots are given below.

Figure: Endoscopic Remission (Maintenance of Mucosal Healing) by Phase of Enrollment: SPD476 – ASA (Difference, 95% CI)



As seen from figure above, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 for endoscopic remission at month 6 for both ITT and PP analyses. The lower limits of the 95% CIs for the difference between SPD476 and Asacol were less than non-inferiority clinical margin M_2 (-4.3%) for both phases 1 and 2 for both ITT and PP analyses. Furthermore, phase 1 ITT analysis also failed to meet non-inferiority criteria (M_1).

For overall, PP analysis just barely met the non-inferiority criterion ($M_{2)}$, but ITT analysis failed to meet non-inferiority criterion.

3.1.1.3.8.1 Intent-to-Treat vs. Per Protocol Analyses

There were 30 SPD476 treated and 29 Asacol treated subjects were excluded from PP population in phase 1. In phase 2, 42 SPD476 treated and 46 Asacol treated subjects were excluded from PP population.

Analyses of the Proportion of Subjects in Endoscopic Remission at Month 6
ITT Population vs. PP Population

	Phase 1		Phase 2	
Analysis	SPD476	Asacol	SPD476	Asacol
ITT	163/208 (78.4%)	165/208 (79.3%)	160/207 (77.3%)	151/203 (74.4%)
PP	148/178 (83.1%)	145/179 (81.0%)	139/165 (84.2%)	129/157 (82.2%)
Excluded From PP	15/30 (50.0%)	20/29 (69.0%)	21/42 (50.0%)	22/46 (47.8%)

Compiled by this reviewer

As seen table above, in the phase 1, more subjects who had endoscopic remission at Month 6 in Asacol treated group were excluded from PP population as compared to SPD476 treated group. No difference was observed in the phase 2.

So, results from PP analysis might be biased in favor of SPD476. in the phase 1.

3.1.1.3.8.2 "True" Intent-to-Treat Analysis

This reviewer also performed "true" ITT analysis including all randomized subjects. The results are given below.

Analysis of the Proportion of Subjects in Endoscopic Remission at Month 6
"true" ITT Population

	SPD476	Asacol	Diff (SPD476 – Asacol)	95% C.I.
Phase 1	163/209 (78.0%)	165/210 (78.6%)	-0.6%	(-8.5%, 7.3%)
Phase 2	160/207 (77.3%)	151/203 (74.4%)	2.9%	(-5.4%, 11.2%)
Overall	323/416 (77.6%)	316/413 (76.5%)	1.1%	(-4.6%, 6.9%)
Combined				(-4.6%, 6.8%)

Compiled by this reviewer.
CI for combined was obtained using DerSimonian and Laird (1986).

As seen from table above, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 of -4.3% for endoscopic remission at month 6 for "true" ITT analysis. The lower limits of the 95% CIs for the difference between SPD476 and Asacol were less than non-inferiority clinical margin M_2 (-4.3%) for both phases for "true" ITT analysis. However, both phase 1 and phase 2 met non-inferiority criteria M_1 (-8.6%).

Furthermore, for overall, "true" ITT analysis was close to meet non-inferiority criterion M_2 (-4.3%).

Meta analysis was used to combine phase 1 and phase 2, it resulted 95% C.I. of (-4.6%, 6.8%). The combined phase 1 and phase 2 "true" ITT analysis was also close to meeting non-inferiority criterion M_2 (-4.3%).

3.1.1.3.8.1 Treatment by Country Interaction

Only 38 US patients (5.6%) were enrolled in this study. The results showed that the differences (SPD476- Asacol) for US were -6% and -18% for ITT and Per Protocol populations, respectively. But, due to small sample size, US results might not be interpreted

As this reviewer's request, the sponsor performed analysis of country effect on primary efficacy endpoint by phase for Per Protocol population.

The results are given below.

Analysis of Country Effect on the Proportion of Subjects in Endoscopic Remission (Maintenance of Mucosal Healing) at Month 6 (Per Protocol Population)

	SPD476 2.4g/day QD		ASACOL 1.6g/day divided BID		Difference (%)
Number of subjects in endoscopic remission/Number of subjects (%)					
Phase 1 of Enrollment					
Number of Subjects	178		179		
Asia	8/10	(80.0)	2/7	(28.6)	51.43
Canada	0/3	(0.0)	3/3	(100.0)	-100.00
Central and South America	15/19	(78.9)	9/13	(69.2)	9.72
Eastern Europe	43/51	(84.3)	43/54	(79.6)	4.68
India	20/22	(90.9)	24/28	(85.7)	5.19
Russia	44/48	(91.7)	43/46	(93.5)	-1.81
USA	6/9	(66.7)	7/8	(87.5)	-20.83
Western Europe	12/16	(75.0)	14/20	(70.0)	5.00
Odds Ratio (SPD476 – ASACOL)	1.20				
95% CI (SPD476 – ASACOL)	(0.70, 2.08)				
p-value (Breslow-Day Test)	0.0890				
Phase 2 of Enrollment					
Number of Subjects	165		157		
Asia	5/9	(55.6)	4/10	(40.0)	15.56
Australia/New Zealand	3/5	(60.0)	3/3	(100.0)	-40.00
Canada	5/8	(62.5)	5/7	(71.4)	-8.93
Central and South America	17/19	(89.5)	15/19	(78.9)	10.53
Eastern Europe	43/50	(86.0)	46/53	(86.8)	-0.79
India	35/35	(100.0)	31/34	(91.2)	8.82
South Africa	13/15	(86.7)	11/15	(73.3)	13.33
USA	10/12	(83.3)	9/9	(100.0)	-16.67
Western Europe	8/12	(66.7)	5/7	(71.4)	-4.76
Odds Ratio (SPD476 – ASACOL)	1.21				
95% CI (SPD476 – ASACOL)	(0.65, 2.24)				
p-value (Breslow-Day Test)	0.3990				

As seen from table above, the differences (SPD476- Asacol) for USA were -20.8% and -6.7% for phase 1 and phase 2, respectively, for PP analysis. But, due to small sample size, the USA results might not be interpretable.

The sponsor also performed analysis of country effect on primary efficacy endpoint by phase for ITT population.

The results are given below.

Analysis of Country Effect on the Proportion of Subjects in Endoscopic Remission (Maintenance of Mucosal Healing) at Month 6 (ITT Population)

	SPD476 2.4g/day QD		ASACOL 1.6g/day divided BID		Difference (%)
Number of subjects in endoscopic remission/Number of subjects (%)					
Phase 1 of Enrollment					
Number of Subjects	208		208		
Asia	8/11	(72.7)	2/7	(28.6)	44.16
Canada	1/6	(16.7)	5/6	(83.3)	-66.67
Central and South America	16/21	(76.2)	17/22	(77.3)	-1.08
Eastern Europe	47/58	(81.0)	47/61	(77.0)	3.99
India	25/31	(80.6)	27/32	(84.4)	-3.73
Russia	45/51	(88.2)	45/49	(91.8)	-3.60
USA	7/11	(63.6)	8/10	(80.0)	-16.36
Western Europe	14/19	(73.7)	14/21	(66.7)	7.02
Odds Ratio (SPD476 – ASACOL)	0.96				
95% CI (SPD476 – ASACOL)	(0.60, 1.55)				
p-value (Breslow-Day Test)	0.1664				
Phase 2 of Enrollment					
Number of Subjects	207		203		
Asia	6/10	(60.0)	4/11	(36.4)	23.64
Australia/New Zealand	6/8	(75.0)	4/5	(80.0)	-5.00
Canada	5/9	(55.6)	6/8	(75.0)	-19.44
Central and South America	22/26	(84.6)	23/29	(79.3)	5.31
Eastern Europe	44/57	(77.2)	49/59	(83.1)	-5.86
India	42/50	(84.0)	35/51	(68.6)	15.37
South Africa	14/18	(77.8)	12/17	(70.6)	7.19
USA	11/13	(84.6)	10/12	(83.3)	1.28
Western Europe	10/16	(62.5)	8/11	(72.7)	-10.23
Odds Ratio (SPD476 – ASACOL)	1.19				
95% CI (SPD476 – ASACOL)	(0.75, 1.89)				
p-value (Breslow-Day Test)	0.6373				

As seen from table above, the differences (SPD476- Asacol) for USA were -16.4% and 1.3% for phase 1 and phase 2, respectively, for ITT analysis. But, due to small sample size, the USA results might not be interpretable.

This reviewer performed "true" ITT analysis for USA. The results are given below.

Analysis of the Proportion of Subjects in Endoscopic Remission at Month 6 for USA "true" ITT Population

	SPD476	Asacol	Diff (SPD476 – Asacol)	95% C.I.
Phase 1	7/12 (58.3%)	8/10 (80.0%)	-21.7%	(-59.0%, 15.7%)
Phase 2	11/13 (84.6%)	10/12 (83.3%)	1.3%	(-27.5%, 30.1%)
Combined				(-30.1%, 15.5%)

Compiled by this reviewer

As seen from table above, the differences (SPD476- Asacol) for USA were -21.7% and 1.3% for phase 1 and phase 2, respectively, for "true" ITT analysis. But, due to small sample size, the USA results might not be interpretable.

3.1.1.3.8.2 Subgroup Analyses

Subgroup analyses of proportion of subjects in endoscopic remission at Month 6 by phase for gender, age (<55 vs. ≥55), race (Caucasian vs. non Caucasian), smoking, disease, time since recent acute episode, and acute episodes. Results from subgroup analyses are given in Appendix Table 5.

3.1.1.3.9 Analyses of Secondary Efficacy Endpoints

3.1.1.3.9.1 Time to Relapse

Relapse was defined as withdrawal from the study due to lack of efficacy. Subjects who withdrew for any other reason were censored at the date of their withdrawal. Subjects who completed the study were censored at the date of their study completion. The time to relapse was estimated as the time from the date of randomization to the date that the subject withdrew due to relapse.

Analysis of the time to relapse is summarized by phase of enrollment for the ITT Population is given below.

Analysis of the Time to Relapse by Phase of Enrollment (ITT Population)

	SPD476 2.4g/day QD	ASACOL 1.6g/day divided BID
Phase 1 of Enrollment		
Number of Subjects	208	208
Subjects who withdrew due to relapse (n, %)	31 (14.9)	27 (13.0)
Subjects censored[a] (n, %)	177 (85.1)	181 (87.0)
Hazard Ratio (SPD476 versus ASACOL)[b]		1.15
95% CI		(0.69, 1.93)
p-value (log-rank test)		0.5869
Phase 2 of Enrollment		
Number of Subjects	207	203
Subjects who withdrew due to relapse (n, %)	20 (9.7)	30 (14.8)
Subjects censored[a] (n, %)	187 (90.3)	173 (85.2)
Hazard Ratio (SPD476 versus ASACOL)[b]		0.66
95% CI		(0.37, 1.15)
p-value (log-rank test)		0.1398
Results of Study Overall		
Number of Subjects	415	411
Subjects who withdrew due to relapse (n, %)	51 (12.3)	57 (13.9)
Subjects censored[a] (n, %)	364 (87.7)	354 (86.1)
Hazard Ratio (SPD476 versus ASACOL)[b]		0.89
95% CI		(0.61, 1.30)
p-value (log-rank test)		0.5455

[a] Subjects were censored at their date of withdrawal or completion if they did not withdraw due to lack of efficacy.
[b] Calculated using the Cox proportional hazards model.
BID=twice daily; QD=once daily.
Data Source: Table 2.5.2 and Figure 2

As seen from table above, in the ITT Population for Phase 1 of enrollment, 14.9% of subjects in the SPD476 group withdrew due to relapse compared with 13.0% of

subjects in the ASACOL group. For Phase 2 of enrollment, 9.7% of subjects in the SPD476 group withdrew due to relapse compared with 14.8% of subjects in the ASACOL group.

Kaplan-Meier curves showed that for the time to relapse by phase of enrollment for the ITT Population, there was no statistically significant difference between treatment groups in the time to relapse using the log-rank test for the ITT Population (p=0.5869 and p=0.1398 for Phase 1 and Phase 2 of enrollment, respectively).

3.1.1.3.9.2 Change from Baseline in the Modified UC-DAI Score

The modified Ulcerative Colitis Disease Activity Index (UC-DAI) consists of 4 individual parameters (stool frequency, rectal bleeding, endoscopy score [mucosal appearance], and Physician's Global Assessment; PGA), and each of these 4 parameters were assessed individually on a scale of 0-3, with a higher score indicative of more severe UC.

A summary of the modified UC-DAI score by phase of enrollment for the ITT population is given below.

Change from Baseline in Modified UC-DAI Score by Phase of Enrollment (ITT Population)

Timepoint/Statistics	SPD476 2.4g/day QD	ASACOL 1.6g/day divided BID	Overall
Phase 1 of Enrollment			
Number of Subjects	208	208	416
Month 6			
n	167	170	337
Mean (SD)	0.080 (1.0485)	0.120 (1.3512)	0.100 (1.2091)
Median	0.000	0.000	0.000
Min-Max	-2.00 – 5.67	-3.00 – 7.00	-3.00 – 7.00
Endpoint			
n	194	195	389
Mean (SD)	0.717 (2.0742)	0.801 (2.3139)	0.759 (2.1952)
Median	0.000	0.000	0.000
Min-Max	-2.00 – 9.00	-3.00 – 9.67	-3.00 – 9.67
Phase 2 of Enrollment			
Number of Subjects	207	203	410
Month 6			
n	164	152	316
Mean (SD)	0.089 (1.4147)	-0.050 (1.1372)	0.022 (1.2886)
Median	0.000	0.000	0.000
Min-Max	-3.00 – 10.00	-2.33 – 5.00	-3.00 – 10.00
Endpoint			
n	185	176	361
Mean (SD)	0.602 (2.2243)	0.803 (2.5264)	0.700 (2.3752)
Median	0.000	0.000	0.000
Min-Max	-3.00 – 11.00	-2.33 – 11.00	-3.00 – 11.00

Analysis of the change from baseline to Month 6 in the modified UC-DAI score by phase of enrollment for the ITT population is summarized below.

Analysis of the Change from Baseline to Month 6 in Modified UC-DAI Score by Phase of Enrollment (ITT Population)

		SPD476 2.4g/day QD	ASACOL 1.6g/day divided BID
Phase 1 of Enrollment			
Number of Subjects		208	208
Month 6	n (%)	167 (80.3)	170 (81.7)
	Least squares mean of change from baseline	0.067	0.132
	Difference in least squares mean (SPD476 – ASACOL)[a]		-0.07
	95% CI		(-0.31, 0.18)
Phase 2 of Enrollment			
Number of Subjects		207	203
Month 6	n (%)	164 (79.2)	152 (74.9)
	Least squares mean of change from baseline	0.104	-0.066
	Difference in least squares mean (SPD476 – ASACOL)[a]		0.17
	95% CI		(-0.11, 0.45)

As seen from Table above, the differences in the least squares mean between SPD476 and ASACOL from baseline to Month 6 were small for both phases of enrollment, indicating comparable changes from baseline in modified UC-DAI scores between treatment groups for both phases.

3.1.1.3.9.3 Change from Baseline in Stool Frequency and Rectal Bleeding Scores

The stool frequency scores reflect the number of stools more than normal each day and were assessed on a scale from 0-3 (0 = normal, 1 = 1-2 more than normal per day, 2 = 3-4 more than normal per day, and 3 ≥ 4 more than normal per day).

A summary of the average stool frequency score by phase of enrollment for the ITT population is given in Appendix Table 6.

As seen from Appendix Table 6, for both phases of enrollment, the changes from baseline in stool frequency scores throughout the study were generally comparable between treatment groups, and the majority of subjects had a stool frequency score of 0 at each timepoint recorded during the study.

The average stool frequency score at baseline was similar between treatment groups and between the 2 phases of enrollment. Among subjects enrolled during Phase 1, 82.7 of subjects in the SPD476 group at baseline had a stool frequency score of 0 compared with 81.3 of subjects in the ASACOL group. Among subjects enrolled during Phase 2, 80.7 of subjects in the SPD476 group at baseline had a stool frequency score of 0 compared with 75.9% of subjects in the ASACOL group.

The average stool frequency score at Month 6 was also similar between treatment groups and between phases of enrollment. Among subjects enrolled during Phase 1, 76.9% of subjects in the SPD476 group had a stool frequency score of 0 compared with 72.6% of subjects in the ASACOL group. There were 3 (1.7%) subjects in each treatment group who had a stool frequency score of 3 at endpoint for Phase 1 of enrollment. Among subjects enrolled during Phase 2, a somewhat smaller proportion of subjects in the SPD476 group (65.2%) had a stool frequency score of 0 at Month 6 than that observed for Phase 1 of enrollment. However, there were 0 (0%) subjects in either treatment group who had a stool frequency score of 3 at Month 6 for Phase 2 of enrollment.

Rectal bleeding was assessed on a scale from 0-3 (0 = no rectal bleeding, 1 = streaks of blood, 2 = obvious blood, 3 = mostly blood).

A summary of the average rectal bleeding score by phase of enrollment for the ITT population is provided in Appendix Table 7.

As seen from Appendix Table 7, the changes from baseline in rectal bleeding scores throughout the study were generally comparable between treatment groups among subjects by phase of enrollment, and the majority of subjects had a rectal bleeding score of 0 at each timepoint recorded during the study. At baseline, the vast majority of subjects in both treatment groups had a rectal bleeding score of 0 (92.3% SPD476 and 92.8% ASACOL for Phase 1 of enrollment; 94.2% SPD476 and 95.6% ASACOL for Phase 2 of enrollment). At Month 6 among subjects enrolled during Phase 1, 74.5% of subjects in the SPD476 group had a rectal bleeding score of 0 compared with 76.4% of subjects in the ASACOL group. Similarly, at Month 6 among subjects enrolled during Phase 2, 72.5% of subjects in the SPD476 group had a rectal bleeding score of 0 compared with 70.9% of subjects in the ASACOL group.

3.1.1.3.9.4 Endoscopy Score

An endoscopy was performed at baseline and the end of study, and mucosal appearance was scored on a scale from 0-3, with 0 = normal (intact vascular pattern; no friability or granulation), 1 = mild (erythema, decreased vascular pattern, minimal granularity), 2 = moderate (marked erythema, granularity, friability, absent vascular pattern, bleeding with minimal trauma, no ulcerations), and 3 = severe (ulceration, spontaneous bleeding).

Analysis of the endoscopy score by phase of enrollment for the ITT Population is given in Appendix Table 8.

As seen from Appendix Table 8, from baseline to Month 6 for the ITT Population, the proportions of subjects with improvement, same scores, or worsening scores were generally comparable between treatment groups for both phases of enrollment. For Phase 1 of enrollment, improvements or same scores were achieved by a higher proportion of subjects in the SPD476 group from baseline to Month 6 (72.6% SPD476 vs. 71.6% ASACOL). For Phase 2 of enrollment, improvement or same scores were achieved by

comparable proportions of subjects in each treatment group (72.9% SPD476 vs. 71.9% ASACOL).

3.1.1.3.9.5 PGA Score

The PGA was performed at baseline and the end of study and was scored on a scale from 0-3, with 0 = no active disease, 1 = mild disease, 2 = moderate disease, and 3 = severe disease. Analysis of the PGA score by phase of enrollment for the ITT Population is given in Appendix Table 9.

As seen from Appendix Table 9, for both phases of enrollment for the ITT Population, improvements or same scores were achieved by a slightly higher proportion of subjects in the SPD476 group compared with the ASACOL group from baseline to Month 6 (74.0% SPD476 versus 73.6% ASACOL for Phase 1 of enrollment; 72.0% SPD476 versus 69.5% ASACOL for Phase 2 of enrollment).

3.2 Evaluation of Safety

3.2.1 Study SPD476-304

Of the 415 subjects in the SPD476 group, 154 (37.1%) had at least 1 TEAE, compared with 148/411 (36.0%) subjects in the ASACOL group. Nine subjects had TEAEs that were serious (6 subjects in the SPD476 group and 3 subjects in the ASACOL group); none of the SAEs were considered by the investigator to be related to treatment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup analyses of proportion of subjects in endoscopic remission at Month 6 by phase for gender, age (<55 vs. ≥55), and race (Caucasian vs. non Caucasian), Results from subgroup analyses are given in Appendix 10.

4.2 Other Special/Subgroup Population

Subgroup analyses of proportion of subjects in endoscopic remission at Month 6 by phase by countries. Result from this subgroup analysis is given below.

Analysis of Country Effect on the Proportion of Subjects in Endoscopic Remission (Maintenance of Mucosal Healing) at Month 6 (ITT Population)

	SPD476 2.4g/day QD		ASACOL 1.6g/day divided BID		Difference (%)
Number of subjects in endoscopic remission/Number of subjects (%)					
Phase 1 of Enrollment					
Number of Subjects	208		208		
Asia	8/11	(72.7)	2/7	(28.6)	44.16
Canada	1/6	(16.7)	5/6	(83.3)	-66.67
Central and South America	16/21	(76.2)	17/22	(77.3)	-1.08
Eastern Europe	47/58	(81.0)	47/61	(77.0)	3.99
India	25/31	(80.6)	27/32	(84.4)	-3.73
Russia	45/51	(88.2)	45/49	(91.8)	-3.60
USA	7/11	(63.6)	8/10	(80.0)	-16.36
Western Europe	14/19	(73.7)	14/21	(66.7)	7.02
Odds Ratio (SPD476 – ASACOL)	0.96				
95% CI (SPD476 – ASACOL)	(0.60, 1.55)				
p-value (Breslow-Day Test)	0.1664				
Phase 2 of Enrollment					
Number of Subjects	207		203		
Asia	6/10	(60.0)	4/11	(36.4)	23.64
Australia/New Zealand	6/8	(75.0)	4/5	(80.0)	-5.00
Canada	5/9	(55.6)	6/8	(75.0)	-19.44
Central and South America	22/26	(84.6)	23/29	(79.3)	5.31
Eastern Europe	44/57	(77.2)	49/59	(83.1)	-5.86
India	42/50	(84.0)	35/51	(68.6)	15.37
South Africa	14/18	(77.8)	12/17	(70.6)	7.19
USA	11/13	(84.6)	10/12	(83.3)	1.28
Western Europe	10/16	(62.5)	8/11	(72.7)	-10.23
Odds Ratio (SPD476 – ASACOL)	1.19				
95% CI (SPD476 – ASACOL)	(0.75, 1.89)				
p-value (Breslow-Day Test)	0.6373				

As seen from table above, the differences (SPD476- Asacol) for USA were -16.4% and 1.3% for phase 1 and phase 2, respectively, for ITT analysis. But, due to small sample size, the USA results might not be interpretable.

5. SUMMARY AND CONCLUSION

5.1 Statistical Issues and Collective Evidence

The statistical issues listed below were identified at this NDA filing meeting:

- Sample Size increased from 410 to 826 during the trial due to change to clinical assumptions
    - 410, original sample size based on Per Protocol results
    - Protocol amended when only 39 patients still going. Sample size based on ITT results
    - Sample size doubled without justification
- Non-inferiority margin of 10%
    - obtained from meta analysis without 50% discount for assay sensitivity
    - 10% seems to be too large.
    - Not agreed
    - Should be in the range of 3.8% to 4.6% (in house review)
- Enrolled only 38 US patients (5.6%)
    - The results for US was -6% for ITT
    - The results for US was -18% for PP
    - Due to small sample size, US results might not be interpreted

Study was initiated on April 8, 2005 to enroll 410 subjects. Amendment 2 was made on March 20, 2007 to revise clinical assumption based on ITT population instead of PP population and to enroll additional 416 patients.

Protocol amendment was submitted to FDA on April 23, 2007. Study was completed on September 7, 2009. Protocol was finalized a week later on September 14, 2009. Statistical Analysis Plan (SAP) was finalized a few days later on September 17, 2009.

However, this adjustment to sample size was unplanned. This was not adaptation- post hoc adjustment of study. Any traditional analysis might not be trusted. The confidence interval of the traditional analysis cannot be interpreted properly. Without the specific plan for adjustment, it cannot be known what the valid adjustment is.

Since the phase 2 population was different from the phase 1 population; overall results were driven by phase 2, So, only results from the phase 1 could be interpreted statistically.

The sponsor's non-inferiority margin of 10% obtained from the meta analysis without 50% discount for assay sensitivity. Margin of 10% seemed to be too large and might not be acceptable.

As per request from this reviewer, the sponsor applied the new FDA non-inferiority guidance, based on Mesalamine Study Group trial (1996) to obtain that M_1 would be defined as -8.6%. Assuming that maintained at least 50% of M_1, M_2 would be defined

-4.3% as the desired non-inferiority margin. .

For pre-specified primary efficacy endpoint, proportion of subjects in endoscopic remission at Month 6, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 (-4.3%) for both ITT and PP analyses. Furthermore, phase 1 ITT analysis also failed to meet non-inferiority criteria M_1 (--8.6%).

For overall, PP analysis just barely met the non-inferiority criterion ($M_{2)}$, but ITT analysis failed to meet non-inferiority criterion.

Based on this reviewer's "true" ITT analysis including all randomized subjects, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 (-4.3%) but met non-inferiority criteria M_1 (-8.6%). Furthermore, for overall, "true" ITT analysis was close to meet non-inferiority criterion M_2 (-4.3%).

Meta analysis was used to combine phase 1 and phase 2 for the "true" ITT population, it resulted 95% C.I. of (-4.6%, 6.8%), which was also close to meet non-inferiority criterion M_2 (-4.3%).

The differences (SPD476- Asacol) for US were -16.4% and 1.3% for phase 1 and phase 2, respectively, for ITT analysis. But, due to small sample size, the US results might not be interpretable.

5.2 Conclusions and Recommendations

The sponsor submitted a single non-inferiority study (SPD476-304), comparing SPD476 2.4 g/day QD vs. Asacol 1.6 g/day BID for the claim of maintenance of remission, (b) (4) of ulcerative colitis.

The study was initiated on April 8, 2005 to enroll 410 subjects. Amendment 2 was made on March 20, 2007 to revise the clinical assumption of the treatment group response rates based on ITT population instead of PP population and to enroll additional 416 patients.

A protocol amendment was submitted to FDA on April 23, 2007. The study was completed on September 7, 2009, and the protocol was finalized a week later on September 14, 2009. The Statistical Analysis Plan (SAP) was finalized a few days later on September 17, 2009.

However, this adjustment to sample size was not planned prior to the start of the study, and should not be considered an adaptive study design change but a post hoc adjustment of study size. Any traditional analysis might not be trusted. In this reviewer's opinion, the confidence interval of the traditional analysis cannot be interpreted properly. Without a pre-specified plan for adjustment, there is no proper way to correct for a valid adjustment.

Since study population enrolled after the amendment (phase 2) was different from the pre-amendment population (phase 1), and the overall results were driven by phase 2, only the results from the phase 1 can be interpreted statistically.

The sponsor's non-inferiority margin of 10% obtained from the meta analysis did not incorporate a 50% discount for assay sensitivity. The margin of 10% seems to be too large and might not be acceptable.

As requested from this reviewer, the sponsor applied the principles of the FDA non-inferiority guidance, using the Mesalamine Study Group trial (1996) to conclude that marginal M_1 would be defined as -8.6%. Assuming that at least 50% of M_1 should be maintained, M_2 would be defined as -4.3% as the non-inferiority margin preferred by this reviewer.

For the pre-specified primary efficacy endpoint, proportion of subjects in endoscopic remission at Month 6, both phase 1 and phase 2 failed to meet the non-inferiority criteria M_2 (-4.3%) for both ITT and PP analyses. Furthermore, the phase 1 ITT analysis also failed to meet non-inferiority criteria M_1 (--8.6%).

For the overall study population, the non-inferiority criterion (M_2) was just met for the PP analysis, but not for the ITT analysis .

Based on this reviewer's "true" ITT analysis including all randomized subjects, both phase 1 and phase 2 failed to meet non-inferiority criteria M_2 (-4.3%) but met non-inferiority criteria M_1 (-8.6%). However, for the overall population, the "true" ITT analysis was close to meeting the non-inferiority criterion M_2 (-4.3%).

The reviewer's meta analysis was also used to combine phase 1 and phase 2 for the "true" ITT population, it resulted in a 95% C.I. of the treatment group difference (SPD476 – Asacol) of (-4.6%, 6.8%), which was also close to meet non-inferiority criterion M_2 (-4.3%).

The differences (SPD476- Asacol) for US subject were -16.4% and 1.3% for phase 1 and phase 2, respectively, for the ITT analysis. But, due to small sample size (38 subjects), the US results are not interpretable.

In conclusion, this study has shown that non-inferiority was inconclusive based on results from the phase 1 for non-inferiority margin (M_2). However, if the non-inferiority margin (M_1) would be considered "acceptable" as a clinical non-inferiority margin, this study just would meet (albeit marginally) that non-inferiority criterion. However, even these results may not be statistical persuasive given the unplanned increase in sample size. There is the additional issue of this being a single study that requires a higher level of statistical evidence; however, single maintenance trials at nominal significance levels have been utilized previously for this indication.

6 APPENDIX

Table 1 Major Protocol Deviation (ITT Population)

Table 14: Major Protocol Deviations (ITT Population)

Deviation	SPD476 2.4g/day QD N=415		ASACOL 1.6g/day divided BID N=411		Overall N=826	
	N	(%)	N	(%)	N	(%)
Any deviation	72		75		147	
Failed inclusion criteria	31	(7.5)	37	(9.0)	73	(8.8)
Failed exclusion criteria	5	(1.2)	9	(2.2)	14	(1.7)
Compliance <80%	7	(1.7)	10	(2.4)	17	(2.1)
Did not complete study for reasons other than AE or lack of efficacy	19	(4.6)	22	(5.4)	41	(5.0)
Misrandomization	1	(0.2)	3	(0.7)	4	(0.5)
Missing sigmoidoscopy at Month 6	2	(0.5)	1	(0.2)	3	(0.4)
Prohibited concomitant medication[a]	14[b]	(3.4)	3	(0.7)	17[b]	(2.1)
Sigmoidoscopy >7 days after last dose	1	(0.2)	3	(0.7)	4	(0.5)

[a] Subjects who took prohibited concomitant medications are specified as follows.
SPD476 Subjects: Subject 10016 took mesalazine for UC through Day 1 and systemic steroids (betamethasone) for a nasal polyp during the study, Subject 10021 took colitofalk for UC through Day 1, Subject 11908 took sulfasalazine for colitis, , Subject 19931 took mesalazine through Day 1 and again during the study prior to the final sigmoidoscopy, Subject 20304 took mesalazine (Mesacol) for UC, Subject 20313 took mesalazine (Mesacol) for UC through Day 1, Subject 20408 took mesalazine for UC through Day -2, Subject 27605 took mesalazine for rectal bleeding, Subject 50402 took budesonide for rectal bleeding, Subject 51102 took sulfasalazine (Azulfidine) for UC, Subject 53101 took salazopyrine for UC, Subject 60003 took prednisone for an upper respiratory tract infection, Subject 60301 took prednisone for brachial neuritis, Subject 62101 took ASACOL for UC, and Subject 62601 took steroids (hydrocortisone and prednisone [Pulmison]) for asthma. Subject 12127 wastook mesalazine for UC through Day -1
ASACOL Subjects: Subject 10022 took interferon for treatment of multiple sclerosis, Subject 12012 took systemic steroids (dexamethasone) for neck pain, and Subject 14804 took steroids (cortivazol) for sciatalgia.

[b] Subjects 12127 and 20408 were incorrectly included in the source table (Table 1.8) as having taken a prohibited concomitant medication (mesalazine) during the study. However, prior to the database lock, concomitant medication data for these subjects were queried, and it was determined that they discontinued pre-study mesalazine before study medication was administered. Thus, these 2 subjects did not take a prohibited concomitant medication. Subject 12127 was incorrectly excluded from the per protocol analysis set because of this error. However, Subject 20408, who was also excluded from the per protocol analysis set, had a protocol deviation of an inclusion criterion and was appropriately excluded.

Data Source: Table 1.8 and Listing 4.1

Table 2 Demographic Characteristics and Ulcerative History (Safety Population)

Table 9: Demographic Characteristics (Safety Population)

	SPD476 2.4g/day QD N=415		ASACOL 1.6g/day divided BID N=411		Overall N=826	
	N	(%)	N	(%)	N	(%)
Gender						
Male	212	(51.1)	214	(52.1)	426	(51.6)
Female	203	(48.9)	197	(47.9)	400	(48.4)
Ethnic Origin						
Caucasian	272	(65.5)	259	(63.0)	531	(64.3)
Asian/Pacific Islander	103	(24.8)	106	(25.8)	209	(25.3)
Hispanic	19	(4.6)	23	(5.6)	42	(5.1)
Black	9	(2.2)	4	(1.0)	13	(1.6)
Other	12	(2.9)	19	(4.6)	31	(3.8)
Smoking History						
Never Smoked	289	(69.6)	297	(72.3)	586	(70.9)
Previously Smoked	92	(22.2)	73	(17.8)	165	(20.0)
Currently Smokes	34	(8.2)	41	(10.0)	75	(9.1)
Age						
N	415		411		826	
Mean (SD)	45.0	(14.05)	45.2	(13.44)	45.1	(13.74)
Median	45.0		45.0		45.0	
Min - Max	18-85		18-85		18-85	

Data Source: Table 1.2.1

Table 2 Demographic Characteristics and Ulcerative Colitis History (Safety Population) (Continued)

Table 12: Ulcerative Colitis History (Safety Population)

	SPD476 2.4g/day QD N=415		ASACOL 1.6g/day divided BID N=411		Overall N=826	
Duration Since Time of Diagnosis (weeks)						
n	415		411		826	
Median	226.9		231.9		228.7	
Min-Max	2-2301		0[a]-2315		0[a]-2315	
Method of Diagnosis (n, %)						
Sigmoidoscopy	137	(33.0)	135	(32.8)	272	(32.9)
Colonoscopy	337	(81.2)	331	(80.5)	668	(80.9)
Barium Enema	11	(2.7)	13	(3.2)	24	(2.9)
Compatible Histology	412	(99.3)	403	(98.1)	815	(98.7)
Number of Acute Episodes in Last Year (n, %)						
0	0		2	(0.5)	2	(0.2)
1-2	395	(95.2)	393	(95.6)	788	(95.4)
3-4	18	(4.3)	15	(3.6)	33	(4.0)
5-6	2	(0.5)	0		2	(0.2)
≥7	0		1	(0.2)	1	(0.1)
Number of Acute Episodes Since Diagnosis (n, %)						
1-2	132	(32.4)	134	(33.3)	266	(32.8)
3-4	160	(39.2)	143	(35.6)	303	(37.4)
5-6	48	(11.8)	45	(11.2)	93	(11.5)
≥7	68	(16.7)	80	(19.9)	148	(18.3)
Missing	7		9		16	
Full Extent of Disease (cm)						
n	360		359		719	
Median	50.0		50.0		50.0	
Min-Max	15-160		14-190		14-190	
Classification of Most Recent Acute Episode (n, %)						
Left-sided	307	(74.9)	308	(76.4)	615	(75.6)
Involvement of Transverse Colon	21	(5.1)	22	(5.5)	43	(5.3)
Pancolitis	82	(20.0)	73	(18.1)	155	(19.1)
Missing	5		8		13	
Rectal Involvement (n, %)						
Yes	371	(89.8)	358	(88.6)	729	(89.2)
No	42	(10.2)	46	(11.4)	88	(10.8)
Missing	2		7		9	

Table 3 Analysis of Country Effect on the Proportion of Subjects in Endoscopic Remission at Month 6 (ITT Population)

Table 18: Analysis of Country Effect on the Proportion of Subjects in Endoscopic Remission (Maintenance of Mucosal Healing) at Month 6 (ITT Population)

	SPD476 2.4g/day QD N=415		ASACOL 1.6g/day divided BID N=411		Difference (%)
Number of subjects in endoscopic remission/Number of subjects (%)					
Asia	14/21	(66.7)	6/18	(33.3)	33.33
Australia/NZ	6/8	(75.0)	4/5	(80.0)	-5.00
Canada	6/15	(40.0)	11/14	(78.6)	-38.57
Central and South America	38/47	(80.9)	40/51	(78.4)	2.42
Eastern Europe	91/115	(79.1)	96/120	(80.0)	-0.87
India	67/81	(82.7)	62/83	(74.7)	8.02
Russia	45/51	(88.2)	45/49	(91.8)	-3.60
South Africa	14/18	(77.8)	12/17	(70.6)	7.19
USA	18/24	(75.0)	18/22	(81.8)	-6.82
Western Europe	24/35	(68.6)	22/32	(68.8)	-0.18
Odds Ratio (SPD476 – ASACOL)	1.08				
95% CI (SPD476 – ASACOL)	(0.77, 1.50)				
P-value (Breslow Day Test)	0.2621				

Note: Subjects with missing data at Month 6 were assumed to be failures. A CMH test was used to compare the proportion of subjects in endoscopic remission (maintenance of mucosal healing) stratified by pooled country.
Data Source: Table 2.2.2

APPEARS THIS WAY ON ORIGINAL

Table 4 Reason for the 16-month Delay in Enrollment

Activity	Start Date	Planned Completion Date	Actual Completion Date	Comment
FPFV Phase 1			08 Apr 2005	Subject 32701 (Salcedo, USA)
End of Study Planning Meetings	Nov - Dec 2006		01 Dec 2006	The protocol assumed a response rate of 70% for SPD476 and 65% for ASACOL. During planning for the sNDA maintenance submission the new statistician (not the original statistician) reminded the clinical and regulatory team of the clinical assumption of 5% superiority of SPD476 compared to ASACOL used in determining the protocol sample size and the impact if the assumption was not met. None of the current study team members had been involved in the original discussions. Consequently, they were not aware of these assumptions. On 1 Dec 2006, the study team concluded that Shire's Strategy Team, which had responsibility for recommending overall product strategy, needed to be made aware of the clinical assumptions behind the sample size and the potential impact on the study results.
Strategy Team Meeting	05 Dec 2006		05 Dec 2006	The new statistician presented the issue to the Strategy Team, which recommended further examination of the situation to assess the effects of continuing the study with no changes versus amending the study to increase the sample size. There were still several patients ongoing in the study at this time, and the study remained blinded during these discussions.
Maintenance Scenario Planning Meetings	05 Dec 2006		07 Dec 2006	Shire's SPD476 study team (including regulatory, statistics, and clinical) discussed the various scenarios, including amending the study's clinical assumptions and increasing the sample size. The study team was aware that the study data needed to remain blinded if the sample size were to increase.
	12 Dec 2006		12 Dec 2006	Shire Senior Management discussed the various scenarios and asked the SPD476 study team to present additional information at a meeting that included all Shire R&D functions supporting this program (ie, Shire's Development Team Meeting), scheduled for 22 Dec 2006.
Development Team	22 Dec 2006		22 Dec 2006	The Development Team discussed the issues and decided that the clinical assumption of 65% response for subjects receiving ASACOL should be amended to 70%, the same as for SPD476.
Strategy Team Meeting	22 Dec 2006		22 Dec 2006	The Strategy Team approved the recommendation of the R&D Development Team, without unblinding the study. At this point, several patients were still ongoing in the

				study.
Last Patient Last Visit (LPLV) in Clinic for Phase 1			25 Jan 2007	Subject 24822 (Karnafel, Poland). The study remained blinded.
Feasibility Study	Jan 2007	April 2007	April 2007	A feasibility study was conducted to determine site participation in Phase 2 recruitment.
Protocol Amendment 2	21 Jan 2007	09 Mar 2007	20 Mar 2007	Protocol Amendment 2, which outlined the addition of Phase 2 recruitment to the study, was submitted to the FDA on 23 April 2007.
Decision to Manufacture New Supplies	Feb 2007	Feb 2007		Shire made the decision to discard remaining supplies from phase I because the expiry date of study drug was 31 Aug 2007 and the sites would not be activated soon enough to use study drug with this expiry date.
LPLV Phase 1			24 Feb 2007	30 day follow-up visit for LPLV in Phase 1.
ASACOL Placebo Manufacture	15 Feb 2007	May 2007	August 2007	The originally planned start date in May was not met because placebo matching the ASACOL tablet did not meet tablet disintegration specifications and re-manufacture was required. Minor adjustments were made to the equipment/over-encapsulation process, and a new batch was manufactured that passed the disintegration specification. Re-manufacture and over-encapsulation delayed this activity by 3 months to August 2007.
Labeling Approval Process	Mar 2007	Apr 2007	24 Aug 2007	Labeling process for study drug supplies took several months in order to gain advice on new label booklets and updated labeling proof creation and approval for new countries participating in the trial. In addition, labeling for the countries currently participating in the study needed to be updated. The label approval process was initiated with the original CRO and was concluded with the new CRO (see below).
Packaging and Release		Jul 2007	16 Oct 2007	Packaging and release occurred in a timely fashion once labeling proofs were created and reviewed.
CRO Transition	Jun 2007	September 2007	January 2008	The management of the study was transferred from PPD Development to ICON Clinical Research Limited. A protocol amendment (Amendment 3) to change the CRO was written and submitted to FDA on 4 Oct 2007; it was approved by Chesapeake Central IRB on 16 Oct 2007.
FPFV Phase 2			07 Nov 2007	Subject 32907 (Shivakumar, US)
FPFV Randomized Phase 2			21 Nov 2007	Subject 32907. The study remained blinded throughout this process.

Table 5 Subgroup Analyses of Proportion of Subjects in Endoscopic Remission at Month 6 by Phase

Subgroup Analyses of Proportion of Subjects in Endoscopic Remission at Month 6 by Phase (ITT Population)

Subgroup	Phase 1 SPD476	Phase 1 Asacol	Phase 1 Diff (SPD-Asacol)	Phase 1 95% CI	Phase 2 SPD476	Phase 2 Asacol	Phase 2 Diff (SPD-Asacol)	Phase 2 95% CI
Gender								
Male	80/101 (79.2%)	94/114 (82.5%)	-3.3%	(-13.8%, 7.3%)	86/111 (77.5%)	74/100 (74.0%)	3.5%	(-8.1%, 15.1%)
Female	83/107 (77.6%)	71/94 (75.5%)	2.0%	(9.7%, 13.8%)	74/96 (77.1%)	77/103 (74.8%)	2.3%	(-9.6%, 14.2%)
Age								
<55	123/158 (77.8%)	122/155 (78.7%)	-0.9%	(-10.0%, 8.3%)	112/143 (78.3%)	109/151 (72.2%)	6.1%	(-3.7%, 16.0%)
≥55	40/50 (80.0%)	43/53 (81.1%)	-1.1%	(-16.4%, 14.2%)	48/64 (75.0%)	42/52 (80.8%)	-5.8%	(-20.8%, 9.3%)
Race								
Caucasian	124/154 (80.5%)	126/156 (80.8%)	-0.3%	(-9.0%, 8.5%)	86/118 (72.9%)	83/103 (80.6%)	-7.7%	(-18.8%, 3.4%)
Non-Caucasian	39/54 (72.2%)	39/52 (75.0%)	-2.8%	(-19.6%, 14.0%)	74/89 (83.1%)	68/100 (68.0%)	15.2%	(3.1%, 27.2%)
Smoking								
Current or Previous	44/60 (73.3%)	54/65 (83.1%)	-9.7%	(24.2%, 4.7%)	51/66 (77.3%)	37/49 (75.5%)	1.8%	(-14.0%, 17.5%)
Never	119/148 (80.4%)	111/143 (77.6%)	2.8%	(-6.6%, 12.1%)	109/141 (77.3%)	114/154 (74.0%)	3.3%	(-6.5%, 13.1%)
Disease								
Left side	123/157 (78.3%)	126/154 (81.8%)	-3.5%	(-12.3%, 5.4%)	110/150 (73.3%)	115/154 (74.7%)	-1.3%	(-11.2%, 8.5%)
Other	37/47 (78.7%)	37/52 (71.2%)	7.6%	(-9.4%, 24.6%)	50/56 (89.3%)	34/43 (79.1%)	10.22%	(-4.4%, 24.8%)
Time since recent aute episode								
≤ 12 weeks	55/80 (68.8%)	61/78 (78.2%)	-9.5%	(-23.1%, 4.2%)	58/77 (75.3%)	52/78 (66.7%)	8.7%	(-5.6%, 22.9%)
12- 24	57/65 (87.7%)	46/59 (78.0%)	9.7%	(-3.5%, 23.0%)	44/58 (75.9%)	51/60 (85.0%)	-9.1%	(-23.4%, 5.1%)
24-36	36/45 (80.0%)	31/39 (79.5%)	0.5%	(-16.7%, 17.8%)	34/42 (81.0%)	31/42 (73.8%)	7.1%	(-10.7%, 25.0%)
>36	15/18 (83.3%)	26/31 (83.9%)	-0.5%	(-22.1%, 21.0%)	24/30 (80.0%)	17/23 (73.9%)	6.1%	(-16.9%, 29.0%)

Table 5 Subgroup Analyses of Proportion of Subjects in Endoscopic Remission at Month 6 by Phase (continued)

Subgroup Analyses of Proportion of Subjects in Endoscopic Remission at Month 6 by Phase (ITT Population)

Subgroup	Phase 1 SPD476	Phase 1 Asacol	Phase 1 Diff (SPD-Asacol)	Phase 1 95% CI	Phase 2 SPD476	Phase 2 Asacol	Phase 2 Diff (SPD-Asacol)	Phase 2 95% CI
Acute eisodes								
≤2	57/74 (77.0%)	60/71 (84.5%)	-7.5%	(-20.2%, 5.3%)	47/58 (81.0%)	43/63 (68.3%)	12.8%	(-2.5%, 29.1%)
2-4	59/70 (84.3%)	54/70 (77.1%)	7.1%	(-5.9%, 20.2%)	73/90 (81.1%)	53/73 (72.6%)	8.5%	(-4.5%, 21.5%)
4-10	28/40 (70.0%)	34/46 (73.9%)	-3.9%	(-23.0%, 15.1%)	27/39 (69.2%)	40/47 (85.1%)	-15.9%	(-33.6%, 1.8%)
>10	16/21 (76.2%)	13/15 (86.7%)	-10.5%	(-35.5%, 14.6%)	10/16 (62.5%)	13/17 (76.5%)	-14.0%	(-45.1%, 17.2%)

Complied by this reviewer.

Table 6 Summary of Average Stool Frequency Score (ITT Population)

Table 2.7.2 : Summary of Average Stool Frequency Score (ITT Population - Phase I)

		----- SPD476 2.4g/d QD ------		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Number of subjects		208		208		416	
Screening	N	208		208		416	
	Mean	0.046		0.042		0.044	
	SD	0.2085		0.1806		0.1948	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.67		1.00		1.67	
	0	196 (94.2%)		195 (93.8%)		391 (94.0%)	
	>0-<1	6 (2.9%)		7 (3.4%)		13 (3.1%)	
	1-<2	6 (2.9%)		6 (2.9%)		12 (2.9%)	
	2-<3	0		0		0	
	3	0		0		0	
Baseline	N	207		207		414	
	Mean	0.089		0.101		0.095	
	SD	0.2304		0.2626		0.2468	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.33		2.00		2.00	
	0	172 (82.7%)		169 (81.3%)		341 (82.0%)	
	>0-<1	28 (13.5%)		30 (14.4%)		58 (13.9%)	
	1-<2	7 (3.4%)		7 (3.4%)		14 (3.4%)	
	2-<3	0		1 (0.5%)		1 (0.2%)	
	3	0		0		0	

Note: Change denotes change from baseline. The stool frequency scores reflect the number of stools more than normal/day.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

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Table 2.7.2 : Summary of Average Stool Frequency Score (ITT Population - Phase I)

		SPD476 2.4g/d QD		Asacol 1.6g/d BID		Overall	
		Actual	Change	Actual	Change	Actual	Change
Month 1	N	195	194	195	194	390	388
	Mean	0.077	-0.003	0.123	0.019	0.100	0.008
	SD	0.2517	0.2997	0.3447	0.3379	0.3023	0.3192
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.33	0.00	-1.00	0.00	-1.33
	Max	1.67	1.33	2.33	1.67	2.33	1.67
	0	172 (82.7%)		166 (79.8%)		338 (81.3%)	
	>0-<1	16 (7.7%)		17 (8.2%)		33 (7.9%)	
	1-<2	7 (3.4%)		11 (5.3%)		18 (4.3%)	
	2-<3	0		1 (0.5%)		1 (0.2%)	
	3	0		0		0	
Month 3	N	184	183	180	179	364	362
	Mean	0.079	0.006	0.098	-0.004	0.088	0.001
	SD	0.2537	0.3028	0.2899	0.2998	0.2720	0.3009
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.00	0.00	-1.00	0.00	-1.00
	Max	2.50	2.50	2.00	2.00	2.50	2.50
	0	157 (75.5%)		154 (74.0%)		311 (74.8%)	
	>0-<1	24 (11.5%)		18 (8.7%)		42 (10.1%)	
	1-<2	2 (1.0%)		7 (3.4%)		9 (2.2%)	
	2-<3	1 (0.5%)		1 (0.5%)		2 (0.5%)	
	3	0		0		0	

Note: Change denotes change from baseline. The stool frequency scores reflect the number of stools more than normal/day.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.2 : Summary of Average Stool Frequency Score (ITT Population - Phase I)

		----- SPD476 2.4g/d QD ------		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Month 6	N	168	167	171	170	339	337
	Mean	0.085	0.008	0.099	-0.002	0.092	0.003
	SD	0.3117	0.3640	0.2890	0.3130	0.3001	0.3387
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.00	0.00	-1.67	0.00	-1.67
	Max	2.00	2.00	2.00	1.33	2.00	2.00
	0	150 (72.1%)		146 (70.2%)		296 (71.2%)	
	>0-<1	11 (5.3%)		16 (7.7%)		27 (6.5%)	
	1-<2	5 (2.4%)		8 (3.8%)		13 (3.1%)	
	2-<3	2 (1.0%)		1 (0.5%)		3 (0.7%)	
	3	0		0		0	
Endpoint	N	199	198	198	197	397	395
	Mean	0.218	0.136	0.281	0.178	0.249	0.157
	SD	0.5681	0.6165	0.6616	0.6654	0.6166	0.6409
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.33	0.00	-1.67	0.00	-1.67
	Max	3.00	3.00	3.00	3.00	3.00	3.00
	0	160 (76.9%)		151 (72.6%)		311 (74.8%)	
	>0-<1	17 (8.2%)		19 (9.1%)		36 (8.7%)	
	1-<2	13 (6.3%)		16 (7.7%)		29 (7.0%)	
	2-<3	6 (2.9%)		8 (3.8%)		14 (3.4%)	
	3	3 (1.4%)		4 (1.9%)		7 (1.7%)	

Note: Change denotes change from baseline. The stool frequency scores reflect the number of stools more than normal/day.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.2 : Summary of Average Stool Frequency Score (ITT Population - Phase II)

		----- SPD476 2.4g/d QD -----		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Number of subjects		207		203		410	
Screening	N	207		203		410	
	Mean	0.068		0.072		0.070	
	SD	0.2044		0.2279		0.2161	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.00		1.33		1.33	
	0	181 (87.4%)		180 (88.7%)		361 (88.0%)	
	>0-<1	20 (9.7%)		16 (7.9%)		36 (8.8%)	
	1-<2	6 (2.9%)		7 (3.4%)		13 (3.2%)	
	2-<3	0		0		0	
	3	0		0		0	
Baseline	N	206		203		409	
	Mean	0.107		0.138		0.122	
	SD	0.2580		0.2846		0.2717	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.33		1.33		1.33	
	0	167 (80.7%)		154 (75.9%)		321 (78.3%)	
	>0-<1	29 (14.0%)		39 (19.2%)		68 (16.6%)	
	1-<2	10 (4.8%)		10 (4.9%)		20 (4.9%)	
	2-<3	0		0		0	
	3	0		0		0	

Note: Change denotes change from baseline. The stool frequency scores reflect the number of stools more than normal/day.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.2 : Summary of Average Stool Frequency Score (ITT Population - Phase II)

		----- SPD476 2.4g/d QD ------		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Month 1	N	194	194	195	195	389	389
	Mean	0.153	0.043	0.144	0.014	0.148	0.028
	SD	0.3958	0.3867	0.3209	0.3062	0.3598	0.3485
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.33	0.00	-1.00	0.00	-1.33
	Max	3.00	2.67	2.00	2.00	3.00	2.67
	0	156 (75.4%)		153 (75.4%)		309 (75.4%)	
	>0-<1	25 (12.1%)		27 (13.3%)		52 (12.7%)	
	1-<2	11 (5.3%)		14 (6.9%)		25 (6.1%)	
	2-<3	1 (0.5%)		1 (0.5%)		2 (0.5%)	
	3	1 (0.5%)		0		1 (0.2%)	
Month 3	N	179	179	175	175	354	354
	Mean	0.134	0.022	0.120	-0.008	0.127	0.008
	SD	0.3647	0.3682	0.3468	0.3608	0.3555	0.3644
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.33	0.00	-1.33	0.00	-1.33
	Max	2.67	2.33	2.00	2.00	2.67	2.33
	0	149 (72.0%)		148 (72.9%)		297 (72.4%)	
	>0-<1	16 (7.7%)		15 (7.4%)		31 (7.6%)	
	1-<2	12 (5.8%)		11 (5.4%)		23 (5.6%)	
	2-<3	2 (1.0%)		1 (0.5%)		3 (0.7%)	
	3	0		0		0	

Note: Change denotes change from baseline. The stool frequency scores reflect the number of stools more than normal/day.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.2 : Summary of Average Stool Frequency Score (ITT Population - Phase II)

		----- SPD476 2.4g/d QD ------		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Month 6	N	166	166	153	153	319	319
	Mean	0.147	0.044	0.111	-0.004	0.130	0.021
	SD	0.3715	0.3858	0.3267	0.3861	0.3506	0.3861
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.33	0.00	-1.00	0.00	-1.33
	Max	2.67	2.67	2.00	2.00	2.67	2.67
	0	135 (65.2%)		130 (64.0%)		265 (64.6%)	
	>0-<1	18 (8.7%)		14 (6.9%)		32 (7.8%)	
	1-<2	12 (5.8%)		8 (3.9%)		20 (4.9%)	
	2-<3	1 (0.5%)		1 (0.5%)		2 (0.5%)	
	3	0		0		0	
Endpoint	N	192	191	181	181	373	372
	Mean	0.307	0.208	0.331	0.199	0.319	0.203
	SD	0.6830	0.6945	0.7216	0.7307	0.7011	0.7114
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.33	0.00	-1.00	0.00	-1.33
	Max	3.00	3.00	3.00	3.00	3.00	3.00
	0	143 (69.1%)		134 (66.0%)		277 (67.6%)	
	>0-<1	20 (9.7%)		16 (7.9%)		36 (8.8%)	
	1-<2	19 (9.2%)		20 (9.9%)		39 (9.5%)	
	2-<3	4 (1.9%)		5 (2.5%)		9 (2.2%)	
	3	6 (2.9%)		6 (3.0%)		12 (2.9%)	

Note: Change denotes change from baseline. The stool frequency scores reflect the number of stools more than normal/day.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 7 Summary of Average Rectal Bleeding Score (ITT Population)

Table 2.7.4 : Summary of Average Rectal Bleeding Score (ITT Population - Phase I)

		----- SPD476 2.4g/d QD -----		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Number of subjects		208		208		416	
Screening	N	208		208		416	
	Mean	0.016		0.010		0.013	
	SD	0.0913		0.0797		0.0856	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.00		1.00		1.00	
	0	200 (96.2%)		204 (98.1%)		404 (97.1%)	
	>0-<1	7 (3.4%)		3 (1.4%)		10 (2.4%)	
	1-<2	1 (0.5%)		1 (0.5%)		2 (0.5%)	
	2-<3	0		0		0	
	3	0		0		0	
Baseline	N	207		207		414	
	Mean	0.035		0.047		0.041	
	SD	0.1425		0.1928		0.1694	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.00		1.33		1.33	
	0	192 (92.3%)		193 (92.8%)		385 (92.5%)	
	>0-<1	13 (6.3%)		9 (4.3%)		22 (5.3%)	
	1-<2	2 (1.0%)		5 (2.4%)		7 (1.7%)	
	2-<3	0		0		0	
	3	0		0		0	

Note: Change denotes change from baseline.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

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Table 2.7.4 : Summary of Average Rectal Bleeding Score (ITT Population - Phase I)

		SPD476 2.4g/d QD		Asacol 1.6g/d BID		Overall	
		Actual	Change	Actual	Change	Actual	Change
Month 1	N	195	194	195	194	390	388
	Mean	0.037	0.004	0.050	0.003	0.043	0.004
	SD	0.1913	0.2081	0.2736	0.2977	0.2358	0.2565
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.00	0.00	-1.33	0.00	-1.33
	Max	2.00	2.00	2.67	2.00	2.67	2.00
	0	184 (88.5%)		185 (88.9%)		369 (88.7%)	
	>0-<1	8 (3.8%)		7 (3.4%)		15 (3.6%)	
	1-<2	2 (1.0%)		1 (0.5%)		3 (0.7%)	
	2-<3	1 (0.5%)		2 (1.0%)		3 (0.7%)	
	3	0		0		0	
Month 3	N	184	183	180	179	364	362
	Mean	0.044	0.021	0.061	0.011	0.053	0.016
	SD	0.2584	0.2440	0.2376	0.2642	0.2481	0.2539
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.00	0.00	-1.00	0.00	-1.00
	Max	2.50	1.83	2.00	1.33	2.50	1.83
	0	177 (85.1%)		164 (78.8%)		341 (82.0%)	
	>0-<1	2 (1.0%)		12 (5.8%)		14 (3.4%)	
	1-<2	4 (1.9%)		3 (1.4%)		7 (1.7%)	
	2-<3	1 (0.5%)		1 (0.5%)		2 (0.5%)	
	3	0		0		0	

Note: Change denotes change from baseline.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.4 : Summary of Average Rectal Bleeding Score (ITT Population - Phase I)

		SPD476 2.4g/d QD		Asacol 1.6g/d BID		Overall	
		Actual	Change	Actual	Change	Actual	Change
Month 6	N	168	167	171	170	339	337
	Mean	0.062	0.042	0.066	0.027	0.064	0.035
	SD	0.2464	0.2432	0.2815	0.3191	0.2643	0.2837
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-0.67	0.00	-1.00	0.00	-1.00
	Max	2.00	2.00	2.00	2.00	2.00	2.00
	0	155 (74.5%)		159 (76.4%)		314 (75.5%)	
	>0-<1	7 (3.4%)		5 (2.4%)		12 (2.9%)	
	1-<2	5 (2.4%)		5 (2.4%)		10 (2.4%)	
	2-<3	1 (0.5%)		2 (1.0%)		3 (0.7%)	
	3	0		0		0	
Endpoint	N	199	198	198	197	397	395
	Mean	0.225	0.191	0.223	0.179	0.224	0.185
	SD	0.5633	0.5177	0.5911	0.5865	0.5766	0.5524
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-0.67	0.00	-1.00	0.00	-1.00
	Max	3.00	2.67	3.00	3.00	3.00	3.00
	0	163 (78.4%)		165 (79.3%)		328 (78.8%)	
	>0-<1	10 (4.8%)		10 (4.8%)		20 (4.8%)	
	1-<2	16 (7.7%)		13 (6.3%)		29 (7.0%)	
	2-<3	8 (3.8%)		8 (3.8%)		16 (3.8%)	
	3	2 (1.0%)		2 (1.0%)		4 (1.0%)	

Note: Change denotes change from baseline.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.4 : Summary of Average Rectal Bleeding Score (ITT Population - Phase II)

		----- SPD476 2.4g/d QD ------		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Number of subjects		207		203		410	
Screening	N	207		203		410	
	Mean	0.023		0.021		0.022	
	SD	0.1414		0.1245		0.1331	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.00		1.00		1.00	
	0	201 (97.1%)		196 (96.6%)		397 (96.8%)	
	>0-<1	2 (1.0%)		5 (2.5%)		7 (1.7%)	
	1-<2	4 (1.9%)		2 (1.0%)		6 (1.5%)	
	2-<3	0		0		0	
	3	0		0		0	
Baseline	N	206		203		409	
	Mean	0.028		0.025		0.026	
	SD	0.1309		0.1282		0.1294	
	Median	0.000		0.000		0.000	
	Min	0.00		0.00		0.00	
	Max	1.00		1.00		1.00	
	0	195 (94.2%)		194 (95.6%)		389 (94.9%)	
	>0-<1	9 (4.3%)		7 (3.4%)		16 (3.9%)	
	1-<2	2 (1.0%)		2 (1.0%)		4 (1.0%)	
	2-<3	0		0		0	
	3	0		0		0	

Note: Change denotes change from baseline.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.4 : Summary of Average Rectal Bleeding Score (ITT Population - Phase II)

		----- SPD476 2.4g/d QD ------		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Month 1	N	194	194	195	195	389	389
	Mean	0.058	0.029	0.055	0.036	0.057	0.033
	SD	0.2302	0.2000	0.2229	0.2378	0.2263	0.2195
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-0.67	0.00	-1.00	0.00	-1.00
	Max	1.67	1.33	2.00	2.00	2.00	2.00
	0	178 (86.0%)		179 (88.2%)		357 (87.1%)	
	>0-<1	9 (4.3%)		11 (5.4%)		20 (4.9%)	
	1-<2	7 (3.4%)		4 (2.0%)		11 (2.7%)	
	2-<3	0		1 (0.5%)		1 (0.2%)	
	3	0		0		0	
Month 3	N	179	179	175	175	354	354
	Mean	0.032	0.002	0.038	0.017	0.035	0.009
	SD	0.2051	0.2357	0.1782	0.1866	0.1920	0.2127
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-1.00	0.00	-1.00	0.00	-1.00
	Max	2.33	2.33	1.67	1.33	2.33	2.33
	0	172 (83.1%)		164 (80.8%)		336 (82.0%)	
	>0-<1	5 (2.4%)		9 (4.4%)		14 (3.4%)	
	1-<2	1 (0.5%)		2 (1.0%)		3 (0.7%)	
	2-<3	1 (0.5%)		0		1 (0.2%)	
	3	0		0		0	

Note: Change denotes change from baseline.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 2.7.4 : Summary of Average Rectal Bleeding Score (ITT Population - Phase II)

		----- SPD476 2.4g/d QD ------		----- Asacol 1.6g/d BID -----		---------- Overall ----------	
		Actual	Change	Actual	Change	Actual	Change
Month 6	N	166	166	153	153	319	319
	Mean	0.086	0.056	0.050	0.026	0.069	0.042
	SD	0.3091	0.3063	0.2411	0.2745	0.2787	0.2914
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-0.33	0.00	-1.00	0.00	-1.00
	Max	2.33	2.33	2.00	2.00	2.33	2.33
	0	150 (72.5%)		144 (70.9%)		294 (71.7%)	
	>0-<1	7 (3.4%)		4 (2.0%)		11 (2.7%)	
	1-<2	8 (3.9%)		4 (2.0%)		12 (2.9%)	
	2-<3	1 (0.5%)		1 (0.5%)		2 (0.5%)	
	3	0		0		0	
Endpoint	N	192	191	181	181	373	372
	Mean	0.188	0.159	0.273	0.245	0.229	0.201
	SD	0.5055	0.4989	0.6484	0.6513	0.5800	0.5789
	Median	0.000	0.000	0.000	0.000	0.000	0.000
	Min	0.00	-0.33	0.00	-1.00	0.00	-1.00
	Max	3.00	3.00	3.00	3.00	3.00	3.00
	0	161 (77.8%)		147 (72.4%)		308 (75.1%)	
	>0-<1	9 (4.3%)		6 (3.0%)		15 (3.7%)	
	1-<2	16 (7.7%)		15 (7.4%)		31 (7.6%)	
	2-<3	5 (2.4%)		11 (5.4%)		16 (3.9%)	
	3	1 (0.5%)		2 (1.0%)		3 (0.7%)	

Note: Change denotes change from baseline.
Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 8 Summary of Analysis of the Endoscopy Score (ITT Population)

Table 2.10.2 : Analysis of the Endoscopy Score (ITT Population - Phase I)

		SPD476 2.4g/d QD		Asacol 1.6g/d BID	
Number of subjects		208		208	
Baseline	Normal	126	(60.6%)	129	(62.0%)
	Mild	82	(39.4%)	79	(38.0%)
	Moderate	0		0	
	Severe	0		0	
	Missing score	0		0	
Month 6	Normal	113	(54.3%)	114	(54.8%)
	Mild	50	(24.0%)	51	(24.5%)
	Moderate	7	(3.4%)	7	(3.4%)
	Severe	0		1	(0.5%)
	Missing score	38	(18.3%)	35	(16.8%)
Change at Month 6*	Improved	23	(11.1%)	25	(12.0%)
	Same	128	(61.5%)	124	(59.6%)
	Worsened	19	(9.1%)	24	(11.5%)
	Unknown	38	(18.3%)	35	(16.8%)
Number of subjects with improved/same scores		151	(72.6%)	149	(71.6%)
Difference in proportions (SPD476 - Asacol)				0.010	
95% CI for difference in proportions †				(-0.081, 0.101)	

* Change at Month 6 and Endpoint is relative to Baseline.
† Calculated using the normal approximation to the binomial distribution.
Note: Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.
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Table 2.10.2 : Analysis of the Endoscopy Score (ITT Population - Phase II)

		SPD476 2.4g/d QD		Asacol 1.6g/d BID	
Number of subjects		207		203	
Baseline	Normal	105	(50.7%)	108	(53.2%)
	Mild	102	(49.3%)	94	(46.3%)
	Moderate	0		1	(0.5%)
	Severe	0		0	
	Missing score	0		0	
Month 6	Normal	103	(49.8%)	108	(53.2%)
	Mild	57	(27.5%)	43	(21.2%)
	Moderate	6	(2.9%)	4	(2.0%)
	Severe	2	(1.0%)	1	(0.5%)
	Missing score	39	(18.8%)	47	(23.2%)
Change at Month 6*	Improved	28	(13.5%)	29	(14.3%)
	Same	123	(59.4%)	117	(57.6%)
	Worsened	17	(8.2%)	10	(4.9%)
	Unknown	39	(18.8%)	47	(23.2%)
Number of subjects with improved/same scores		151	(72.9%)	146	(71.9%)
Difference in proportions (SPD476 - Asacol)				0.010	
95% CI for difference in proportions †				(-0.081, 0.102)	

* Change at Month 6 and Endpoint is relative to Baseline.
† Calculated using the normal approximation to the binomial distribution.
Note: Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 9 Summary of Analysis of the Physician's Global Assessment (PGA) Score (ITT Population)

Table 2.11.2 : Analysis of Physician's Global Assessment Score (ITT Population - Phase I)

		SPD476 2.4g/d QD		Asacol 1.6g/d BID	
Number of subjects		208		208	
Baseline	No active disease	188	(90.4%)	185	(88.9%)
	Mild disease	20	(9.6%)	23	(11.1%)
	Moderate disease	0		0	
	Severe disease	0		0	
	Missing score	0		0	
Month 6	No active disease	147	(70.7%)	146	(70.2%)
	Mild disease	21	(10.1%)	24	(11.5%)
	Moderate disease	2	(1.0%)	3	(1.4%)
	Severe disease	0		0	
	Missing score	38	(18.3%)	35	(16.8%)
Change at Month 6*	Improved	7	(3.4%)	13	(6.3%)
	Same	147	(70.7%)	140	(67.3%)
	Worsened	16	(7.7%)	20	(9.6%)
	Unknown	38	(18.3%)	35	(16.8%)
Number of subjects with improved/same scores		154	(74.0%)	153	(73.6%)
Difference in proportions (SPD476 - Asacol)				0.005	
95% CI for difference in proportions †				(-0.085, 0.094)	

* Change at Month 6 and Endpoint is relative to Baseline.
† Calculated using the normal approximation to the binomial distribution.
Note: Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.
PROGRAM: TEF26ITT.SAS FILENAME: T02_11_02.DOC 05JAN2011 Page 1 of 2

Table 2.11.2 : Analysis of Physician's Global Assessment Score (ITT Population - Phase II)

		SPD476 2.4g/d QD		Asacol 1.6g/d BID	
Number of subjects		207		203	
Baseline	No active disease	159	(76.8%)	160	(78.8%)
	Mild disease	47	(22.7%)	42	(20.7%)
	Moderate disease	1	(0.5%)	1	(0.5%)
	Severe disease	0		0	
	Missing score	0		0	
Month 6	No active disease	125	(60.4%)	127	(62.6%)
	Mild disease	37	(17.9%)	26	(12.8%)
	Moderate disease	5	(2.4%)	2	(1.0%)
	Severe disease	1	(0.5%)	1	(0.5%)
	Missing score	39	(18.8%)	47	(23.2%)
Change at Month 6*	Improved	14	(6.8%)	13	(6.4%)
	Same	135	(65.2%)	128	(63.1%)
	Worsened	19	(9.2%)	15	(7.4%)
	Unknown	39	(18.8%)	47	(23.2%)
Number of subjects with improved/same scores		149	(72.0%)	141	(69.5%)
Difference in proportions (SPD476 - Asacol)				0.025	
95% CI for difference in proportions †				(-0.068, 0.118)	

* Change at Month 6 and Endpoint is relative to Baseline.
† Calculated using the normal approximation to the binomial distribution.
Note: Percentages are based on the number of subjects in the ITT population for each treatment group.
Baseline is defined as the last non-missing assessment prior to first dose of study medication.
Endpoint is defined as data from the Month 6 or, early withdrawal visit if subject withdrew prior to Month 6.

Table 10 Subgroup Analyses of Proportion of Subjects in Endoscopic Remission at Month 6 by Phase by Gender, Race and Age

Subgroup Analyses of Proportion of Subjects in Endoscopic Remission at Month 6 by Phase by Gender, Race and Age (ITT Population)

Subgroup	Phase 1 SPD476	Phase 1 Asacol	Phase 1 Diff (SPD-Asacol)	Phase 1 95% CI	Phase 2 SPD476	Phase 2 Asacol	Phase 2 Diff (SPD-Asacol)	Phase 2 95% CI
Gender								
Male	80/101 (79.2%)	94/114 (82.5%)	-3.3%	(-13.8%, 7.3%)	86/111 (77.5%)	74/100 (74.0%)	3.5%	(-8.1%, 15.1%)
Female	83/107 (77.6%)	71/94 (75.5%)	2.0%	(9.7%, 13.8%)	74/96 (77.1%)	77/103 (74.8%)	2.3%	(-9.6%, 14.2%)
Age								
<55	123/158 (77.8%)	122/155 (78.7%)	-0.9%	(-10.0%, 8.3%)	112/143 (78.3%)	109/151 (72.2%)	6.1%	(-3.7%, 16.0%)
≥55	40/50 (80.0%)	43/53 (81.1%)	-1.1%	(-16.4%, 14.2%)	48/64 (75.0%)	42/52 (80.8%)	-5.8%	(-20.8%, 9.3%)
Race								
Caucasian	124/154 (80.5%)	126/156 (80.8%)	-0.3%	(-9.0%, 8.5%)	86/118 (72.9%)	83/103 (80.6%)	-7.7%	(-18.8%, 3.4%)
Non-Caucasian	39/54 (72.2%)	39/52 (75.0%)	-2.8%	(-19.6%, 14.0%)	74/89 (83.1%)	68/100 (68.0%)	15.2%	(3.1%, 27.2%)

Compiled by this reviewer.

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/s/

MILTON C FAN
07/14/2011

MICHAEL E WELCH
07/14/2011
See TL memorandum.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number:22-000 **Applicant:** Shire **Stamp Date:** 6/15/10

Drug Name: Lialda (mesalamine) **NDA/BLA Type:** Efficacy **Indication:** (b) (4)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	Electronic submission
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			<55 vs. 55+ for geriatric subgroup
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ? Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No efficacy interim analysis planned.
Appropriate references for novel statistical methodology (if present) are included.		X		
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		Only PP, No sensitivity analyses

Background

Lialda was approved on 16 January 2007, indicated for the induction of remission in patients with active, mild to moderate colitis.

The sponsor seeks for the additional of new indication (maintenance of remission (b) (4) of ulcerative colitis.

The sponsor had submitted a adequate and well-controlled studies trial (SPD476-304) and an open-label study to assess clinical recurrence (SPD476-404), and an open-label extension study to evaluate safety and tolerability (SPD476-303) for the claim.

Review Issues

The review issues are listed below.

1. Single Phase 3 Non-inferiority Study – compare SPD476 2.4 g/day QD vs. Asacol 1.6 g/day BID
2. Sample Size increased from 410 to 826 during the trial due to change to clinical assumptions
3. Non-inferiority margin of 10% obtained from meta analysis without 50% discount for assay sensitivity
4. This study enrolled only 38 US patients (5.6%). The results for US were -6% for ITT and -18% for PP). Due to small sample size, US results might not be interpreted
5. Missing data – 20%

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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

/s/

MILTON C FAN
08/18/2010

MICHAEL E WELCH
08/19/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-000 S-005**	**Brand Name**	**Lialsa**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Mesalamine**
Medical Division	**DGP**	**Drug Class**	**5-aminosalicylate**
OCP Reviewer	**Kristina Estes, PharmD**	**Indication(s)**	**Maintenance of remission of UC**
OCP Team Leader	**Sue Chih Lee, PhD**	**Dosage Form**	**1.2 g Tablet**
Pharmacometrics Reviewer	**n/a**	**Dosing Regimen**	**2.4 g once daily**
Date of Submission	**14 JUN 2010**	**Route of Administration**	**PO**
Estimated Due Date of OCP Review		**Sponsor**	**Shire**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**14 APR 2010**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

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geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**3**		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		2.4 g dose is accepted in Europe and within the range of approved 5-ASA doses globally
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		E-R relationship was not previously established for acute indication
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Kristina Estes 7/29/10
Reviewing Clinical Pharmacologist Date

Sue Chih Lee 8/18/10
Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

KRISTINA E ESTES
08/18/2010

SUE CHIH H LEE
08/18/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

OTHER REVIEW(S)

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 022000/005
APPLICANT	Shire Development Inc
PRODUCT NAME	LIALDA (mesalamine)
SUBMISSION DATE	14 June 2010
PDUFA DATE	14 July 2011
SEALD SIGN-OFF DATE	13 July 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that SEALD review has found that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed 1 July 2011, have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/

LAURIE B BURKE
07/13/2011

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22000/005
APPLICANT	Shire Development Inc.
PRODUCT NAME	LIALDA (mesalamine)
RECEIVED DATE	June 14, 2010
PDUFA DATE	July 14, 2011 (Clinical Efficacy)
SEALD REVIEW DATE	July 1, 2011
SEALD LABELING REVIEWER	Jeanne Marie Delasko, RN, MS Labeling Initiatives Specialist

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

☐ There is no redundancy of information. **[JMD Comment: Since W&P 5.1 in HL deals with renal function, can the statement under Use in Specific Populations be included as the last sentence under W&P 5.1 in HL? It appears that there is duplication of information. Also, shouldn't this statement reference (5.1) and NOT (5.2) in the FPI?]**

☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

☐ A horizontal line must separate the HL and Table of Contents (TOC).

☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.

☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)

• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☒ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action. **[JMDComment: There should be no space between product title and initial U.S. Approval lines. Initial U.S. Approval must be placed immediately beneath the product title. Delete extra space.]**

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☒ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010." **[JMD Comment: Remember to update the RMC date upon approval – 07/2011. Don't leave as "XX/2011."]**

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.

☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

☐ All contraindications listed in the FPI must also be listed in HL.

☒ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**

☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

  ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

  > "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

  ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

  > "The following *adverse reactions* have been identified during post-approval use of (insert drug name). Because these *reactions* are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

  ☐ This section is required and cannot be omitted.

  ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

  - "See FDA-approved patient labeling (Medication Guide)"
  - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information)"
  - "See FDA-approved patient labeling (Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

JEANNE M DELASKO
07/01/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: July 1, 2011

To: Kevin Bugin, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

Marie Kowblansky, Ph.D.
Thomas Oliver, Ph.D.
Office of New Drug Quality Assessment (ONDQA)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Twyla Thompson, Regulatory Review Officer
Lisa Hubbard, Professional Group Leader
Shefali Doshi, Direct-To-Consumer Group Leader
DDMAC

Subject: NDA 022000/S-005
LIALDA® (mesalamine) delayed release tablets for oral use [Lialda]
Supplemental Review of Section 11 – Sponsor's proposed changes

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This consult response pertains to the sponsor's proposed changes to section 11 of the proposed package insert (PI) (submitted June 21, 2011) and concerns which have come up during the course of labeling negotiations.

Reference is made to DGIEP's August 18, 2010, consult request regarding proposed labeling for S-005 for Lialda. In response to this consult request, DDMAC provided comments on June 22, 2011. DDMAC's comments were based on version 9 of the proposed draft marked-up labeling titled, "NDA22000-S005-CleanPLRLabel.doc" accessed via the e-Room (last modified June 15, 2011 at 6:52 pm).

Of note, DDMAC provided comments on the Lialda PI on September 28, 2009, as part of supplement 003. As that time, section 11 read as follows (in pertinent part; bolded emphasis added):

(b) (4)

DDMAC's comment on this text was as follows:

> DDMAC is concerned that this text (bolded emphasis added) may b (b) (4) If not, we suggest deletion.

Reference is also made to DDMAC's April 27, 2010, notice of violation issued to Shire. Prior to issuing this letter, DDMAC consulted DGIEP and received two consult responses dated April 22, 2009, and March 29, 2010, from Dr. Christopher Leptak. DDMAC's notice of violation stated the following (in pertinent part):

> In addition, (b) (4)
>
> (bolded emphasis in original; underlined emphasis added; references omitted):
>
> (b) (4)
>
> The totality of these claims and presentations suggests that, (b) (4) Therefore, these claims and presentations are misleading.

In the version of the PI used for DDMAC's June 22, 2011, labeling review for supplement 005, section 11 read as follows (in pertinent part); DDMAC did not have any comments:

> The tablet is coated with a pH dependent polymer film, which breaks down at or above pH (b) (4) normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients.

During the course of labeling negotiations for supplement 005, the sponsor (Shire) submitted a response to FDA (forwarded to DDMAC by Kevin Bugin on June 21, 2011) in which section 11 was revised to read as follows (in pertinent part):

(b) (4)

At the request of ONDQA, DDMAC has reviewed Shire's June 21, 2011, response and proposed changes to section 11 and offers the following comments. DDMAC is concerned that this text may be used in a promotional context to overstate the efficacy of the drug and imply superiority over other available mesalamine products. We agree with ONDQA's recommendation to revert to the text proposed by FDA in version 9. Of note, our concurrence was conveyed during the June 24, 2011, FDA internal labeling meeting.

Thank you for the opportunity to comment on this proposed material. If you have any questions, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

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/s/

KATHLEEN KLEMM
07/01/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: June 22, 2011

To: Kevin Bugin, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Twyla Thompson, Regulatory Review Officer
Lisa Hubbard, Professional Group Leader
Shefali Doshi, Direct-To-Consumer Group Leader
DDMAC

Subject: NDA 022000/S-005

DDMAC labeling comments for LIALDA® (mesalamine) delayed release tablets for oral use [Lialda]

In response to DGIEP's August 18, 2010, consult request, DDMAC has reviewed the draft package insert (PI) for Lialda and offers the following comments.

DDMAC's comments on the PI are based on version 9 of the proposed draft marked-up labeling titled, "NDA22000-S005-CleanPLRLabel.doc" accessed via the e-Room (last modified June 15, 2011 at 6:52 pm). DDMAC's comments are provided directly on the document attached below.

Thank you for the opportunity to comment on this proposed material. If you have any questions regarding the PI, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

16 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KATHLEEN KLEMM
06/22/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 8, 2011

TO: Roland Girardet, Regulatory Project Manager
Klaus Gottlieb, Medical Officer
Division of Gastroenterology Products

FROM: Khairy Malek, M.D., Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-000/S-005

APPLICANT: Shire Pharmaceuticals

DRUG: Lialda (mesalamine Delayed Release Tablets 1.2g)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS:
1. Induction of remission in patients with active mild to moderate ulcerative colitis
2. Maintenance of remission, (b) (4) in ulcerative colitis.

CONSULTATION REQUEST DATE: August 30, 2010
Inspection Summary Goal Date: 1/5/2011
DIVISION ACTION GOAL DATE: 4/14/2011
PDUFA DATE: 4/14/2011

I. BACKGROUND:

Mesalamine (Asacol) is an approved drug for the treatment of ulcerative colitis and in maintaining remission, but it is necessary for patients to take several tablets in divided daily doses.

Shire Pharmaceuticals submitted this application for the use of a new preparation, SPD476, which differs from all other oral forms of mesalamine in having a double matrix. (b) (4) This results in a homogenous and gradual release of 5-ASA in the colon over 48 hours and so can be given once daily.

A single pivotal study, SPD476-304, was submitted in support of the application.
The primary objective of the new study was to compare the maintenance of mucosal healing at 6 months between SPD476 given once daily in a 2.4 g dose and Asacol 1.6 g given twice daily.

Brief Summary of the Protocol: SPD476-304, titled "A Phase III, Randomized, double-blind, parallel-group, active comparator study to compare the efficacy and safety of SPD476 (mesalamine) 2.4g/day once daily (QD) with Asacol 1.6g/day twice daily (BID) in the maintenance of remission in Patients with ulcerative colitis".

This was a randomized, double-blind, parallel group, non-inferiority, active comparator study. Subjects visited the clinic 5 times: Screening; Baseline; Month 1; Month3; and Month 6 which was the end of the study. At Baseline and End of Study/early withdrawal, subjects underwent an endoscopy to assess mucosal appearance. Subjects were required to complete a diary for the week prior to each visit as well as short questionnaire at Baseline, Visit 4 (Month 3), and at the end of the study to assess their quality of life.

Primary Efficacy Parameter:
The primary efficacy variable was the percentage of subjects in endoscopic remission (maintenance of mucosal healing) at Month 6 in each treatment group as defined by an endoscopy score of ≤ 1.

This single protocol was inspected for this NDA, and one clinical investigator site was selected for inspection. The clinical investigator site was selected for inspection due to the following:

- There was insufficient domestic data
- The site had a relatively higher enrollment
- All subjects at this site had endoscopic remission at Month 6 with both the investigational product and the active comparator, which was unexpected.

II. RESULTS (by Site):

Name of CI	Protocol # and # of Subjects	Inspection Date	Final Classification
K T Shenoy, M.D. Head, Depatment of Gastroenterology; Sree Gokulam Medical College Thiruvananthapuram Karinchathi Road Venjaramoodu P.O.; Trivandrum-695607 India	SPD476-304 Site 205 28/27 Subjects	12/6/2010 to 12/10/2010	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Name of CI: K.T.Shenoy, M.D.-Site 205
   Head, Department of Gastroenterology; Sree Gokulam Medical College
   Thiruvananthapuram Karinchathi Road; Venjaramoodu P.O.;
   Trivandrum-695607; India

   a. What was inspected: The field investigator reviewed the records of all 27 subjects who were enrolled, and all completed the study. No subject withdrew consent or was terminated before completion. All enrolled subjects met inclusion/exclusion criteria. All consent forms were obtained before any study procedures were initiated. The field investigator reviewed all CRFs, source documents, medical records, study visit timeframes, endoscopy evaluations, evaluation of UC, IVRS documented stool and blood frequency, drug accountability, concomitant medications, laboratory reports, adverse reactions and verification of data listings. There was no limitation to the inspection.

   b. General observations/commentary:

      The study appeared to have been conducted adequately. No electronic data systems were used to gather or generate clinical data. An IVRS system was utilized to obtain subject screening numbers, randomization numbers; assign medicine kits and to document stool frequency and incidence of blood in the stool. There were no discrepancies between the source, CRFs and data supplied to the FDA. The field investigator reviewed the endoscopy images and reports

done at baseline and at the end of the study. There were no SAEs reported and all AEs were reported in the source documents, CRFs and were forwarded to the Ethics Committee. The monitoring was provided by "ICON" and there were 12 monitoring reports reviewed by the field investigator. Drug Accountability Records were all intact and well documented.

No significant issues were noted during the inspection and a Form FDA 483 was not issued.

c. Assessment of Data Integrity:
The data generated at this site appear reliable and can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

One foreign clinical investigator site was inspected in support of this application. The study appears to have been conducted adequately, and the data are considered reliable in support of the NDA.

{See appended electronic signature page}

Khairy Malek, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

KHAIRY W MALEK
02/09/2011

TEJASHRI S PUROHIT-SHETH
02/09/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	11/10/2010
To:	Donna Griebel, M.D., Director, Division of Gastroenterology Products
Through:	Diane K. Wysowski, M.P.H., Ph.D., Acting Team Leader, Division of Epidemiology, Office of Surveillance and Epidemiology
	Judy A. Staffa, Ph.D., Acting Director, Division of Epidemiology, OSE
From:	Christian Hampp, Ph.D., B.S.Pharm., Visiting Associate/Epidemiologist, Division of Epidemiology, OSE
Subject:	Epidemiologic analysis of non-traffic related accidental deaths and suicides in clinical trials of Lialda
Drug Name(s):	mesalazine (Lialda®) delayed release tablets
Submission Number:	S-005
Application Type/Number:	NDA 022-000
Applicant/sponsor:	Shire Pharmaceuticals
OSE RCM #:	2010-2166

CONTENTS

EXECUTIVE SUMMARY

Lialda® (mesalazine; Shire US Inc., NDA 22-000) gained market approval on January 16, 2007, for the induction of remission of active, mild to moderate ulcerative colitis. In reviewing clinical trials in support of the Efficacy Supplement S-005 to add maintenance of remission as a labeled indication, the Division of Gastroenterology Products (DGP) noted two unexpected deaths in a single study, both in patients treated with twice-daily (BID) Lialda. One case occurred in an older male subject in Lithuania, who fell while intoxicated with alcohol, categorized as suicide on the death certificate. The other case was a young woman from Hungary who died from an electric shock while vacuuming her car. DGP has requested consultation on the probability of these fatalities occurring by chance in the Lialda study population.

This analysis was based on data from three clinical trials submitted by the sponsor in support of NDA 22-000, S-005. Data were pooled across the three trials to create two separate denominators that contain both fatalities: all patients exposed to Lialda, and patients exposed to Lialda BID. The probability of observing the deaths found in the clinical trials amid a literature-based background incidence rate of non-traffic accidental deaths and suicides was simulated. A SAS macro created hypothetical populations of 100,000 subjects with background mortality rates ranging from 5-120/100,000 subject-years with special attention to the landmark points 20, 60 and 100 deaths per 100,000 subject-years. For each population, 10,000 random samples with the size of each of the two denominators were drawn with replacement. These 10,000 samples then provided an estimate of the number of deaths that would be expected to occur in the clinical trials under the null hypothesis of no drug effect on non-traffic related accidental deaths and suicides.

When both cases were treated separately, there was a significant chance to observe each case. At a low background rate of 20/100,000 there was a 19.1% chance in the Lialda population and a 6.3% chance in the Lialda BID population to observe one fatality. This background rate would be applicable to both cases, however with suicide rates as high as 85/100,000 and alcohol-related fatal injury rates of 115/100,000 in males in Lithuania where the suicide/accident case occurred, the chance to observe one of these cases in the Lialda population would increase to 60-70% if all patients were part of this high-risk population. Taking both cases together, at a chance of approximately 13% to observe two fatalities amid a background incidence rate of 60/100,000 subject-years, the finding for the overall Lialda clinical trials population is within expectations. At the same background rate, the Lialda BID population experienced this outcome only approximately 1.5% of the time; however, this subgroup has limited validity since it was selected with the knowledge that it contains both outcomes.

To summarize, from a statistical perspective, both fatalities could have occurred by chance. However, the statistical view offers only one perspective to the determination of whether the fatalities could be a consequence of exposure to Lialda. From the brief description available to the FDA, neither of the cases offers a tangible causal link to the drug. In fact, the electric shock provides a compelling alternative cause of death, making it difficult to establish a link to Lialda exposure. If this electric shock case is considered confounded and removed from the list of potential drug-related adverse events, the remaining suicide/accident case falls within the expected frequency of events, regardless of exposure.

1 BACKGROUND/HISTORY

Lialda® (mesalazine; Shire US Inc., NDA 22-000) has gained market approval on January 16, 2007, for the induction of remission of active, mild to moderate ulcerative colitis. Mesalazine has been used since 1987, but the novelty of Lialda is its MMX Multi Matrix System® core resulting in delayed release of the active ingredient. In reviewing clinical trials in support of the Efficacy

Supplement S-005 to add maintenance of remission as a labeled indication, the Division of Gastroenterology Products noted two unexpected deaths in a single study, both in patients treated with twice-daily (BID) Lialda. One case occurred in an older male in Lithuania, who fell while intoxicated with alcohol but was categorized as suicide on the death certificate. The other case was a young woman from Hungary who died following electric shock while vacuuming her car. The occurrence of two unusual fatalities in a single study raised concerns and led to the following questions to be answered in this consult (sequence of questions rearranged):

1. What is the appropriate denominator? For example, should the denominator be all patients exposed to any dose of mesalazine regardless of study phase adjusted by exposure time, or broken up by individual study segments?
2. What is a reasonable assumption for background risk (the study population consists of a mixture of participants from study sites in different countries or geographic regions)?
3. Is age adjustment required?
4. What is the likelihood of two non-traffic fatal accidents occurring purely by chance in the population at risk?
5. Lastly, we would appreciate an overall assessment of whether the results obtained from the above analysis might be interpreted as a safety signal.

Both fatalities have the appearance of causality unrelated to exposure to Lialda; however, the request for consultation states that information was scanty and mostly based on foreign death certificates, and autopsy results have not yet been made available to the FDA. This consult first provides a calculation on the probability of the two fatalities occurring at random without regarding criteria for causality, and a final assessment interprets these findings in the light of apparent etiology.

2 METHODS AND MATERIALS

2.1 EXPOSURE TIME AND FATAL OUTCOMES IN CLINICAL TRIALS OF LIALDA

This analysis was based on data from three clinical trials submitted by the sponsor in support of NDA 22-000, S-005. Study SPD476-303 was a phase-III, open label, randomized clinical trial exposing patients to Lialda 2.4 g/d once daily (QD) during a 2-month acute phase and then randomizing to either Lialda 2.4 g/d QD or BID during a 12-months maintenance phase with one additional month of follow-up. Study SPD476-304 was the pivotal phase-III safety and efficacy study, a randomized, double blind, non-inferiority trial, exposing subjects to either Lialda 2.4g/d QD or Asacol (mesalazine) 1.6g/d BID for the duration of 6 months with one additional month of follow-up. Lastly, SPD476-404 was a phase-IV, open-label, uncontrolled study following patients on Lialda 2.4-4.8g/d QD during a 2-month acute phase and 2.4g/d QD during a 12-month maintenance phase with 7 additional days of follow-up. Details on exposure, follow-up and fatalities are listed in the following table:

Table 1. Exposure time and fatal outcomes in clinical trials of Lialda

Study SPD476	Exposure	N (safety)	Duration [months]	Person-time [yrs]	Deaths
-303					
Acute Phase	Lialda 4.8g/d (2.4g BID)	312	2	52	1: subject fell while intoxicated with alcohol
Maintenance Phase	Lialda 2.4g/d QD	225	12+1*	244	0
	Lialda 2.4/d (1.2g BID)	234	12+1*	254	1: electric shock
-304					
	Lialda 2.4g/d QD	415	6+1*	242	0
	Asacol (mesalazine) 1.6g/d (0.8g BID)	411	6+1*	240	0
-404					
Acute Phase	Lialda 2.4-4.8g/d QD	138	2	23	0
Maintenance Phase	Lialda 2.4g/d QD	208	12+0.25†	212	0
Total	Lialda			1027	2
	Lialda BID			306	2

*one additional month of follow-up; †seven additional days of follow-up.
Acronyms: BID: twice daily; QD: once daily

The occurrence of two fatalities in the Lialda arms allows for the selection of various denominators of exposed patients. The study in which both cases occurred (SPD476-303) should not be analyzed in isolation given that the other studies provide additional exposure time and outcome information. An analysis of fatalities associated with mesalazine as an active ingredient in any formulation would require a meta-analysis on all clinical trials of mesalazine conducted over the past decades and would be beyond the scope of this request for consultation. Two denominators are appropriate for this analysis: all phase-III/IV exposure to Lialda and exposure to the BID administration schedule of Lialda, the latter however with limited statistical validity as discussed below. The inclusion of high-dose Lialda (4.8 g/d) does not seem appropriate due to limited exposed person-time and the occurrence of only a single case.

For each of the denominators, exposed person-time and number of deaths were pooled across the studies' cohorts (table 1). Owing to the small number of outcome events, no modeling was done to incorporate within- and between-study variation.

2.2 BACKGROUND INCIDENCE RATES FOR NON-TRAFFIC FATAL ACCIDENTS AND SUICIDES

One of the fatal cases in the Lialda studies occurred to a 67-year-old male in Lithuania, who fell from an 8th floor balcony. His death certificate categorizes the case as a suicide; however, the incidence was not witnessed and the subject was intoxicated with alcohol, therefore accidental death remains a possibility. The second case was a 25-year-old female from Hungary who died following electric shock while vacuuming her car. The subject had visual signs of electric injury. To identify appropriate background rates for the first case, rates of alcohol-related non-traffic

fatalities as well as suicide rates relevant to the case's country of origin, as well as other study sites, where searched. For the second case, rates for fatal non-traffic accidents were identified, regardless of causal link to alcohol.

Rehm et al. reported alcohol-attributable deaths for several central and eastern European countries for the year 2002 and found a pronounced geographic difference ranging from 27 alcohol-attributable premature deaths per 100,000 subject-years in Sweden to 290/100,000 in Russia (1). For Lithuania, 2,156 alcohol-attributable deaths were reported, among them 1,122 unintentional injuries, amounting to the high rate of 115 alcohol-related unintentional injury deaths per 100,000 subject-years for males (females: 22/100,000). For all countries, rates were higher for males and females younger than 45 compared to older subjects. No information was found on rates of unintentional deaths in Hungary, the country where one of the cases in the mesalazine studies occurred. Instead, van Beeck et al. found an average of 15-20 non-traffic accidental deaths per 100,000 subject-years in the Netherlands between 1980-1995 (2). Rates of suicides in 55-64 year-old males in Lithuania were at a high level of 84.8/100,000 subject-years between 1994 and 2003 (3). In contrast, suicide rates ranged from only 3.3 in females in the UK to 31.7/100,000 in Finnish males (4). These suicide rates are likely underestimates as a consequence of incomplete suicide coding on death certificates.

Overall, male gender, younger age, and alcohol consumption were major contributing factors to unintentional injury deaths. These factors were important considerations for the choice of the appropriate background rate to provide a context for this simulation. The Lialda study populations had median ages in the mid-forties and balanced gender distributions. The studies were multinational, but it is remarkable that both deaths occurred in eastern-European countries. Statistical adjustment for these factors did not seem prudent, owing to the small number of events. Instead, an array of background incidence rates ranging from 5-120 deaths per 100,000 subject-years was simulated and special attention was given to three landmark points along this range: 20, 60, and 100 deaths per 100,000 subject-years.

The probability of observing the deaths found in the clinical trials amid a literature-based background incidence rate of accidental/suicidal deaths was simulated in SAS 9.1 (SAS Institute, Cary, NC). A SAS macro was created to establish hypothetical populations of 100,000 subjects with a background death rate ranging from 5-120/100,000 subject-years. For each of the populations, 10,000 random samples with the size of each of the two denominators (Lialda and Lialda BID, table 1) were drawn with replacement. These 10,000 random samples then provided an estimate of the number of deaths that would be expected to occur in the clinical trials under the null hypothesis of no drug effect on accidental/suicidal deaths. Estimates for the chance to find at least one and at least two deaths were extracted to allow interpretation of occurrence of both cases separately or jointly.

3 RESULTS

Figures 1 and 2 display the results of the simulation on the probability of observing at least one or at least two non-traffic fatal accidents in the Lialda and Lialda BID populations. Tables 1 and 2 provide detailed estimates for the landmark background incidence rates of 20, 60, and 100 fatalities per 100,000 subject-years.

Figure 1. Results of the simulation on the probability of observing at least one non-traffic fatal accident or suicide in the Lialda and Lialda BID populations.

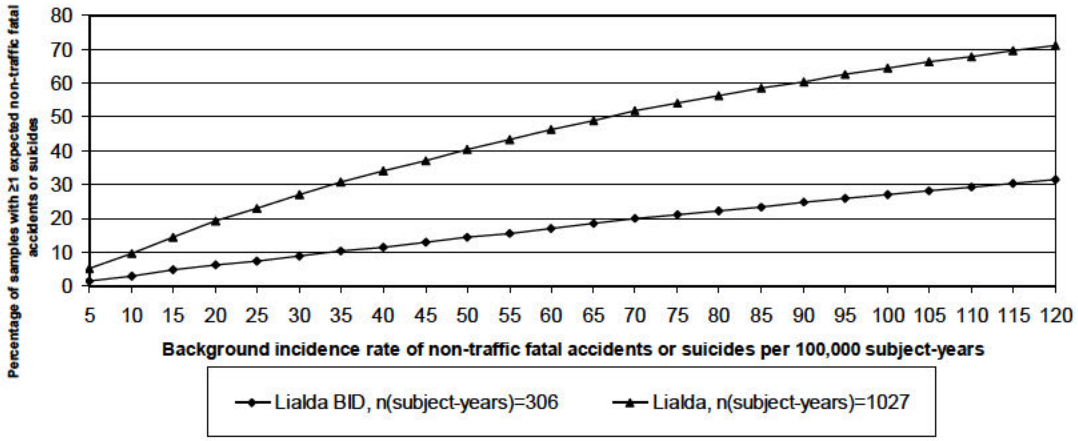

Table 2. Percentage of samples with ≥1 expected fatality*

Exposure	Background rate [fatal accidents/100,000 subject-years]		
	20	60	100
Lialda	19.1%	46.2%	64.4%
Lialda BID	6.3%	17.0%	27.0%

*due to large number of repetitions, confidence intervals are exceedingly narrow and therefore, omitted form the tables

Figure 2. Results of the simulation on the probability of observing two or more non-traffic fatal accidents or suicides in the Lialda and Lialda BID populations.

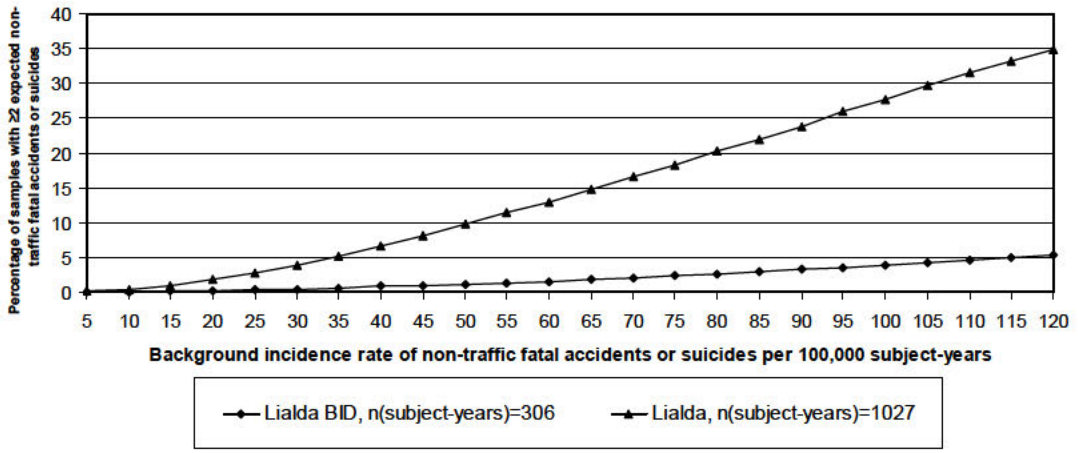

Table 3. Percentage of samples with ≥2 expected fatalities

Exposure	Background rate [fatal accidents/100,000 subject-years]		
	20	60	100
Lialda	1.87%	12.93%	27.69%
Lialda BID	0.26%	1.49%	3.93%

4 DISCUSSION AND RECOMMENDATIONS

As this simulation showed, the probability of observing non-traffic fatal accidents or suicides by chance depends highly on assumptions for the background incidence and the size of the drawn sample. Not surprisingly, as a consequence of the larger sample size of all subjects exposed to Lialda, it is much more likely to observe fatalities in the entire Lialda population than in the Lialda BID subgroup. It should be noted that the results ought not to be interpreted as p-values. Because of the possibility of choosing from different potential denominators, multiple testing becomes an issue, increasing the chance of false-positive findings. This is especially noteworthy in the case of Lialda BID, where only the cohorts containing the fatalities were selected, with the knowledge that they contained the fatalities, thus raising concerns about the scientific validity of this subgroup-analysis.

When both cases were treated separately, there was a significant chance to observe each case. With suicide rates of 85/100,000 and rates of alcohol-related fatal injuries of 115/100,000 males in Lithuania, the chance to observe one of these cases in the Lialda population would be 60-70% if all subjects were part of this high-risk population. Since this was not the case, even at the much lower background rate of 20/100,000 subject-years, there was a 19.1% chance in the Lialda population and a 6.3% chance in the Lialda BID population to observe one fatality. This background rate would also be applicable to the second case, since it falls within the estimate of 15-20 non-traffic accidental deaths per 100,000 subject-years, as observed in the Netherlands.

To account for their different etiology when both fatalities were considered jointly, the appropriate background incidence rate should be the sum of suicide and non-traffic fatal accident incidence rates. At a chance of approximately 13% to observe two fatalities amid a background incidence rate of 60/100,000 subject-years, the finding for the overall Lialda clinical trials population is within expectations. At the same background rate, the Lialda BID population experienced this outcome only approximately 1.5% of the time. For reasons of multiple testing and questionable validity of this subgroup analysis, this should not be taken in isolation as evidence against the null hypothesis of no increased fatalities with Lialda BID exposure. At a higher background rate, more representative of the countries where the fatalities occurred, the chance to observe two random fatalities approaches 5% (figure 2), suggesting that these cases may not be a consequence of exposure to Lialda BID.

A limitation to this analysis is that, in agreement with the request for consultation, only fatal events were considered. In many cases where a causative agent is associated with an increase in fatalities, it also increases the risk for non-fatal events along the causal pathway. If a biological mechanism of the drug's supposed effects on mortality can be hypothesized, an analysis should also include drug effects on non-fatal precursors.

To summarize, from a statistical perspective, both fatalities could have occurred by chance. However, the statistical view offers only one perspective to the determination of whether the fatalities could be a consequence of exposure to Lialda. From the brief description available to the FDA, neither of the cases offers a tangible causal link to the drug. In fact, the electric shock provides a compelling alternative cause of death, making it difficult to establish a link to Lialda exposure. If this electric shock case is considered confounded and removed from the list of potential drug-related adverse events, the remaining suicide/accident case falls well within the expected frequency of events, regardless of exposure.

Christian Hampp, Ph.D.

5 REFERENCES

1. Rehm J, Sulkowska U, Manczuk M, et al. Alcohol Accounts for a High Proportion of Premature Mortality in Central and Eastern Europe. Int J Epidemiol 2007 Apr;36(2):458-67.
2. van Beeck EF, Looman CW, Mackenbach JP. Mortality Due to Unintentional Injuries in The Netherlands, 1950-1995. Public Health Rep 1998 Sep;113(5):427-39.
3. Tamosiunas A, Reklaitiene R, Virviciute D, et al. Trends in Suicide in a Lithuanian Urban Population Over the Period 1984-2003. BMC public health 2006;6:184.
4. Kelly BD, Davoren M, Mhaolain AN, et al. Social Capital and Suicide in 11 European Countries: an Ecological Analysis. Soc Psychiatry Psychiatr Epidemiol 2009 Nov;44(11):971-7.

cc: Girardet R /Gottlieb K /Korvick J /Griebel D /DGP
Patel N /Wysowski D /Staffa J /Hampp C/OSE

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/s/

CHRISTIAN HAMPP
11/10/2010

JUDY A STAFFA
11/10/2010

DSI CONSULT: Request for Clinical Inspections

Date: August 30, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Khairy Malek, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Division of Gastroenterology Products (DGP)
Klaus Gottlieb, M.D.,M.B.A., Clinical Reviewer
Anil Rajpal, M.D., Acting Clinical Team Leader, DGP

From: Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager, DGP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-022000/S-005
Applicant: Shire Pharmaceuticals

Applicant Regulatory Contact:
Harris Rotman, Ph.D.
Phone: (484) 595-8048
Email: harotman@shire.com

Drug Proprietary Name: LIALDA (mesalamine) Delayed Release Tablets, 1.2 g
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): induction of remission in patients with active, mild to moderate ulcerative colitis and for the maintenance of remission. (b) (4) in ulcerative colitis. *(The underlined portion is the new indication the applicant is seeking)*

PDUFA:
Action Goal Date: 04/14/2011
Inspection Summary Goal Date: 1/5/2011

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Subjects enrolled/Subjects for per-protocol-analysis	Indication
Site 205 Dr K T Shenoy Sree Gokulam Medical College and Research Foundation Prof. & Head Dept. of Gastroenterology Venjaramoodu P.O Trivandrum India 695607 Additional information: Affiliated to Kerala University, Thiruvananthapuram Karinchathi Road, Venjaramoodu P.O. Trivandrum Trivandrum - 695607 Phone: 0472-2875757, 2875777 Fax: 0472-2875777	SPD476-304	28/27	Maintenance of remission in ulcerative colitis (see below)

III. Site Selection/Rationale

The pivotal study SPD476-304 was mostly conducted abroad with only 42 patients contributed by 16 domestic study sites. The four largest sites overall were located in India and the Czech Republic: Ludhiana India n=49, Pribram Czech Republic n=32, Trivandrum India n=28, Tabor Czech Republic n=28 . We selected Trivandrum India for inspection because it was the only site among these 4 sites in which all of the patients were in endoscopic remission at 6 months with either drug (Lialda and Asacol). Although this is certainly possible, it is not expected that all 27 patients at a single site would be in endoscopic remission.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

__x__ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__x__ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

The pivotal study SPD476-304 included a total of 826 patients, and was mostly conducted abroad. Only 42 patients were contributed by 16 domestic study sites; most domestic sites had 2 or less patients per site. The foreign site selected for inspection (Trivandrum India) was the only site among the 4 sites with the highest enrollment in which all of the patients were in endoscopic remission at 6 months with either drug (Lialda and Asacol). Although this is certainly possible, it is not expected that all 27 patients at a single site would be in endoscopic remission.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Roland Girardet, *M.H.S., M.S., M.B.A., Regulatory Project Manager 301-796-3827 or Klaus Gottlieb, M.D, M.B.A.., Medical Officer* at 301-796-1969.

Concurrence: (as needed)

_____X_____ Medical Reviewer
_____X_____ Medical Team Leader
_____X_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

ROLAND GIRARDET
08/30/2010

KLAUS T GOTTLIEB
08/30/2010

ANIL K RAJPAL
08/30/2010

DONNA J GRIEBEL
08/30/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 022000/S-005

Name of Drug: LIALDA (mesalamine) Delayed Release Tablets, 1.2 g

Applicant: Shire Development Inc.

Material Reviewed:

Submission Date(s): 06/14/2010

Receipt Date(s): 06/14/2010

Submission Date of Structure Product Labeling (SPL): 06/14/2010

Type of Labeling Reviewed: SPL (pdf)

Background and Summary

On June 14, 2010, Shire Development Inc. submitted Prior Approval Supplement 005 to NDA 022000 requesting the addition of an indication for *the maintenance of remission,* (b) (4) *in ulcerative colitis*. The following PLR labeling review of the package insert was based on the Structured Product Labeling (SPL) version of the package insert submitted in XML and converted to pdf format. It should be noted that the applicant also submitted an annotated Word version of the package insert. The comments included in this review pertain only to the SPL version of the package insert. The applicant also included carton and container labeling as part of their submission, however, they are not proposing any changes to this labeling. The carton and container labeling was not reviewed.

Review

HIGHLIGHTS

1. There is no "Recent Major Changes" section within the Highlights. This section must be included with the following two subsections:
   - Indications and Usage (1) Month/Year of approval
   - Dosage and Administration (2) Month/Year of approval
2. (b) (4)
3. The revised date at the end of the highlights sections must be the date the supplement is approved.
4. According to CFR 201.57(d) (9), sections and subsections that contain Recent Major Changes must include a vertical line in the left margin "margin mark" identifying the new text. No such vertical lines are included in the left margin next to the new text in sections (1) and (2) in the Highlights.

FULL PRESCRIBING INFORMATION: CONTENTS

5. Identifying numbers must be separated from section and subsection headings must by at least two square "m"s (i.e., two squares of the size of the letter "m" in 8 point type). Additional space should be added between identifying numbers and section and subsection headings to meet this requirement.

FULL PRESCRIBING INFORMATION (FPI)

6. [redacted] (b) (4) Another form of emphasis such as italics or underling must be used for this text. Bold formatting should only be used in the section and subsection headings.
7. Cross references must be to section headings only, [redacted] (b) (4)
8. [redacted] (b) (4) The preferred format for cross-referencing is to use italicized and non-underlined text as follows: *[See Drug Interactions (7)]*.
9. According to CFR 201.57(d)(9), sections and subsections that contain Recent Major Changes must include a vertical line in the left margin ("margin mark") identifying the new text. [redacted] (b) (4)
10. Carton and Container labeling and the Package Insert should be submitted in separate files.

Recommendations

The deficiencies identified above should be communicated to the applicant in the 74-day letter or in a separate communication along with instructions to resubmit updated labeling. This updated version of labeling will be used for further labeling discussions.

Roland Girardet, M.H.S., M.S., M.B.A.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Richard Ishihara
Chief, Project Management Staff

Drafted: RG, 08/19/2010
Revised/Initialed:
Finalized:
Filename: RPM Labeling Review (NDA 022000/S-005).doc
CSO LABELING REVIEW OF PLR FORMAT

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

ROLAND GIRARDET
08/27/2010

RICHARD W ISHIHARA
08/27/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022000 BLA# N/A	NDA Supplement #:S- 005 BLA STN # N/A	Efficacy Supplement Type SE- 1
Proprietary Name: LIALDA Established/Proper Name: mesalamine Dosage Form: Delayed Release Tablets Strengths: 1.2 g		
Applicant: Shire Pharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: 06/14/2010 Date of Receipt: 06/14/2010 Date clock started after UN: N/A		
PDUFA Goal Date: 04/14/2011	Action Goal Date (if different): N/A	
Filing Date: 08/13/2010	Date of Filing Meeting: July 29, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): maintenance of remission (b) (4) in ulcerative colitis		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 066193	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	**X**			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	**X**			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		**X**		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		**X**		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		**X**		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		**X**		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		**X**		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			**X**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		**X**		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**X**		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			**X**	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			**X**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**			This information was not provided in the initial submission however it was subsequently submitted on 07/02/2010
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	**X**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**X**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	**X**			This information was not provided in the initial submission however it was subsequently submitted on 07/02/2010
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person*	**X**			

debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"				

Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			**X**	There is on CMC technical section

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**X**			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		**X**		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	**X**			A request for deferral with a pediatric plan is included.
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	**X**			The sponsor included a request for a deferral of studies in pediatric patients ages 5-17 years and submitted a pediatric plan for this age group. A waiver to study ages 0-5 was granted on 9/4/07.
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request?		**X**		

If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)				

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***		**X**		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	**X**			
Is the PI submitted in PLR format?	**X**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			**X**	PI was submitted in PLR format
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		**X**		Will send DDMAC consult after filing
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			**X**	There is no MedGuide, PPI, IFU with this drug
REMS consulted to OSE/DRISK?			**X**	There is no REMS with this drug
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		**X**		Will send DMEPA consult after filing
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		**X**		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** March 11, 2010 ***If yes, distribute minutes before filing meeting***	**X**			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		**X**		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: 07/29/2010

BLA/NDA/Supp #: NDA 022000/S-005

PROPRIETARY NAME: LIALDA

ESTABLISHED/PROPER NAME: mesalamine

DOSAGE FORM/STRENGTH: Delayed Release Tablets, 1.2 g

APPLICANT: Shire

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): The sponsor proposed to add the following to the existing indication: "*maintenance of remission,* [redacted] (b) (4) *in ulcerative colitis*"

BACKGROUND: On June 14, 2010, Shire submitted an efficacy supplement to add a maintenance indication to Lialda (mesalamine) Delayed Release Tablets 1.2 g. This drug was originally approved on January 16, 2007.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Roland Girardet	Y
	CPMS/TL:	Richard Ishihara	N
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y
Clinical	Reviewer:	Ii-Lun Chen/Klaus Gottlieb	Y both were present
	TL:	Anil Rajpal	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (*for antimicrobial*	Reviewer:	N/A	N/A

products)			
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	Kristina Estes	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:	Milton Fan	Y
	TL:	Mike Welch	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sushanta Chakder	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Yong Wang	N
	TL:	Marie Kowblansky	N
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	N
	TL:	N/A	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Facility Review/Inspection	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OSE/DMEPA (proprietary name)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Bioresearch Monitoring (DSI)	Reviewer:	Khairy Malek	N

	TL:	N/A	N/A

Other reviewers		
Other attendees	Wayne Amchin, DDMAC	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: No comments.	☐ Not Applicable
CLINICAL **Comments**: No comments other than that the application appears complete for filing	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

mitigation, treatment or prevention of a disease	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: No clinical pharmacology section was submitted as part of this supplemental application, therefore, clinical pharmacology will only be involved in reviewing the proposed pediatric plan and in labeling discussions.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: The Biostatistical Reviewer noted there were likely to be some review issues to be communicated to the sponsor in the 74-day letter; however, the supplemental application appeared to be acceptable for filing.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: No nonclinical data submitted as part of the supplemental application therefore nonclinical will only be involved in labeling discussions.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy	☒ Not Applicable

supplements only) **Comments**:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: No CMC information was submitted other than a request for categorical exclusion, therefore, CMC will only be involved in labeling discussions.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: No inspections required	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division Director (Donna Griebel, M.D., Director) **21st Century Review Milestones (see attached)** (optional): • **Stamp Date: 06/14/2010** • **Filing Date: 8/13/2010** • **74-Day Letter: 8/27/2010** • **Primary Review Completion Date: 3/10/11** • **Secondary Review Completion Date: 3/17/2011** • **CDTL Review Completion Date: 3/24/2011** • **Send Proposed Labeling/PMCs/PMRs to Sponsor: 3/17/2011** • **PDUFA Application Goal Date: 04/14/2011** **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other

	pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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

/s/

ROLAND GIRARDET
07/29/2010

RICHARD W ISHIHARA
07/30/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022000/S-005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22000 SUPPL # 005 HFD # 180

Trade Name LIALDA DELAYED RELEASE TABLETS 1.2G

Generic Name Mesalamine

Applicant Name Shire Development Inc

Approval Date, If Known 07/14/2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 022301 Apriso

NDA# 020049 Pentasa

NDA# 019618 Rowasa

NDA# 021252 Canasa

NDA# 019651 Asacol

NDA# 021830 Asacol HD

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SPD476-304: MATRx Maintenance: A Phase 3, Randomised, Multi-centre, Double-blind, Parallel Group, Active Comparator Study to Compare the Efficacy and Safety of SPD476 (Mesalazine) 2.4g/day Once Daily (QD) With Asacol 1.6g/day Twice Daily (BID) in the Maintenance of Remission in Patients With Ulcerative Colitis

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

SPD476-304: MATRx Maintenance: A Phase 3, Randomised, Multi-centre, Double-blind, Parralel Group, Active Comparator Study to Compare the Efficacy and Safety of SPD476 (Mesalazine) 2.4g/day Once Daily (QD) With Asacol 1.6g/day Twice Daily (BID) in the Maintenance of Remission in Patients With Ulcerative Colitis

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 066193 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Kevin Bugin
Title: Regulatory Health Project Manager
Date: June 27, 2011

Name of Office/Division Director signing form: Andrew Mulberg
Title: Division Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

KEVIN B BUGIN
07/14/2011

ANDREW E MULBERG
07/14/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 2200 BLA #	NDA Supplement # 005 BLA STN #	If NDA, Efficacy Supplement Type: 005
Proprietary Name: LIALDA Established/Proper Name: mesalamine Dosage Form: Delayed Release Tablets, 1.2g		Applicant: Shire Pharmaceuticals Agent for Applicant (if applicable):
RPM: Kevin Bugin		Division: DGIEP

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 07/14/2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	07/14/2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 07/14/2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	07/14/2011
• Original applicant-proposed labeling	06/14/2010; 10/01/2010
• Example of class labeling, if applicable	Asacol Label – 05/2010

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	06/14/2010
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 08/27/2011 ☒ DMEPA Email 06/08/2011 ☐ DRISK ☒ DDMAC 06/22/2011 ☒ SEALD 07/01/2011 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	07/30/2010
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 12/15/2010 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	07/07/2010; 08/27/2010; 10/07/2010; 10/14/2010;

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	12/08/2010; 03/04/2011; 03/04/2011; 07/05/2011;
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 07/14/2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 07/14/2011
PMR/PMC Development Templates *(indicate total number)*	☒ None See PeRC Template
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A See CDTL Review.
• Clinical review(s) *(indicate date for each review)*	07/29/2010; 07/11/2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Review – 07/11/2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None Epi Review – 11/10/2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 02/09/2011

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 07/14/2011
Statistical Review(s) *(indicate date for each review)*	☐ None 08/19/2010; 07/14/2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 08/18/2010; 07/08/2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 08/03/2010; 06/09/2011
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 07/30/2010; 07/11/2011
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Product Quality Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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

/s/

KEVIN B BUGIN
07/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults**

From: Kristina Estes, Pharm.D.	**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**

DATE: 7/8/11	NDA No: **22000** Suppl No.: 005		DATE OF DOCUMENT	6/14/10
NAME OF DRUG **Lialda (mesalamine)**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Shire

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ **LABELING** REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW):* [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☒ E-mail comments to: Project Manager ☒Medical☐Chemist☐Pharm-Tox ☐Micro☐Pharmacometrics☐ Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [26 Jun 2009]	☐ Formal Review/Memo (attached) ☒See comments below ☐See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☒ **NEED BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR** ☐ **NA**

COMMENTS/SPECIAL INSTRUCTIONS:

BACKGROUND: The current efficacy supplement was submitted in support of a new indication for maintenance of remission of ulcerative colitis. There were no proposed changes to clinical pharmacology portions of the label. However, during labeling discussions, the clinical division sought clarification regarding the appropriateness of a drug interaction identified in the current label. An interaction of azathiprine and 6-mercaptopurine (6-MP) with mesalamine (not Lialda) is listed in the Drug Interactions section and this interaction is not identified in other mesalamine labels. See label below.

Currently Approved Label

7 DRUG INTERACTIONS

No investigations of interaction between LIALDA and other drugs have been performed. However, the following are reports of interactions between mesalamine medications and other drugs.

7.1 Nephrotoxic agents, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions.

7.2 Azathioprine or 6-mercaptopurine

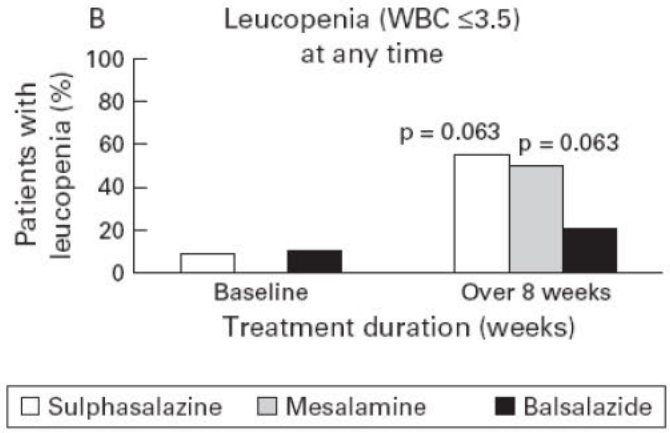
The concurrent use of mesalamine can increase the potential for blood disorders.

The interaction was present in the initial approved labeling from 2007, although the format was non-PLR. Therefore, the interaction was listed in the PRECAUTIONS section of the label and was not reviewed by the clinical pharmacology reviewer at that time. The sponsor did not provide the results of any drug interaction studies with the original submission. The azathioprine/6-MP interaction may have originated from the literature [*Gut* 2001;49:656-664] or may have been included to be consistent with the azathioprine and 6-MP labels.

Both 6-MP and its prodrug azathioprine are metabolized by thiopurine methyltransferase (TPMT) to form 6-MMP. Patients with low or intermediate TPMT activity are at risk of myelosuppression caused by accumulation of an active thiopurine metabolite 6-TGN. Mesalamines and other benzoic acid derivatives have been reported to reversibly inhibit the activity of TPMT *in vitro*. The *Gut* article describes a study of 34 patients with Crohn's disease of whom 10 received their usual azathioprine or 6-MP treatment with or without 4 g mesalamine (Pentasa 1g QID) for eight weeks. The other subjects received either sulphasalazine or balsalazide in addition to azathioprine or 6-MP. Patients with low TPMT activity were not eligible to participate.

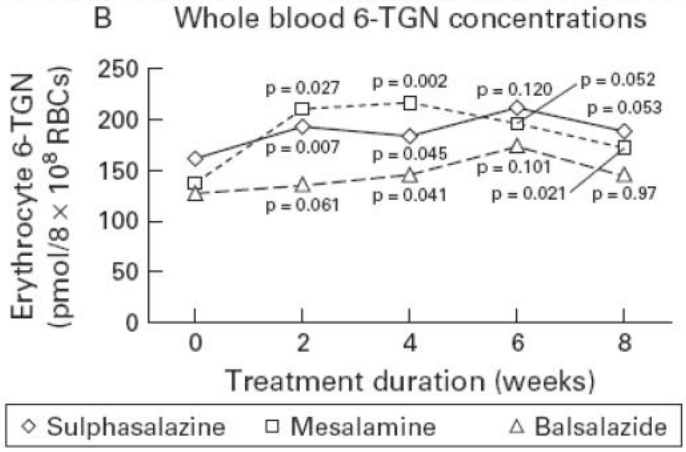
Study Results

The percentage of patients with clinically important leukopenia by treatment group.



Over the eight week study, 5 (50%) of the patients who received mesalamine in addition to their usual dose of azathioprine or 6-MP were found to have leukopenia (WBC count ≤ 3.5×10^9/l) that was not present at baseline. This incidence would not be expected from treatment with azathioprine or 6-MP alone or from treatment with mesalamine alone.

The mean whole blood 6-TGN concentrations at each study visit according to treatment group.



An increase in the concentration of 6-TGN, the active metabolite associated with myelosuppression, in whole blood was observed for patients who received mesalamine and sulphasalazine compared to baseline.

The investigators concluded that the interaction was significant based on the incidnece of leukopenia and the increase in 6-TGN concentrations.

In addition to the results of the study, the interaction is present in both the azathioprine and 6-MP labels.

The PRECAUTIONS section of the Imuran (azathiporine) label states the following:

Use with Aminosalicylates: There is in vitro evidence that aminosalicylate derivatives (e.g., sulphasalazine, mesalazine, or olsalazine) inhibit the TPMT enzyme. Concomitant use of these agents with IMURAN should be done with caution.

The PRECAUTIONS section of the Purinethol (mercaptopurine) label states the following:

As there is *in vitro* evidence that aminosalicylate derivatives (e.g., olsalazine, mesalazine, or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent mercaptopurine therapy (see **WARNINGS**).

RECOMMENDATION: It is reasonable to keep in the label the mesalamine interaction with azathioprine and 6-MP. However, we recommend the statemtn under 7.2 be revised to read "**The concurrent use of mesalamine with azathioprine or 6-mercaptopurine ~~can~~ may increase the ~~potential~~ risk for blood disorders**." The interaction is present in the azathioprine and 6-MP labels although it is described as a potential interaction based on *in vitro* data. The results of the clinical study described in *Gut* support the *in vitro* results although it is not definitive due to the small sample size and the lack of a placebo arm in the study. The potential interaction is not limited to Lialda. Therefore, the interaction should also be described in the labels of other mesalamine products for consistency.

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/s/

KRISTINA E ESTES
07/08/2011

SUE CHIH H LEE
07/08/2011

Bugin, Kevin

From: Bugin, Kevin
Sent: Wednesday, June 15, 2011 8:19 PM
To: Rotman, Harris
Cc: Mota, Linda; 'Wigley, Mary Beth'; Dewey, Maureen
Subject: NDA22000/S005 - Draft Labeling Comments and Required Postmarketing Study - June 15, 2011
Attachments: NDA22000-S005-RedLinedPLRLabel_FDA1.doc

Hi Harris,

Reference is made to you supplemental application dated June 14, 2010, for NDA 022000/S-00 5 LIALDA Delayed Release Tablets, 1.2 G. Please find attached an annotated WORD document containing FDA's revisions to your proposed patient package insert label. Of note, please assist us by completing or verifying the information in the two pieces of text highlighted in the annotated document.

Additionally, you will be responsible for the following required postmarketing study under the Pediatric Research Equity Act (PREA). Upon review of the required pediatric studies, submit to your supplemental NDA a timetable identifying the following milestone dates: **Final Protocol Submission Date, Study Completion Date, and the Final Study Report Submission Date**.

- Deferred pediatric study under PREA for the maintenance of remission of ulcerative colitis in pediatric patients 6 years and older

If you have any questions or comments, please do not hesitate to contact me. Of note, I will be on leave from tomorrow, June 16, through Friday, June 17. During this time you may contact my colleague, Maureen Dewey, if you have anything urgent.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

++

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/s/

KEVIN B BUGIN
07/05/2011

Bugin, Kevin

From: Baugh, Denise
Sent: Wednesday, June 08, 2011 1:15 PM
To: Bugin, Kevin
Cc: Bridges, Todd; Patel, Nitin M. (CDER/OSE)
Subject: NDA 22000/S005 Lialda - DMEPA comments

Follow Up Flag: Follow up
Flag Status: Red

Hi, Kevin!

As discussed in the meeting today for the above application, DMEPA recommends the following revision in the Dosage and Administration Section under Highlights of Prescribing Information:

Revise [redacted] (b) (4) to read "For maintenance of remission, two 1.2 g tablets should be taken once daily with food".

Thanks!

Denise

Denise Baugh, PharmD, BCPS
Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Surveillance and Epidemiology
Bldg 22, Room 4428
(301)796-2266

Together Everyone Achieves More"

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22000/S-005 **INFORMATION REQUEST**

Shire Development, Inc.
Attention: Harris Rotman, Ph.D.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rotman:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LIALDA (mesalamine) Delayed Release Tablets, 1.2 g.

We also refer to your submission dated February 22, 2011.

We are reviewing the Statistics section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

1. There is a discrepancy between the datasets (in the submission dated June 14, 2010) and the Response to FDA Information Request document (in the submission dated February 22, 2011) in the number of subjects that received Asacol 1.6 g/day in phase 1 of Study SPD476-304. [The terms "phase 1" and "phase 2" were defined in your Response to Information Request dated September 20, 2010. Phase 1 is based on the pre-amendment sample size; phase 2 is based on the additional sample added by the amendment (excludes the pre-amendment sample).] From the efficacy datasets submitted, we found that 210 subjects were enrolled before July 20, 2006 (estimated date of dosing of last subject in phase 1), but the Response to FDA Information Request document indicates there were 209 subjects enrolled in phase 1. Please clarify.

2. It appears that new subjects were not enrolled for approximately 16 months after the estimated date of dosing of the last subject in phase 1. In the datasets, there is a 16 month gap from the date of the last subject in phase 1 receiving the first dose of study medication (July 20, 2006) to the date of the next subject receiving the first dose of study medication (November 22, 2007). The response to information request dated September 20, 2010, does not discuss this delay in enrollment. Please explain the reasons for the 16 month delay in enrollment, and describe the procedures you used to ensure that the data was blinded during this time period.

If you have questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
03/04/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22000/S-005

REVIEW EXTENSION – EFFICACY SUPPLEMENT

Shire Development, Inc.
Attention: Harris Rotman, Ph.D.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rotman:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LIALDA (mesalamine) Delayed Release Tablets, 1.2 g.

On February 22, 2011, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 14, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 16, 2011.

If you have questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
03/04/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22000S-005

INFORMATION REQUEST

Shire Development, Inc.
Attention: Harris Rotman, Ph.D.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rotman:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LIALDA (mesalamine) Delayed Release Tablets, 1.2 g.

We also refer to your submissions dated June 14, June 25, July 02, July 15, September 10, September 20, September 24, October 01, October 08, October 26, November 02, and November 19, 2010.

We are reviewing the Biometrics section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your supplemental application. Please provide:

1. Details of any correspondence between Shire and FDA regarding clinical study SPD476-304 regarding the study sample size amendment and dates of relevant submissions.

2. Separate Clinical Study Reports for the two phases (i.e., “phase 1” and “phase 2”) of study SPD476-304. [The terms “phase 1” and “phase 2” were defined in your Response to Information Request dated September 20, 2010. Phase 1 is based on the pre-amendment sample size; phase 2 is based on the additional sample added by the amendment (excludes the pre-amendment sample).]

3. Separate analyses of the primary efficacy endpoint in the ITT (all patients randomized) population for phase 1, phase 2, and phase 1 and 2 combined.

4. Separate analyses of the secondary efficacy endpoints in the ITT population for phase 1, phase 2, and phase 1 and 2 combined.

If you have questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
12/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022000/S-005 **INFORMATION REQUEST**

Shire Development, Inc.
Attention: Harris Rotman, Ph.D.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rotman:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LIALDA (mesalamine) Delayed Release Tablets, 1.2 g.

We also refer to your submission dated September 10, 2010, which provided a response to the clinical request for information included in our filing communication letter dated August 27, 2010.

We are reviewing your response and have the following comments and additional information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

Study Subject 71105:

In the cover letter of your response, you state that you are unable to provide the autopsy report for study subject 71105 due to the privacy law in Lithuania. We request that you provide copies of written correspondence, accompanied by good quality translations, with the Lithuanian authorities to document the request for the autopsy report and subsequent denial of this request.

Study Subject 56210:

In the cover letter of your response, you state that you are able to provide an autopsy report for Study Subject 56210, however, it appears as if the document included in the body of your submission entitled “Halottvizsgalati Bizonyitvany” is a death certificate rather than an autopsy report. We request that you attempt to obtain an autopsy report for this subject and provide written documentation, accompanied by good quality translations, of all related correspondence with Hungarian authorities, if you are unable to obtain this report.

In addition, it appears that the translation of the document entitled “Halottvizsgalati Bizonyitvany” is incomplete and many entries are translated as “illegible.” We request that you obtain a more complete translation of this document to help us understand the significance of the information in the document. Of particular interest is the meaning of the handwritten note in the lower margin of the document followed by three apparent exclamation marks.

If you have questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
10/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OSE/DEPI
Mail: OSE

FROM: Roland Girardet, Regulatory Project Manager, Office of Drug Evaluation III/Division of Gastroenterology Products, Phone: 301-796-3827

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/08/2010		22000/S-005	Protocol Synopsis	10/09/2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
LIALDA (mesalamine) Delayed Release Tablets, 1.2 g			11/08/2010

NAME OF FIRM: Shire

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Dear OSE, DGP requests consultation from DEPI for information regarding two non-traffic related accidental deaths in a study using mesalamine for the maintenance of remission of ulcerative colitis. Christian Hampp is familiar the specific issue described below.

Background:

In study SPD476-303, two non-traffic fatal accidents were observed. The study had two components, an acute phase enrolling 312 subjects and a maintenance phase enrolling 225 and 234 subjects in a once-daily and twice daily regimen of mesalamine, respectively (see attached study synopsis). These deaths were coded to be related to suicide (acute phase) and electrical accident, respectively. Both deaths occurred in the twice daily treatment regimen. Unlike deaths which occur within the natural course of a serious illness, these fatalities were unexpected. The clinical information provided regarding these cases is very scanty and mostly based on foreign death certificates. Autopsies

were apparently performed but the sponsor has as of yet not been able to make them available to us.

In our preliminary research we have identified one paper which reports that overall survival of patients in a population based study of IBD patients from North America was similar to that expected in the US White population[1]. We also identified a paper with mortality rates due to unintentional injuries in the Netherlands spanning the years 1950-1995[2]. While current mortality in the Netherlands may be reflective of the situation in Western Europe at large, the data may not be entirely applicable to the study population in this study.

Specific questions:

We request a pharmaco-epidemiologic analysis of the above situation. Our specific questions are:

1. What is the likelihood of two non-traffic fatal accidents occurring purely by chance in the population at risk?
2. What is the appropriate denominator? For example, should the denominator be all patients exposed to any dose of mesalamine regardless of study phase adjusted by exposure time, or broken up by individual study segments?
3. What is a reasonable assumption for background risk (the study population consists of a mixture of participants from study sites in different countries or geographic regions)?
4. Is age adjustment required?
5. Lastly we would appreciate an overall assessment of whether the results obtained from the above analysis might be interpreted as a safety signal.

Reference List

1. Jess T, Loftus EV, Harmsen WS et al. Survival and cause specific mortality in patients with inflammatory bowel disease: a long term outcome study in Olmsted County, Minnesota, 1940-2004. Gut 2006;55(9):1248-1254.

2. van Beeck EF, Looman CWN, Mackenbach JP. Mortality due to unintentional injuries in the Netherlands, 1950-1995. Public Health Reports 1998;113(5):427-439.

If there are any questions, please feel free to contact me or the Medical Officer (Klaus Gottlieb, MD, ph: 301-796-1969) at your earliest convenience.

Best,

Roland Girardet
Regulatory Project Manager
Ph: 301-796-3827

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

ROLAND GIRARDET
10/08/2010

Girardet, Roland

From: Girardet, Roland
Sent: Tuesday, October 05, 2010 5:28 PM
To: 'Rotman, Harris'
Cc: Mota, Linda
Subject: Request for Pediatric Deferral Justification (NDA 022000/S-005)

Dear Dr. Rotman,

In reviewing your Supplementary New Drug Application (sNDA) for Lialda (mesalamine) Delayed-Release Tablets, 1.2 g., submitted on June 14, 2010, it has come to our attention that the application did not provide a justification for requesting a deferral of pediatric studies. Per 21 CFR 314.55(b), requests for deferrals of pediatric studies must be accompanied by the grounds for delaying pediatric studies. Please submit this justification as an information amendment to your supplemental application.

If you have any questions about this request, please do not hesitate to contact me at your earliest convenience.

Best Regards,

Roland Girardet, MHS, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: (301) 796-3827
Email: roland.girardet@fda.hhs.gov

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/s/

ROLAND GIRARDET
10/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022000/S-005 **FILING COMMUNICATION**

Shire Development, Inc.
Attention: Harris Rotman, Ph.D.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rotman:

Please refer to your June 14, 2010, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LIALDA (mesalamine) Delayed Release Tablets, 1.2 g.

We also refer to your submissions dated June 25, 2010, July 2, 2010 and July 15, 2010.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is April 14, 2011.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 17, 2011.

During our filing review of your supplemental application, we identified the following potential review issues:

1. In Study SPD 476-304, the sample size was increased from 410 to 826 during the trial due to a change in clinical assumptions. The timing, procedures and documentation relating to this increase in sample size are unclear. We consider this adaptive sample size adjustment to be unplanned, and consequently the interpretation of your primary analysis

results is questionable. The impact of this adaptive sample size adjustment on the primary efficacy endpoint needs to be evaluated, and some appropriate adjustment to the statistical significance level should be considered.

2. Your non-inferiority margin of 10% was obtained by estimating 50% of treatment effect observed in the Mesalamine Study Group trial referenced in your submission. However, this procedure should take into consideration study-to-study variability of treatment effect and a "discount factor" (we recommend 50%) should also be applied to account for uncertainty due to the "constancy assumption."

3. Analyses of the U.S. data showed a negative treatment effect for Lialda. Analyses of intrinsic and extrinsic factors that might cause regional differences in treatment effect, particularly for U.S. and non-U.S. regions, need to be conducted.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application.

We request that you submit the following information:

Statistical

1. Provide study details regarding planning, execution and documentation of your sample size adjustment. This should include detailed patient enrollment information at the time of the sample size increase.

2. Evaluate the impact of your adaptive sample size adjustment on the primary efficacy endpoint results using appropriate statistical methods and sensitivity analyses.

3. Re-evaluate your non-inferiority margin taking into account the study-to-study variability of treatment effects and apply a 50% discount for the "constancy assumption."

4. Conduct analyses to evaluate both intrinsic and extrinsic factors that would result in regional differences in treatment effect between U.S. and non-U.S. regions.

Clinical

1. Submit additional information regarding the two deaths that occurred in study SPD-476-303. Your responses should include copies of medical records, summary statements, death certificates, autopsy reports or other documents accompanied by English translations that would help us make an independent determination of whether or not the deaths were possibly related to study medications.

   Study subject 71105, a 67-year-old Caucasian male, died 7 days after the last dose of study medication after having suffered an unwitnessed fall. Since there is at least one

report describing serious central nervous system side effects which were attributed to mesalamine, more information on this fatal SAE is necessary before discounting any possible association. An autopsy report is apparently available and every effort should be made to procure the report.

Study subject 56210, a 25-year-old Caucasian female, died due to an electrical accident involving household current. While fatalities in these circumstances are certainly possible, they are unusual and an underlying heart condition may have been a contributing factor. The patient was previously diagnosed with mitral valve prolapse syndrome and murmur. How this diagnosis was made and what symptoms the patient had (for example, palpitations and chest pain) may be relevant since myocarditis with serious cardiac arrhythmias has been described in patients taking mesalamine.

Labeling

The following deficiencies have been identified in the package insert submitted in SPL as part of your supplement application. The package insert should be revised according to the comments listed below and resubmitted for further review.

HIGHLIGHTS

1. There is no "Recent Major Changes" section within the Highlights. This section must be included with the following two subsections:
   - Indications and Usage (1) Month/Year of approval
   - Dosage and Administration (2) Month/Year of approval

2. [redacted] (b) (4)

3. The revised date at the end of the highlights sections should be the date the supplement is approved.

4. In accordance with 21 CFR 201.57(d)(9), sections and subsections that contain Recent Major Changes must include a vertical line in the left margin "margin mark" identifying the new text. [redacted] (b) (4)

FULL PRESCRIBING INFORMATION: CONTENTS

5. Identifying numbers must be separated from section, and subsection headings must by at least two square "m"s (i.e., two squares of the size of the letter "m" in 8 point type). Additional space should be added between identifying numbers and section and subsection headings to meet this requirement.

FULL PRESCRIBING INFORMATION

6. [redacted] (b) (4)

[redacted] (b) (4) Another form of emphasis such as italics or underlining should be used for this text. Bold formatting should only be used in the section and subsection headings.

7. Cross references should be to section headings only, [redacted] (b) (4)

8. [redacted] (b) (4) The preferred format for cross-referencing is to use italicized and non-underlined text as follows: *[See Drug Interactions (7)]*.

9. In accordance with 21 CFR 201.57(d)(9), sections and subsections that contain Recent Major Changes should include a vertical line in the left margin ("margin mark") identifying the new text. [redacted] (b) (4)

10. Carton and Container labeling and the Package Insert should be submitted in separate files.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the partial waiver granted on September 4, 2007, for the pediatric study requirement for this application for pediatric patients less than 5 years of age.

We acknowledge receipt of your request for a partial deferral of pediatric studies in patients 5 to 17 years of age for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

DONNA J GRIEBEL
08/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Roland Girardet, Regulatory Project Manager, Office of Drug Evaluation III, Division of Gastroenterology Products (DGP), 301-796-3827

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
08/18/2010		22000/S-005	Package Insert	06/14/2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
LIALDA (mesalamine) Delayed Release Tablet, 1.2 g	Standard		03/07/2011

NAME OF FIRM: Shire Development, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

DGP requests OSE review of the labeling (PI) for NDA 022000, Supplement-005. This is an efficacy supplement to add an indication of - *maintenance of remission*, [redacted] (b) (4) *, in ulcerative colitis*. This is an eCTD submission. The most recent version of the package insert will be available via the eRoom link below. No changes to the carton and container labeling has been proposed as part of this supplement and there is no PPI.

Mid-Cycle Meeting: [12/03/2010]
Wrap-Up Meeting: [03/02/2011]
Labeling Meetings: [03/08/2011, 03/15/2011, 03/24/2011, 03/28/2011, 03/31/2011, 04/05/2011]
PDUFA Goal Date:[04/14/2011]

The package insert is available via the links below:
Global submit link: \\cdsesub1\EVSPROD\NDA022000\022000.enx (Submit date: 06/14/2010)
eRoom link - http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_16ce5

If there are any questions, please feel free to contact me.

-Roland Girardet, Regulatory Project Manager, DGP, 301-796-3827	
SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

ROLAND GIRARDET
08/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Roland Girardet, Regulatory Project Manager, Office of Drug Evaluation III, Division of Gastroenterology Products, 301-796-3827

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
08/18/2010		NDA 22000/S-005	Package Insert

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
LIALDA (meslamine) Delayed Release Tablets, 1.2 g	Standard		2nd labeling meeting (3/15/2011)

NAME OF FIRM:	
Shire Development, Inc.	PDUFA Date: 04/14/2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)

- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT

- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:

Global submit link: \\cdsesub1\EVSPROD\NDA022000\022000.enx (Submit date: 06/14/2010)

eRoom link - http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_16ce5

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

DGP requests DDMAC review of the Package Insert for NDA 022000, Supplement-005. This is an efficacy supplement to add an indication of - *maintenance of remission*, [redacted] (b) (4), *in ulcerative colitis*. This is a eCTD submission. The most recent version of the label will be available via the eRoom link above.

Mid-Cycle Meeting: [12/03/2010]
Labeling Meetings: [03/08/2011, 03/15/2011, 03/24/2011, 03/28/2011, 03/31/2011, 04/05/2011]
Wrap-Up Meeting: [03/02/2011]

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

ROLAND GIRARDET
08/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-000/S-005 **INFORMATION REQUEST**

Shire Development, Inc.
Attention: Harris Rotman, Ph.D.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rotman:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lialda® (mesalamine) Delayed Release Tablets.

We also refer to your submission dated June 14, 2010.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

Please provide an environment assessment or a claim for a categorical exclusion to support the proposed change in the supplement.

If you have questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Hasmukh B. Patel, Ph.D.
Branch Chief
Branch III, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

HASMUKH B PATEL
07/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022000/S-005 **PRIOR APPROVAL SUPPLEMENT**

Shire Development, Inc.
Attention: Harris Rotman, Ph.D.
Director, Global Regulatory Affairs
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Dr. Rotman:

We have received your June 14, 2010, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	LIALDA (mesalamine) Delayed Release tablets, 1.2 g
NDA Number:	022000
Supplement number:	005
Date of supplement:	June 14, 2010
Date of receipt:	June 14, 2010

This supplemental application proposes the following changes: The addition of clinical information to the US Prescribing Information (USPI) based on three clinical studies in the maintenance of remission of ulcerative colitis, and revision of the current indication to include "*maintenance of remission,* [redacted] (b) (4) *, of ulcerative colitis.*"

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 13, 2010 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 14, 2011.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable

clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,* to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at:

http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Roland Girardet, M.H.S., M.S., M.B.A.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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/s/

ROLAND GIRARDET
06/24/2010

Girardet, Roland

From: Girardet, Roland
Sent: Wednesday, June 23, 2010 6:53 PM
To: 'Rotman, Harris'
Cc: Mota, Linda
Subject: NDA 022000/S-005 eCTD module 5.3.5.3. technical issues

Dear Dr. Rotman,

Please refer to your prior approval efficacy supplement eCTD submission for LIALDA (mesalamine) Delayed Release tablets 1.2 g dated June 14, 2010.

We have encountered some technical and formatting eCTD submission issues with module 5.3.5.3. which need to be corrected in order for this section or your supplement to be reviewed. Specifically, this module does not contain study tagging files (STF.xml) so the information for the ISS, Trial 304 and their associated files are not being displayed correctly. None of the ISS or Trial 304 .xpt files are appearing under their study tag headings. Additionally, it appears there are very few dataset files in .xpt format provided in this module.

Please resubmit module 5.3.5.3. with the appropriate files and formatting in order for us to continue to evaluate your submission. If you have any questions regarding these technical and formatting issues please contact esub@fda.hhs.gov. Additional information regarding eCTD submissions can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

If you have any general questions regarding this request, please feel free to contact me at 301-796-3827.

Best regards,

Roland Girardet, MHS, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: (301) 796-3827
Email: roland.girardet@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22000	SUPPL-5	SHIRE DEVELOPMENT INC	LIALDA DELAYED RELEASE TABLETS 1.2G

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ROLAND GIRARDET
06/24/2010