CLINICAL REVIEW

Application Type	Pediatric (b) (4) supplement for NDA 21830/6 (Asacol HD) and NDA 19651/24 (Asacol).
Application Number(s)	sNDA 21830/6 sNDA 19651/24
Priority or Standard	10 month standard
Submit Date(s)	December 21, 2012
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Division / Office	DGIEP
Reviewer Name(s)	Juli Tomaino, MD, Medical Officer Anil Rajpal, MD, Team Leader
Review Completion Date	September 16, 2013
Established Name	Mesalamine
(Proposed) Trade Name	Asacol HD 800mg
Therapeutic Class	5-aminosalicylic acid (5-amino-2-hydroxybenzoic acid)
Applicant	Warner Chilcott
Formulation(s)	400mg delayed release tablets
Dosing Regimen	1.2 g/day to (b) (4) g/day twice daily oral
Indication(s)	Mildly- to- moderately active ulcerative colitis
Intended Population(s)	Pediatric patients ages 5 -17 years old

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, (b) (4) is acceptable to support recommendation for approval of Asacol 400mg for the treatment of mildly to moderately active ulcerative colitis in patients ages 5 years and older, after agreement with revised labeling for Asacol HD and Asacol.

1.2 Risk Benefit Assessment

The current pediatric (b) (4) supplement fulfills the PREA PMR 319-1 under Asacol HD (NDA 021830). The submission included one clinical trial that evaluated the safety and efficacy of Asacol 400 mg delayed release tablets over 6 weeks trial duration for 82 pediatric patients ages 5 to 17 years old for the treatment of mildly to moderately active ulcerative colitis. The safety data were collected from three pediatric, uncontrolled clinical trials. The safety profile was found to be similar to the known safety profile of Asacol 400mg delayed release tablets.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A REMS is not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Ulcerative colitis (UC) is a chronic, relapsing and remitting type of inflammatory bowel disease (IBD) of the mucosa in the colon. The incidence of UC in children is approximately 2/100,000 in the United States.[1] Symptoms of UC include abdominal pain, vomiting, hematochezia, tenesmus, fatigue, anemia, weight loss, delayed growth and puberty, and decreased bone mineralization. Pediatric onset is often more severe with higher colectomy and hospitalization rates than in adult onset cases.[2,3] The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Crohn's and Colitis Organization (ECCO) published a Guideline for Management of Pediatric UC in 2012.[4] The recommended

[1] Kugathasan S. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. J Pediatr. 2003; 143(4):525-31.
[2] Hyams JS, et al. Clinical outcomes of ulcerative colitis in children. JPeds 1996; 129: 81-88
[3] Turner D, Walsh CM, Benchimol EI, et al. Severe paediatric ulcerative colitis: incidence, outcomes and optimal timing for second-line therapy. Gut 2008;57:331-8
[4] Turner D, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines.J Pediatr Gastroenterol Nutr. 2012; 55(3):340-61.

diagnostic work up includes a medical history, physical exam, colonoscopy and upper endoscopy, laboratory investigations (complete blood count, chemistry, liver function panel, erythrocyte sedimentation rate, iron panel, C-reactive protein), and stool cultures to exclude infections such as *Clostridium difficile*, and possibly immunologic testing in younger children. The gold standard to diagnose UC is endoscopy and histologic exam. The biochemical markers of inflammation may aid in the diagnosis but surrogate biomarkers that closely correlate with intestinal inflammation still need to be identified. Fecal calprotectin and lactoferrin are proteins found in neutrophils that play a role in the innate immune response. These proteins have been found in stool samples of patients with IBD; however, further studies need to be performed to identify the role of these proteins in the diagnosis and management of IBD.[5]

Few of the therapies used to induce and maintain remission of pediatric UC have been studied in pediatric clinical trials and information has been extrapolated from adult data.[5] Aminosalicylate therapy is effective in mild to moderate UC.[6] Balsalazide (Colazal)[7] and sulfasalazine (Azulfidine)[8] have been approved with pediatric indications. Sulfasalazine contains sulfapyridine, an inert carrier responsible for many of the associated side effects, and the active anti-inflammatory moiety, mesalamine. Mesalamine, a 5-aminosalicylate (5-ASA), is a topical anti-inflammatory. The newer 5-ASA agents, Asacol and Pentasa, do not utilize the sulfapyridine component.[5] The guidelines for management of pediatric UC state that oral 5-ASA therapy, mesalamine or sulfasalazine, is recommended as first line therapy for induction of remission in mildly to moderately active pediatric UC. [4] According to the guidelines, the recommended mesalamine dose is 60 to 80 mg/kg/day divided in two daily doses, up to a maximum of 4.8 g daily. Although not evidence based, doses of up to 100 mg/kg/day are sometimes used in clinical practice.[2] Table 1 below lists the currently available oral mesalamine-containing drugs for treatment of UC. Mesalamine-containing therapies are widely used off-label in treatment of pediatric UC patients.

2.1 Product Information

Asacol (mesalamine) 400mg delayed-release tablets and Asacol HD 800mg delayed-release tablets are in the pharmacologic class of aminosalicylates. Asacol and Asacol HD are not bioequivalent. Both products are discussed in this review because the approval of Asacol (1992) pre-dates PREA PMR/PMCs. This pediatric (b) (4) supplement was submitted to the Asacol HD NDA (021830) to fulfill the PREA requirement (PMR 391-1). Asacol 400mg tablets were determined to be the pediatric formulation for use in this pediatric trial (b) (4) and Asacol contains the same active moiety approved for the same indications. The reader is referred to the PeRC PREA Subcommittee meeting minutes, dated April 9, 2008. Asacol 400mg is indicated for the

[5] Rufo P, Bousvaros A. Current Therapy of Inflammatory Bowel Disease in Children. Pediatr Drugs. 2006; 8(5): 279-302
[6] Kornbluth AA. Meta-analysis of the effectiveness of current drug therapy of ulcerative colitis J Clin Gastroenterol. 1993; 16(3):215-8.
[7] Colazal label, last updated November 2, 2007, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020610s017lbl.pdf
[8] Azulfidine, http://dailymed nlm.nih.gov/dailymed/lookup.cfm?setid=ddbe69f3-bd55-45f3-a64f-f60226c744c4#nlm34067-9

treatment of mildly to moderately active UC at a dose of 2.4 g/day (800 mg divided three times daily), and for the maintenance of remission of UC at a dose of 1.6g/day in divided doses. Asacol HD 800mg is approved for the treatment of moderately active UC at a dose of 4.8g/day (two 800mg tablets administered three times daily for 6 weeks); safety and effectiveness beyond 6 weeks has not been established.[9] Mesalamines are thought to act as topical anti-inflammatory medications in the intestine by inhibition of prostaglandin and leukotriene synthesis.

Each Asacol delayed-release tablet contains 400 mg of mesalamine. The Asacol delayed-release tablets (b) (4) acrylic based resin, Eudragit S (methacrylic acid copolymer B, NF), which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action. Mesalamine has the chemical name 5-amino-2-hydroxybenzoic acid, molecular weight: 153.1, and molecular formula: C7H7NO3. Inactive ingredients include colloidal silicon dioxide, dibutyl phthalate, edible black ink, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, methacrylic acid copolymer B (Eudragit S), polyethylene glycol, povidone, sodium starch glycolate, and talc.[10]

2.2 Tables of Currently Available Treatments for Proposed Indications

Current therapies with approved indications for treatment of ulcerative colitis are shown in the table below.

Table 1 : Current Therapies with Approved Indications for Treatment of Ulcerative Colitis[11]

Drug name	Indication	Approved Pediatric indication (yes/no)
Apriso (mesalamine)	Maintenance of remission of UC in adults	No
Asacol (mesalamine)	Treatment of mildly to moderately active UC and for the maintenance of remission of UC	No
Asacol HD (mesalamine)	Treatment of moderately active UC	No
Lialda (mesalamine)	Induction of remission in adults with mild to moderately active UC and for maintenance of remission of UC	No
Pentasa (mesalamine)	Induction of remission and for treatment of patients with mildly to moderately active UC	No
Canasa (mesalamine rectal suppository)	Treatment of adult patients with ulcerative proctitis	No

[9] Asacol HD label, last updated 5/24/2010. Available at http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm
[10] Asacol approved label, last updated 5/24/2010, accessed 6/10/2013. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019651s023lbl.pdf
[11] http://www.accessdata.fda.gov

Rowasa (mesalamine rectal enema and suppository)	Treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis	No
Colazal (balsalazide sodium)	Treatment of mildly to moderately active UC in patients 5 years and older	Yes
Azulfidine (sulfasalazine)	Treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis. The safety and effectiveness of in pediatric patients below the age of two years with ulcerative colitis have not been established	Yes
Humira (adalimumab)	Inducing and sustaining clinical remission in adults with moderately to severely active Crohn's and Ulcerative colitis	No
Remicade (infliximab)	See below	Yes

Corticosteroids, oral and IV, are approved during acute episodes of Crohn's and UC flares. Rectal preparations, such as Cortifoam enemas, are approved for treatment of ulcerative proctitis.

Remicade (infliximab) is a monoclonal antibody, administered through IV infusion, which neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.
Remicade is approved for the indications listed below.[12]

- Crohn's disease: reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy, reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
- Ulcerative Colitis: reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Pediatric Crohn's Disease: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Pediatric Ulcerative Colitis: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Azathioprine (Imuran), 6-mercaptopurine (6MP), and methotrexate are used in the treatment of ulcerative colitis and Crohn's disease; however, the current labels do not include inflammatory bowel disease as approved indications. Cyclosporine, tacrolimus, and mycophenolate mofetil are

[12] Remicade label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5295lbl.pdf

used less frequently in clinical practice for short term treatment of severe pediatric UC.[13] These therapies are used in severe disease when bridging a long-term maintenance therapy or in attempts to delay colectomy, and have not been approved for a pediatric indication.

2.3 Availability of Proposed Active Ingredient in the United States

Oral and rectal mesalamine formulations are approved and marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Renal impairment, acute exacerbation of colitis, and hypersensitivity reaction are associated with mesalamine products.[10]

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Regulatory timeline:

January 1992 : Asacol 400mg delayed release tablets (NDA 19651) approved for the treatment of mild to moderate active ulcerative colitis (UC).

August 1997: Asacol 400mg (NDA 19651) approved for the maintenance of remission of UC. There were no PMC/PMRs requested at that time, however, a written request (WR) for pediatric studies was issued in 2001 and amended on June 27, 2008.

May 29, 2008: Asacol HD 800mg delayed-release tablet (NDA 21830) was approved for treatment of moderately active UC with the following PMR.

PMR 319-1 under NDA 21830 required that the sponsor conduct a study to evaluate PK, safety, and clinical response of pediatric patients, ages 5 to 17 years old with UC, undergoing six weeks of oral mesalamine therapy using an age-appropriate formulation (i.e., an oral mesalamine formulation appropriate for pediatric dosing), such as the approved product, Asacol. The study design was to be a randomized, double-blind study comparing at least two different dose levels of mesalamine and it will enroll at least 40 pediatric patients in each dosing arm. Final report submission completion date was January 15, 2011.

January 20, 2011: In response to the WR for Asacol 400mg (NDA 19651), Warner Chilcott notified the FDA that Study 2008085, titled "A Randomized, Double-blind, Parallel-group Study to Assess the Safety and Efficacy of Asacol (1.2g to 4.8g/day) 400mg Delayed-release Tablets Given Twice Daily for 26 Weeks to Children and Adolescents for the Maintenance of Remission of Ulcerative Colitis", was being terminated early due to enrollment challenges and the WR was

[13] Rufo P, Bousvaros A. Current Therapy of Inflammatory Bowel Disease in Children. Pediatr Drugs. 2006; 8(5): 279-302

no longer being pursued. A final study report was submitted under IND [redacted]. The sponsor planned to complete the pediatric assessment PMR outlined under NDA 21830.

December 21, 2012: [redacted] information was submitted under NDA 21830. The submission included three study reports: (1) PK study, (2) induction of remission study, and (3) maintenance of remission study (terminated early due to lack of enrollment).

- Study 2005018: "A randomized, open-label, parallel-group study to determine the pharmacokinetics of mesalamine following administration of 30 mg/kg/day, 60 mg/kg/day, and 90 mg/kg/day as Asacol 400 mg tablets given every 12 hours for 28 days to 34 children and adolescents (5-17 years of age) with active UC." This final study report was submitted to IND [redacted] on December 20, 2007.

- Study 2007017: "A Randomized, Double-blind, Parallel-group Study to Assess the Safety and Efficacy of Asacol (1.2g to 4.8g/day) Administered as 400mg Delayed-Release Tablets Given every 12 hours for 6 weeks to Children and Adolescents with Mildly to moderately Active Ulcerative Colitis." A final study report was submitted to IND [redacted] on October 28, 2011.

- Study 2008085: "A Randomized, Double-blind, Parallel-group Study to Assess the Safety and Efficacy of Asacol (1.2 to 4.8 g/day) 400 mg Delayed-release Tablets Given Twice Daily for 26 Weeks to Children and Adolescents for the Maintenance of Remission of Ulcerative Colitis." It should be noted that this study was terminated early due to lack of enrollment. The final abbreviated clinical study report was submitted to IND [redacted] on March 2, 2012.

July 31, 2012: NDA 204412 was submitted for WC3045 (mesalamine) delayed-release capsules, 400 mg (WC3045 capsules), a phthalate-free mesalamine formulation. The original submission contained a relative bioavailability study and special dissolution studies to demonstrate bioequivalence to Asacol 400 mg tablets. The new capsule WC3045 capsule is size 0, which is larger than the Asacol 400 mg tablets.

January 15, 2013: [redacted]

(b) (4)

February 1, 2013: NDA 204412 for WC3045 (Delzicol 400mg) was approved for induction and maintenance of mildly to moderately active UC in adults, based on demonstration of bioequivalence to Asacol 400 mg tablets, with the following required post-marketing requirements.

> 2011-1: A randomized, double-blind study in pediatric patients ages 5 – 17 years with ulcerative colitis using an age-appropriate formulation to evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy. The study should compare at least two different dose levels of mesalamine and enroll at least 40 pediatric patients in each dosing arm.
>
> Final protocol submission: 08/2013
> Study completion: 05/2015
> Final report submission: 09/2015
>
> 2011-2: A randomized, double-blind study in pediatric patients ages 5 - 17 years using an age-appropriate formulation for the maintenance of remission of ulcerative colitis.
>
> Final protocol submission: 08/2013
> Study completion: 05/2016
> Final report submission: 09/2016

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission included PDF files individually titled "volumes 1-9". The study report was organized and easy to follow. However, navigation was difficult through the unlabeled volumes. Data sets were provided for efficacy and safety populations. The sponsor responded to all requests for information during the review cycle.

3.2 Compliance with Good Clinical Practices

The sponsor stated that the studies were conducted in accordance with the Institutional Review Board (IRB) and/ or Independent Ethics Committee (IEC), and in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for GCP,

1997; the United States (US) Title 21 Code of Federal Regulations (CFR) parts 50, 56, and 312; and the ethical principles that have their origin in the Declaration of Helsinki.

No site inspections were performed for this study.

Protocol Deviations

Twenty-nine patients in the Low Dose and 25 in the High Dose group had a protocol deviation. Table 2 below shows the protocol deviations. Deviations in the "Other" category included follow-up phone call out of window, fecal biomarkers unable to obtain, visits out of window, and serum biomarker not obtained.

Table 2: Protocol Deviations (mITT population Study 2007017)

Protocol Deviation	Low Dose (N=41) n (%)	High Dose (N=41) n (%)	Overall (N=82) n (%)
OVERALL	29 (70.7%)	25 (61.0%)	54 (65.9%)
Other	23 (56.1%)	21 (51.2%)	44 (53.7%)
Major Deviation in PK Sampling	9 (22.0%)	6 (14.6%)	15 (18.3%)
Inclusion/Exclusion Criteria	5 (12.2%)	5 (12.2%)	10 (12.2%)
Deviation from Treatment Regimen	2 (4.9%)	2 (4.9%)	4 (4.9%)
Excluded Medication	0 (0.0%)	2 (4.9%)	2 (2.4%)

(Source: reproduced from sponsor study report volume 1- Study 2007017 , page 44/3086)

Details on the Inclusion/Exclusion criteria deviations are summarized below in Table 2a. Each of the deviations listed represents a deviation for an individual patient.

Table 2a: Deviations of Inclusion/Exclusion Criteria

Inclusion/Exclusion Protocol Deviation*	Treatment Group	*Week 6 Treatment Assessment: PUCAI	*Week 6 Treatment Assessment: TM-Mayo
Stool Sample Collection			
Stool sample not obtained	High Dose 3.6 g/day	Voluntary study withdraw	Voluntary study withdraw
Stool sample not obtained	Low Dose 2.0 g/day	TS- CR	TS- CR
Stool Sample Results			
Positive stool for ova and parasite	High Dose 4.8 g/day	TF	TS- PR
Stool positive for bacteria	High Dose 2.0 g/day	TF	TS- PR
Positive stool for blastocystis	Low Dose	TS- PR	TS- PR

hominis	1.2 g/day		
Positive stool culture, results received at Week 5	Low Dose 2.0 g/day	TS- PR	TS- PR
Stool culture positive for Salmonella (inadvertently missed)	Low Dose 1.2 g/day	TS- CR	TS- CR
Baseline TM-Mayo Score			
Baseline rectal bleeding score = 0	High Dose 4.8 g/day	TS- CR	TF
Baseline rectal bleeding score = 0	Low Dose 2.4 g/day	TS- PR	TS- PR
Other Exclusion Criteria			
History of fatty liver	High Dose 2.0 g/day	TS- CR	TS- CR

*TS: treatment success, CR: complete response, PR: partial response, TF: treatment failure. Refer to Table 13 for complete definitions. TM-Mayo Score: modified Mayo Score.

The high number of protocol deviations for inclusion/exclusion criteria raise concerns over poor compliance and monitoring. Deviations from inclusion/exclusion criteria could influence efficacy results by including patients who are more or less likely to respond to therapy. Patients with positive stool cultures would not be expected to improve with Asacol. In contrast, patients with baseline rectal bleeding scores of zero on the TM-Mayo may be more likely to respond due to having more mild disease than defined by the inclusion criteria.

In this trial, there were five patients (2 in the high dose group and 3 in the low dose group) who deviated from exclusion criteria and were included in the trial with positive stool cultures. With the exception of the patient with positive salmonella stool culture, the four patients with positive stool cultures were either treatment failures or partial responders at Week 6.

Two patients, who were included in the trial with baseline rectal bleeding scores of zero (inclusion criteria states rectal bleeding and stool frequency scores of at least 1), showed no change in rectal bleeding score at Week 6. One patient had no improvement in stool frequency (score of 2 at baseline and 2 at week 6). The other patient had an improvement of one point in stool frequency (score of 2 at baseline and 1 at week 6). Including patients with baseline scores of zero on the TM-Mayo score could potentially skew the results in favor of a treatment benefit. Conversely, these patients showed little to no improvement at week 6 assessment.

The protocol deviations were balanced between the low dose and high dose groups. In addition, efficacy was extrapolated from adult trials evaluating Asacol for the treatment of mildly to moderately active ulcerative colitis. Therefore, the impact on efficacy due to protocol deviations is less critical when efficacy is extrapolated.

3.3 Financial Disclosures

The sponsor and investigators who participated in Study 2005018, 2007017, and 2008085 stated that they did not enter into any financial agreement. FDA form 3454 was signed and submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new concerns. The formulation remained the same as what is approved for Asacol 400mg delayed release tablets.

4.2 Clinical Microbiology

No new concerns.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology studies were submitted because Asacol is already approved and marketed.

4.4 Clinical Pharmacology

Information in the clinical pharmacology section can be found in the Asacol label, last updated 5/24/2010.[10] In summary, the pediatric NDA supplement included a dose-ranging study in pediatric UC patients that assessed PK and safety following 30 mg/kg/day, 60 mg/kg/day, and 90 mg/kg/day of Asacol, administered twice daily for four weeks. The study adequately characterized PK of mesalamine and its metabolite in pediatric patients, and demonstrated dose-proportionality in exposure over the studied range. Sparse sampling for PK was also included in the pediatric trial (Study 2007017) that evaluated low dose up to 2.4 g/day and high dose up to 4.8 g/day levels. The steady-state average concentrations (Cavg) of mesalamine obtained following the low and high dose levels in this pediatric study suggest exposures similar to those reported at corresponding doses in adult patients.

Asacol is thought to act locally in the colon and systemic exposures (BA ~ 20%) are relevant primarily from a safety perspective. High fat meals do not affect the bioavailability; however, the C_{max} is decreased 47% and delayed 14 hours. The C_{max} occurs between 10 – 16 hours post dose. Asacol is metabolized to N-acetyl-mesalamine in liver and gut prior to excretion in kidney. The apparent half-life is 12 h for mesalamine and 23 hr for its major metabolite (N-acetyl-mesalamine), however, these values are driven by the delayed release of the product and flip-flop pharmacokinetics.

As the site of action is located within the GI tract, traditional exposure-response analyses and systemic exposure matching to adults may not be appropriate or possible for pediatric dose selection. Exposure-response relationships were evaluated with logistic regression models for both systemic plasma concentrations and predicted gut concentrations against the probability of

treatment success for inducing remission at the end of 6 weeks in the sponsor's phase 3 studies (both pediatric and adult data). No exposure-response relationships were identified for either exposure metric for both adults and children. The lack of gut concentration-response relationship was consistent with lack of dose-response observed in the phase 3 trial. Exposure-response was also evaluated for the N-acetyl-metabolite plasma AUC, however due to the high correlation with the parent, no correlation with response was observed. (b) (4) Thus, the sponsor's proposal for the lower of the two studied dose levels is acceptable. (b) (4)

Please refer to clinical pharmacology reviews by Dr. Justin Earp and Dr. Sandhya Apparaju, dated 9/13/2013.

4.4.1 Mechanism of Action

Mesalamine is thought to be the major therapeutically active part of the sulfasalazine molecule in the treatment of ulcerative colitis. Sulfasalazine is converted to equimolar amounts of sulfapyridine and mesalamine by bacterial action in the colon. The usual oral dose of sulfasalazine for active ulcerative colitis is 3 to 4 grams daily in divided doses, which provides 1.2 to 1.6 grams of mesalamine to the colon.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. 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.

4.4.2 Pharmacodynamics

Asacol tablets (b) (4) an acrylic-based resin that delays release of mesalamine until it reaches the terminal ileum and beyond. This has been demonstrated in human studies conducted with radiological and serum markers. Approximately 28% of the mesalamine in Asacol tablets is absorbed after oral ingestion, leaving the remainder available for topical action and excretion in the feces. Absorption of mesalamine is similar in fasted and fed subjects. The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver. It is excreted mainly by the kidney as N-acetyl-5-aminosalicylic acid.

4.4.3 Pharmacokinetics

Mesalamine from orally administered Asacol tablets appears to be more extensively absorbed than the mesalamine released from sulfasalazine. Maximum plasma levels of mesalamine and N-acetyl-5-aminosalicylic acid following multiple Asacol doses are about 1.5 to 2 times higher than those following an equivalent dose of mesalamine in the form of sulfasalazine. Combined mesalamine and N-acetyl-5-aminosalicylic acid AUC's and urine drug dose recoveries following multiple doses of Asacol tablets are about 1.3 to 1.5 times higher than those following an equivalent dose of mesalamine in the form of sulfasalazine.

The Tmax for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid, is usually delayed, reflecting the delayed release, and ranges from 4 to 12 hours. The half-lives of elimination (t1/2elm) for mesalamine and N-acetyl-5-aminosalicylic acid are usually about 12 hours, but are variable, ranging from 2 to 15 hours. There is a large intersubject variability in the plasma concentrations of mesalamine and N-acetyl-5-aminosalicylic acid and in their elimination half-lives following administration of Asacol tablets.

5 Sources of Clinical Data

There were three pediatric clinical trials submitted as part of this pediatric (b) (4) supplement. Two adult studies were referenced as comparisons for efficacy outcomes: studies C3 and C14. The table below summarizes these trials from the sponsor's submission.

5.1 Tables of Studies/Clinical Trials

Table 3: Summary of Studies/Clinical trials

Study	Design	Population	Dose and Duration	Number of Centers and locations
2007017 (CAMP II) Safety, efficacy, and PK in patients with mild to moderately active UC	Phase 3, randomized, double-blind, parallel-group	N = 83* Ages: 5 – 17 years	Randomized to low dose (N=41) or high dose (N=41) groups and stratified by weight (17 to < 33kg, 33 to < 54kg, 54-90kg) and disease severity (mild or moderate) Dose: 1.2 g/day to 4.8 g/day divided twice daily. Duration: 6 weeks	26 centers from the United States, Canada, Croatia, Poland, and Romania
2008085 (CAMP III) Safety and efficacy in patients who maintained remission of UC for one month prior to study start (sponsor terminated study early due to enrollment challenges)	Phase 3, randomized, double-blind, parallel-group Patients continued from study 2007017 after a 30 day run-in period (N = 14), and enrolled new patients who were in remission for at least one month	N = 39 N = 21 at week 26 assessment Ages: 5 – 17 years	Randomized to low dose (N=20) or high dose (N=19) groups and stratified by weight (17 to < 33kg, 33 to < 54kg, 54-90kg) and disease severity (mild or moderate) Dose: 1.2 g /day to 4.8 g/day divided twice daily. Duration: 26 weeks	18 centers from the United States, Canada, and Poland
2005018 (CAMP I) PK	Randomized, single center, open-label, parallel-group, bioavailability study in patients with active UC	N = 34 Ages: 5 – 17 years	Randomized to 30 mg/kg (N=9), 60 mg/kg (N=12), or 90 mg/kg (N=12) divided every 12 hours Duration: 28 days	5 centers in the United States
Adult Studies referenced by sponsor				
C3 Efficacy of low and high doses of Asacol in adult patients with active mild to moderate UC	Randomized, double-blind, placebo-controlled, parallel study	N= 87 Ages: 15 – 70 years	Randomized to placebo (N=11), 1.6 g/day (N=38), or 2.4 g/day (N=38) divided three times daily Duration: 6 weeks	1 center in United States
C14 Efficacy and safety of Asacol vs. placebo on induction of remission of patients with mildly to moderately active UC	Randomized, double-blind, placebo-controlled, multi-center	N = 135 Ages: 18 – 75 years	Randomized to placebo (N=52), 1.6 g/day (N=53), or 2.4 g/day (N=53) divided three times daily Duration: 6 weeks	10 centers in United States

*One patient in the high dose group was randomized but never dosed, therefore, excluded from the mITT analysis.

5.2 Review Strategy

Three pediatric trials were submitted in this pediatric (b) (4) supplement and were reviewed in detail. Study 2007017 was the primary trial to evaluate efficacy and safety of Asacol 400mg delayed release tablets at two dose levels, high and low, for treatment of patients ages 5 to 17 years old with mildly to moderately active UC. Mesalamine products are known to be effective for the treatment of mildly to moderately active UC in adults. The pathophysiology of UC is sufficiently similar between adults and children and the response to treatment with mesalamine is expected to be similar. Therefore, efficacy can be extrapolated from adult trials. Asacol is a locally acting drug in the GI tract and systemic concentrations cannot be used to extrapolate efficacy. Partial extrapolation requires the comparison of a PD measure in children that can be used to determine efficacy. If an acceptable PD marker is identified, dose-ranging studies need to be conducted to determine the dose that achieves the desired PD effect and to evaluate safety at the selected dose.[14,15]

We determined that the stool frequency and rectal bleeding scores from the TM-Mayo could be compared to the same components from Mayo Score used to measure efficacy in the adult Asacol trials. Stool frequency and rectal bleeding were chosen as PD markers because they adequately reflect clinically meaningful signs and symptoms of disease in ulcerative colitis. The same endpoints (stool frequency and rectal bleeding scores from the Mayo Score) in the pediatric study (Study 2007017) were compared to the scores from the two pivotal adult Asacol trials. The proportion of pediatric patients with complete response (remission) at week 6 was approximately 30% and was similar to what was seen in the adult trials. The rectal bleeding and stool frequency scores were comparable between the adult and pediatric trials. The safety data of the pediatric trial (Study 20070717, 2008085, and 2005018) were reviewed for an integrated safety evaluation.

Study 2008085 evaluated safety and efficacy in patients who maintained remission of UC for one month prior to study start over a 26-week study duration. This study was terminated prematurely due to lack of enrollment. Fewer than half of the targeted number of patients were randomized and no formal analysis was performed. Twenty-one of the 39 randomized patients completed 26 weeks (11 in low dose group and 10 in high dose group). Only Study 2007017 is included in this review for the approved indication. Safety data from Study 2008085 are included in the safety review, section 7. Appendix 9.5 contains an overview of Study 2008085.

Study 2005018 was primarily a PK study evaluating bioavailability in a randomized, single center, open label, parallel-group, enrolling 34 patients ages 5 - 17 years old. Patients were randomized to one of three dose levels of Asacol 400 mg delayed release tablets; 30 mg/kg

[14] Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.
[15] Presentation from Dr. Skip Nelson from the Office of Pediatric Therapeutics available at: http://www fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch /UCM361846.pdf.

(N=9), 60 mg/kg (N=12), or 90 mg/kg (N=12) divided every 12 hours for 28 days. Safety data were collected for this study and are included in Section 7 of this review.

5.3 Discussion of Individual Studies/Clinical Trials

Study: 2007017 (CAMP II)
Title: A Randomized, Double-blind, Parallel-group Study to Assess the Safety and Efficacy of Asacol (1.2g to 4.8g/day) Administered as 400mg Delayed-Release Tablets Given every 12 hours for 6 weeks to Children and Adolescents with Mildly to moderately Active Ulcerative Colitis.

Objectives: To evaluate the safety and efficacy of high dose and low dose Asacol (using 400mg delayed release tabs) every 12 hours for 6 weeks in pediatric patients between the ages of 5 -17 years old with mild to moderately active Ulcerative colitis.

Efficacy Endpoints:
Primary endpoint: Proportion of patients who achieved treatment success (TS) measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI), and labeled as PUCAI-TS.

Secondary endpoint: Amended Endpoint- TS. This amended endpoint was similar to PUCAI except that the PUCAI 3-level abdominal pain question was replaced by a 5-level abdominal pain question.

Additional endpoints: Each outcome scale (PUCAI, Amended PUCAI, TM-Mayo) was further broken down into complete response (CR), partial response (PR), treatment failure (TF).

- PUCAI: -CR, -PR, or -TF.
- Amended Endpoint: -CR, -PR, or -TF
- Truncated Mayo score (TM- Mayo): -CR, -PR, or -TF
- Change in disease activity, as determined by the investigator
- Fecal biomarkers: lactoferrin and calprotectin
- Urine mono-n-butyl phthalate measurements

Safety endpoints:
Adverse events (AEs), tolerability (withdrawals, AEs), vital signs, clinical labs, compliance, standardized and replicated weight and height were assessed as safety measures.

Study design: Randomized, double blind, parallel group study
Study Drug: Asacol (mesalamine) 400mg delayed release tablets
Population: Pediatric patients ages 5 – 17 years with mildly to moderately active UC
Dates: Dec 16, 2008 to March 8, 2011
Study centers: There were 26 sites from the United States, Canada, Croatia, Poland, and Romania and included 43 investigators. United States and Poland enrolled the highest number of

patients with 49 and 19, respectively. Canada enrolled 4, Croatia enrolled 6, and Romania enrolled 5 patients. There was a central lab in US and Europe for safety lab determinations and a contract research organization, (b) (4)

Randomization:
Patients were randomized to low dose or high dose, and then stratified by weight (17 to < 33 kg, 33 to < 54 kg, 54-90 kg) and by baseline disease severity (mild and moderate). The doses were selected based on results from a pediatric PK study (Study 2005018), and using weight based dosing (maximum 120 mg/kg/day). Mild disease was defined as a baseline PUCAI score of 10 to 30 and moderate disease was defined as a baseline PUCAI score of 35 to 55. Table 4 shows the treatments administered and treatment groups.

Table 4: Treatment Groups and Treatments Administered - Study 2007017

Treatment Group	Dose Level	Weight Group (kg)	Asacol Dose (g/day)	Dose Range (mg/kg)	AM Dose		PM Dose	
					Asacol 400 mg	Placebo	Asacol 400 mg	Placebo
1	High Dose	17 – < 33	2.0	61 – 118	3	0	2	0
		33 - < 54	3.6	67 – 109	5	0	4	0
		54 – 90	4.8	53 – 89	6	0	6	0
2	Low Dose	17 - < 33	1.2	36 – 71	2	1	1	1
		33 - < 54	2.0	37 – 61	3	2	2	2
		54 - 90	2.4	27 - 44	3	3	3	3

(Source: adapted from sponsor's study report- Study 2007017, dated December 21, 2012, pages 25 and 27)

The route of administration for all groups was oral 400 mg tablets divided every twelve hours for 6 weeks duration. Placebo tablets were given in combination with the active Asacol tablets to maintain blinding through equal numbers of tablets between high and low doses.

Number of subjects:
The planned study was designed for 100 subjects (expected 80 total patients with 40 in each dose group). Eighty-three patients were randomized (41 in the low dose group and 42 in the high dose group). The modified intent to treat (mITT) population included 41 patients in each group. One patient in the high dose group was never dosed and excluded from the mITT analysis. Thirty-six patients per group completed the study.

Safety population:
The safety population analysis included 41 in each group. Five patients in the low dose group and 5 patients in the high dose group withdrew from the study. All five in the low dose group withdrew because of AEs. In the high dose group, 2 patients withdrew due to AEs, 2 withdrew due to lack of treatment effect, and there was 1 voluntary withdrawal.

Inclusion criteria:

- Males and females ages 5-17 years of age
- History of biopsy and endoscopy confirmed UC
- Mildly to moderately active UC (relapse or newly diagnosed) as defined by PUCAI ≥ 10 and ≤ 55
- Patients who do not require steroids for active disease
- Baseline score ≥ 1 for both rectal bleeding and stool frequency as defined by TM-Mayo score
- Body weight ≥ 17 kg and ≤ 90kg.
- Subjects generally in good health and able to swallow Asacol tabs
- Female patients who are pre-menarchal or have a negative urine pregnancy test and, if sexually active, practice acceptable contraception
- Able and willing to participate in the study and follow study procedures

Exclusion criteria:

- Allergy to salicylates
- Co-morbidities: malabsorption, short gut syndrome, co-existing illness, renal disease, hepatic disease, pancreatitis, abuser of drugs or alcohol, history of HIV infection or AIDS, or history of co-existing chronic illness or other condition(s)
- Current renal disease, or a screening blood urea nitrogen (BUN) or creatinine value that is > 1.5 times the upper limit of the age appropriate normal
- Documented history of or current hepatic disease, or liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], total bilirubin) that are > 2 times the upper limit of normal
- Any other screening laboratory test values that would impact the outcome of the study or the safety of the patient
- Oral/IV/IM/rectal corticosteroids (including budesonide) within 30 days of screening visit
- Use of other mesalamine product, Flagyl, or NSAIDs within 7 days
- Use of immunomodulators or biologic therapy within 90 days
- Use of anti-diarrheal or anti-spasmodic within 3 days
- Positive stool culture for C. difficile or ova and parasite

Test dose: 400mg Asacol delayed release tabs dispensed to subjects in seven, 4-day blister cards with a day and a night dose. A 4 week supply included 7 blister cards packed in moisture resistant bags.
Kits: 400mg Asacol tabs. Lots 420237, 426920, 431881.

Matching placebo tabs: Lot 416049. Placebo tabs were given with active tabs to blind between low and high doses.

Duration: 6 week treatment phase. Study center visits occurred at baseline, week 3 and week 6. Subjects who dropped out received a 1 week follow up telephone call to monitor adverse events (AEs). Table 5 below shows the study schedule.

Table 5: Study Schedule of Events

	Screening	Treatment Phase				
Study Procedure	**Day -7 to -1**	**Baseline[a]/ Dosing Day 1**	**Week 1 Phone Visit ± 3 days**	**Week 3 ± 5 days**	**Week 6/ Withdrawal ± 5 days**	**1-week Follow-up Visit ± 3 days[b]**
Informed consent/assent	X					
Medical history	X	X[c]				
Medication history	X	X[c]		X[c]	X[c]	
Personal/Demographic data	X					
Physical examination	X				X	
Body weight/height (replicated for verification)	X	X			X	
Vital signs (heart rate, blood pressure, temperature)	X	X			X	
Hematology/serum chemistry	X	X[d]			X	
Serum sample for biomarkers- OPTIONAL	X	X[d]		X	X	
Serum pregnancy test – CANADA ONLY	X					
Urine pregnancy test	X	X			X	
Urine collection for urinalysis, urinary creatinine and assessment of phthalate	X	X[d]			X	
Stool sample for bacterial pathogens, ova and parasites, and C. difficile		X[e]				
Stool sample for lactoferrin and calprotectin		X		X	X	
AE monitoring	X[f]	X[f]		X	X	X
Distribute PUCAI Diary Cards[g]	X			X		
IVRS Contact	X[h]	X[i]		X[j]		
Remind subject/legal guardian that subject should avoid protocol-excluded medications	X	X		X		
Review dosing instructions/compliance/ return of study medication with subject/legal guardian		X		X	X	
Subjects/legal guardian(s) contacted to assess subject compliance and well-being			X			X
Clinical assessments[k]		X			X	
Final Investigator Assessment					X	
PK blood collection[l]				X	X	

[a] Baseline Visit occurred within 7 days after Screening Visit.
[b] This was a telephone follow-up visit only for subjects who had completed or discontinued treatment and were not rolling over into Study 2008085.
[c] Update only.
[d] Did not need to be repeated if Baseline occurred within 7 days of Screening.
[e] If a previous stool sample collected within the past 30 days was negative for bacterial pathogens, ova and parasites, and *C. difficile*, the stool sample did not need to be collected at this visit.
[f] Only serious study procedure-related non-treatment-emergent AEs were collected.
[g] PUCAI Diary Cards were to be completed 2 days prior AND 1 day prior to Baseline and Week 6 visit
[h] Called to obtain subject number.
[i] Called to randomize subject, obtain kit number to dispense, and obtain PK draw window assignment. A 3-week supply of study medication was dispensed.
[j] Called to obtain kit number to dispense. A 3-week supply of study medication was dispensed.
[k] Included review of PUCAI Diary Cards, completion of PUCAI and 5-level abdominal pain scale, and scoring of stool frequency and rectal bleeding per the TM-Mayo.
[l] Sampling time window of PK blood draw was assigned by IVRS at Baseline Visit. If WD, SAE or AE of tinnitus samples were to be drawn as close to last dose as possible.

(Source: sponsor study report- Study 2007017, dated December 21, 2012, page 30)

Statistical Analysis:
The statistical plan was to perform analysis on a modified Intent to Treat (mITT) population. Primary and secondary categorical endpoints were evaluated using the Cochran-Mantel Haenszel (CMH) test to compare dose levels (high vs. low), and adjusting for weight group and disease severity. Per-protocol analysis was not performed. The study report contains only descriptive analysis and no formal statistical analysis was performed.

Frequency tabulations within each weight group and disease severity combination were generated by dose level and overall. Descriptive statistics (N, mean, SD, median, minimum, maximum) were produced for PUCAI, Amended PUCAI Endpoint, and TM-Mayo scores. Only descriptive statistics (frequency distribution) were provided for the 3 levels of response: CR, PR, and TF. The difference between dose levels was estimated and the 95% confidence interval (CI) was calculated. The continuous endpoints (change from baseline to week 3 and week 6), fecal lactoferrin and fecal calprotectin were analyzed using Koch's nonparametric ANCOVA with fixed effects for dose level (high vs. low), weight group, and disease severity.

Efficacy Results:
The primary endpoint was treatment success as measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI). Secondary endpoints were an Amended PUCAI endpoint (three point abdominal pain question scale was changed to a 5 point scale) and a Modified Mayo score (TM-Mayo). Treatment success on the primary endpoint included complete and partial remission as successes. Secondary endpoints measured complete and partial success independently, as well as treatment failures for each of the three endpoints.

Safety Results:
The three studies used to evaluate efficacy were used to evaluate safety (Study 2007017, 2008085, and 2005018). Patients who received at least one dose of the study drug were included in the safety population and included in safety summary analysis. The sponsor used Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT) to describe adverse events (AEs). The adverse events in the pediatric studies were compared to two adult studies (C3 and C14). Studies C3 and C14 contained a placebo arm. The pediatric studies did not include a placebo control group.

Conclusions:
The difference in treatment success was small between the low and high dose groups as measured by the primary efficacy endpoint (PUCAI), secondary endpoint (Amended PUCAI), and tertiary endpoint (TM-Mayo scores). The safety analysis did not raise any new or unexpected safety concerns from what is already known about Asacol for the treatment of ulcerative colitis.

6 Review of Efficacy- Study 2007017

Efficacy Summary

A randomized, double blinded, parallel group study was performed to evaluate efficacy, safety and PK of two dose levels of Asacol 400mg delayed release tablets, low dose (1.2 – 2.4 g/day) and high dose (2.0 – 4.8 g/day) in pediatric patients with mildly to moderately active ulcerative colitis. The primary efficacy endpoint was measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI). The PUCAI is a noninvasive scoring system to assess severity of disease in pediatric patients with ulcerative colitis. The sponsor defined treatment success (TS) as PUCAI score < 10 at Week 6 (complete response) or reduction of > 20 from baseline to week 6 with week 6 score > 10 (partial response). Treatment failure (TF) was defined as failure to achieve success criteria or study withdrawal due to adverse event or lack of efficacy. Patients were stratified by weight groups and by disease severity for each of the dose levels. The difference between the low dose and high dose groups, as measured by the PUCAI score, was small. PUCAI-TS was observed in 23 (56.1%) in the low dose group (N=41) and 22 (55%) in the high dose group (N =40). The percentages of patients with treatment success, complete, and partial response were similar between the PUCAI an Amended PUCAI. Approximately 70% of patients in each dose group achieved TS as measured by the modified Mayo score (TM-Mayo). The proportion of pediatric patients who were in complete response (remission) at week 6 was approximately 30% and was similar to the results from the adult trials. The rectal bleeding scores were most similar between the pediatric high dose group and the C3 adult trial (4.8 g/day). The rectal bleeding scores for the low dose group in the pediatric trial were similar to the rectal bleeding scores in the C14 adult trial (2.4 g/day). The stool frequency scores were most consistent between the C14 adult trial (2.4 g/day) and both pediatric dose levels (high and low).

This study adheres to the recommended PREA PMR study design, treatment length, patient population, and dose levels as outlined in the Approval letter for Asacol HD dated May 29, 2008. Asacol has been approved in adults using 400mg tablets up to a maximum dose of 2.4g per day. Asacol HD has been approved in adults using 800mg tablets up to a maximum dose of 4.8g per day.

6.1 Indication

This study was submitted as fulfillment of the Pediatric Research Equity Act (PREA) 21 U.S.C. 355c for NDA 21830. In the Approval Letter for Asacol HD (800mg), dated 5/29/2008, the requirement for inclusion of patients ages 0-4 was waived because enrollment of children in this age group would be impossible/highly impractical due to the small number of pediatric patients with ulcerative colitis who are younger than age 5 years old. The Agency recommended a randomized, double blind trial comparing at least 2 dose levels, enrolling at least 40 patients in each dosing arm to include patients with ulcerative colitis ages 5-17 years old to evaluate PK, safety, and clinical response over 6 weeks of therapy with oral mesalamine. The primary objective of the trial was to establish safety and efficacy of high dose and low dose Asacol

(400mg delayed release tablets given every 12 hours for 6 weeks) in children and adolescents with mildly to moderately active ulcerative colitis.

6.1.1 Methods:

The study design is a randomized, double blind, parallel group study evaluating safety and efficacy of high and low dose Asacol using 400mg delayed release tablets every 12 hours for 6 weeks in patients with mildly to moderately active UC. Patients were randomized by weight (17- < 33 kg, 33 - < 54 kg, 54 – 90 kg) and by disease severity (mild and moderate). The trial was designed for 40 patients per dose group with 4 – 5 patients per dose level in the 5 – 8 year old age range. The trial commenced on December 16, 2008 and concluded on March 8, 2011.

Key Inclusion/Exclusion Criteria:

Inclusion criteria:

- Males and females ages 5-17 years old
- History of biopsy and endoscopy confirmed UC
- Mild to moderately active UC (relapse or newly diagnosed) as defined by PUCAI ≥ 10 and ≤ 55
- Patients who do not require steroids for active disease (determined by investigator)
- Baseline score ≥ 1 for both rectal bleeding and stool frequency as defined by TM-Mayo score
- Body weight ≥ 17 kg and ≤ 90kg.
- Subjects generally in good health and able to swallow Asacol tabs
- Females who are pre-menarchal or have a negative pregnancy test, not breast feeding, agree to use contraception

Exclusion criteria:

- Allergy to salicylates
- Co-morbidities: malabsorption, short gut syndrome, co-existing illness, renal disease, hepatic disease, pancreatitis
- Abnormal labs
- Oral/IV/IM/rectal corticosteroids (including budesonide) within 30 days of screening visit
- Use of other mesalamine products, Flagyl, or NSAIDs within 7 days
- Use of immunomodulators or biologic therapy within 90 days
- Use of anti-diarrheal or anti-spasmodic within 3 days
- Positive stool culture for c.diff or ova and parasite

Table 6 below shows the treatment groups and treatments administered. There were three weight groups (17 – < 33 kg, 33 – < 54 kg, and 54 – 90 kg) within each dose level group (high dose and low dose). Each weight category was assigned a weight-based dose. The total Asacol dose (g/day) for each weight group was 2.0 g/day, 3.6 g/day, and 4.8 g/day in the high dose level group and 1.2 g/day, 2.0 g/day, and 2.4 g/day in the low dose level group. Patients were given a fixed dose for the 6 week trial duration of oral Asacol 400mg delayed release tablets, divided every 12 hours for 6 weeks duration. The total daily dose increments were restricted by the Asacol 400mg tablets, which cannot be cut or crushed.

Table 6: Treatment Groups and Treatments Administered - Study 2007017

Treatment Group	Dose Level	Weight Group (kg)	Asacol Dose (g/day)	Dose Range (mg/kg)	AM Dose		PM Dose	
					Asacol 400 mg	Placebo	Asacol 400 mg	Placebo
1	High Dose	17 – < 33	2.0	61 – 118	3	0	2	0
		33 - < 54	3.6	67 – 109	5	0	4	0
		54 – 90	4.8	53 – 89	6	0	6	0
2	Low Dose	17 - < 33	1.2	36 – 71	2	1	1	1
		33 - < 54	2.0	37 – 61	3	2	2	2
		54 - 90	2.4	27 - 44	3	3	3	3

(Source: adapted from sponsor's study report- Study 2007017, pages 25 and 27/3086)

The dose groups included a large range of weight-based doses (mg/kg/day). These doses were compared to the recommended total daily mesalamine doses that are used in clinical practice, though not approved for pediatric indications. Based on the clinical practice guidelines for the management of pediatric ulcerative colitis, oral 5-ASA therapy (mesalamine or sulfasalazine) is recommended as first line therapy for induction of remission of mold to moderately active pediatric UC. The recommended total daily dose of mesalamine ranges from 60 to 80 mg/kg/day divided twice daily to a maximum of 4.8 g/day.[4] Total daily doses of up to 100 mg/kg/day (maximum 4.8 g/day) are sometimes used in clinical practice.[2] The recommended doses in clinical practice for treating pediatric ulcerative colitis more closely resemble the higher dose group as designed in this trial.

6.1.2 Demographics

Table 7 shows the number of patients in each treatment group for the mITT population. There were fewer patients in the lower weight-based dose groups (2.0 g/day and 1.2 g/day), most likely due the lower incidence of UC in younger children. Study 2008085 was terminated early due to challenges with enrollment. (b) (4) , as previously discussed, all three submitted pediatric studies are included in the safety review, Section 7.

Table 7: mITT Population - Treatment Groups (Study 2007017 and Study 2008085)

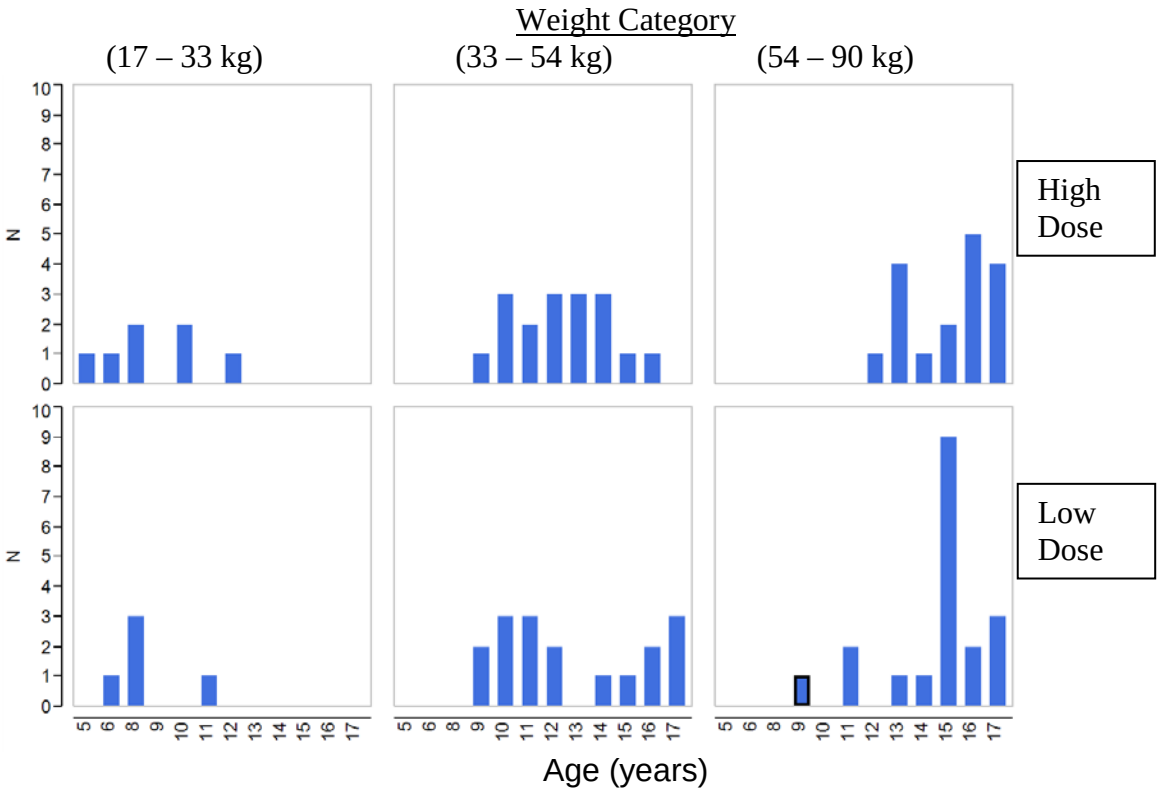
Study 2007017			Study 2008085		
	Asacol Dose (g/day)	**Number of patients N = 82**		**Asacol Dose (g/day)**	**Number of patients N = 39**
High Dose (N =41)	2.0	7	**High Dose (N =19)**	2.0	1
	3.6	17		3.6	6
	4.8	17*		4.8	12
Low Dose (N = 41)	1.2	5	**Low Dose (N = 20)**	1.2	1
	2.0	17		2.0	7
	2.4	19		2.4	12

*N = 17 for mITT analysis. Patient 1048641001 was randomized but voluntarily withdrew and was never dosed.
(Source: Reviewer's own table adapted from sponsor data, Study 2007017 and Study 2008085, dated December 21, 2012)

Figure 1 below shows the age distribution across the weight categories comparing the high dose and low dose groups. Eighty-two patients were included in the mITT population. One 5 year old and two 6 year old patients were enrolled. There were no 7 year old patients in this trial. However, Study 2005018 (28 day duration PK study) included one 5 year old and two 6 year old patients. These patients were all included in the review of safety data and are likely adequate to establish safety in the pediatric UC population who are younger than 6 years of age. There is a lower prevalence of UC in children younger than 6 years of age.[16] Of note, the youngest patient in Study 2008085 (26 week duration) was 8 years of age.

[16] Heyman MD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. J Pediatr. 2005; 146(1):35-40.

Figure 1: Age Distribution: Frequency of Ages across Weight Categories and Dose Groups



(Source: Reviewer's own figure, adapted from sponsor data, Study 2007017, dated December 21, 2012)

Table 8 below describes the demographic and baseline characteristics of the mITT population for Study 2007017.

Table 8: Demographic and Baseline Characteristics by Dose Group (mITT population)

Parameter Statistic/Category	Low Dose (N=41)	High Dose (N=41)	Overall (N=82)
Age			
n	41	41	82
Mean (SD)	13.0 (3.2)	12.8 (3.0)	12.9 (3.1)
Median	14.0	13.0	13.0
Min, Max	6, 17	5, 17	5, 17
Age Category			
5-8	4 (9.8%)	4 (9.8%)	8 (9.8%)
9-17	37 (90.2%)	37 (90.2%)	74 (90.2%)
Sex			
Female	22 (53.7%)	23 (56.1%)	45 (54.9%)
Male	19 (46.3%)	18 (43.9%)	37 (45.1%)
Race Black			
Caucasian	2 (4.9%)	2 (4.9%)	4 (4.9%)
Multi-Racial	37 (90.2%)	39 (95.1%)	76 (92.7%)
	2 (4.9%)	0 (0.0%)	2 (2.4%)
Ethnicity			
Hispanic or Latino	9 (22.0%)	1 (2.4%)	10 (12.2%)
Not Hispanic or Latino	32 (78.0%)	40 (97.6%)	72 (87.8%)
Baseline Weight (kg)			
n	41	41	82
Mean (SD)	52.45 (15.78)	50.93 (16.64)	51.69 (16.13)
Median	52.80	49.80	51.50
Min, Max	23.0, 88.9	17.1, 85.4	17.1, 88.9
Baseline Height (cm)			
n	41	41	82
Mean (SD)	156.74 (16.41)	158.25 (16.37)	157.50 (16.31)
Median	160.90	160.30	160.60
Min, Max	118.0, 182.0	110.0, 190.5	110.0, 190.5
Weight Category			
17 - <33 KG	5 (12.2%)	7 (17.1%)	12 (14.6%)
33 - <54 KG	17 (41.5%)	17 (41.5%)	34 (41.5%)
54 - 90 KG	19 (46.3%)	17 (41.5%)	36 (43.9%)
Disease Severity [a]			
Mild	21 (51.2%)	18 (43.9%)	39 (47.6%)
Moderate	20 (48.8%)	23 (56.1%)	43 (52.4%)

Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day. Dosage was dependent on body weight.
[a] Disease severity is based on total PUCAI score at Baseline.

(Source: sponsor's submission: volume 1- Study 2007017, dated December 21, 2012, page 46/3068)

The two dose groups (high and low) were similar with respect to baseline height and weight, weight categories, sex, and race. The overall study population was 92.7% Caucasian and 54.9% female. The low dose group had a higher percentage of Hispanic or Latino patients compared to the high dose group (22% and 2.4%, respectively). The two dose groups were similar in duration of current flare. Patients with mild and moderate disease comprised approximately half of each dose group. The baseline disease severity, mild or moderate, was determined by PUCAI score at entry to the trial, and was not based on disease history or endoscopic findings. Table 9 below shows the PUCAI scores at baseline for each of the dose level groups (low and high doses).

Table 9: Baseline PUCAI Score for Dose Groups and Disease Severity (Mild and Moderate)

	Mild		Moderate	
PUCAI Score Baseline	Low Dose	High Dose	Low Dose	High Dose
Mean (SD) Median (Min, Max)	22.6 (5.6) 25 (15, 30)	26.1 (4.7) 27.5 (15, 30)	40.5 (4.6) 40.0 (35, 50)	44.8 (7.1) 45.0 (35, 50)

(Source: Reviewer's own table, using sponsor's data, study 2007017, dated December 21, 2012)

The PUCAI scoring is interpreted as score < 10: no disease, 10 -34: mild disease, 35 – 65: moderate disease, and > 65: severe disease. The mean, median, and range of scores show that no patients with severe disease, as measured by the PUCAI, were included in the trial. Importantly, determination of disease severity (mildly to moderately active UC) for inclusion into the trial was based on the PUCAI score at screening and there was not an endoscopic component for evaluating disease severity at inclusion or at the week 6 conclusion of the trial.

Fifty-five of the 82 patients underwent endoscopy within 6 weeks prior to enrollment into the trial. The majority of the patients received an endoscopic score of mild to moderate disease. However, 7 patients were reported to have severe disease by endoscopic score (defined by spontaneous bleeding and ulceration), despite scoring in the mild to moderate range on the PUCAI. Two of the patients with severe endoscopic scores dropped out of the trial for adverse events (one with primary sclerosing cholangitis (PSC) and bloody diarrhea, and the second with worsening UC). The other 5 patients with severe endoscopic scores completed the trial.

Table 10 below describes the disease history in detail including time since diagnosis, extent of disease, and relapse frequency. A high percentage (15.9%) had missing data for extent of disease.

Table 10: Disease History (mITT population)- Study 2007017

Parameter Statistic/Category	Low Dose (N=41)	High Dose (N=41)	Overall (N=82)
Time Since Original Diagnosis (months)			
n	41	41	82
Mean (SD)	11.3 (20.8)	18.6 (35.6)	15.0 (29.2)
Median	1.1	2.2	1.8
Min, Max	0.1, 101.6	0.0, 151.9	0.0, 151.9
Extent of Ulcerative Colitis			
Missing	8 (19.5%)	5 (12.2%)	13 (15.9%)
Proctitis	3 (7.3%)	5 (12.2%)	8 (9.8%)
Proctosigmoiditis	7 (17.1%)	4 (9.8%)	11 (13.4%)
Left-Sided Colitis	10 (24.4%)	6 (14.6%)	16 (19.5%)
Extensive Colitis	3 (7.3%)	4 (9.8%)	7 (8.5%)
Pancolitis	10 (24.4%)	17 (41.5%)	27 (32.9%)
Relapse Frequency			
Relapse More than Once a Month	3 (7.3%)	2 (4.9%)	5 (6.1%)
Relapse Once Every Six Months	3 (7.3%)	3 (7.3%)	6 (7.3%)
Relapse Once Every 6-12 Months	4 (9.8%)	6 (14.6%)	10 (12.2%)
Relapse Less than Once a Year	5 (12.2%)	5 (12.2%)	10 (12.2%)
Relapse Less than Every 18 Months	1 (2.4%)	2 (4.9%)	3 (3.7%)
Newly Diagnosed	25 (61.0%)	23 (56.1%)	48 (58.5%)
Endoscopy in 6 Weeks Prior to Signed ICF			
No	16 (39.0%)	12 (29.3%)	28 (34.1%)
Yes	25 (61.0%)	29 (70.7%)	54 (65.9%)

(Source: Sponsor Study report- Study 2007017, dated December 21, 2012, page 47/3086)
Extensive colitis was defined as presence of disease proximal to splenic flexure. Extent of disease was based on visual endoscopic appearance, not based on histology.

The majority of the patients (48/82) in the mITT population were newly diagnosed. There were 10 patients who had a history of relapse less than once per year and 10 patients who relapsed once every 6 – 12 months. Only 5 patients had a history of relapse more than once per month. This pattern of relapse supports that the majority of patients, who were not newly diagnosed, probably had mild to moderate disease. There was a higher percentage of patients in the low dose group with proctosigmoiditis compared to the high dose group (17.1% vs. 9.8%, respectively), and a higher percentage of patients with pancolitis in the high dose group compared to the low dose group (41.5% vs. 24.4%, respectively). Eight (19.5%) of the patients in the low dose group had missing information on disease extent compared to 5 (12.2%) in the high dose group.

The sponsor made comparisons between the low dose and high dose groups. This method of grouping complicates the interpretation of the results because the dose groups were not mutually exclusive. Both high and low dose groups included patients who received a total daily Asacol dose of 2.0 g/day. Analysis between weight groups may be more appropriate, especially for dose selection and labeling. Table 11 below describes the low dose and high dose groups by the three weight categories and by daily weight-based dose of Asacol.

Table 11: Body Weight Based Dosing of Asacol – Study 2007017

Parameter	Low Dose				High Dose			
	Total (N=41)	17-<33 kg (N=5)	33-<54 kg (N=17)	54-90 kg (N=19)	Total (N=41)	17-<33 kg (N=7)	33-<54 kg (N=17)	54-<90 kg (N=17)
Total Daily Asacol Dose (g/day)		1.2	2.0	2.4		2.0	3.6	4.8
Body Weight Based Dose Range (mg/kg/day)		36 - 71	37 - 61	27 - 44		61 - 118	67 - 109	53 - 89
Body Weight Based Asacol Dose (mg/kg/day)								
n	**41**	**5**	**17**	**19**	**41**	**7**	**17**	**17**
Mean (SD)	**41.6 (7.2)**	**46.6 (4.4)**	**45.3 (7.3)**	**36.9 (4.4)**	**77.4 (12.3)**	**79.9 (19.0)**	**80.8 (11.1)**	**73.0 (9.2)**
Median	**40.7**	**46.9**	**42.3**	**38.2**	**75.0**	**71.4**	**77.4**	**71.7**
(Min, Max)	**(27.0, 59.3)**	**(41.0, 52.2)**	**(37.7, 59.3)**	**(27.0, 43.3)**	**(56.2, 117.0)**	**(63.3, 117.0)**	**(67.4, 102.9)**	**(56.2, 87.1)**

(Source: sponsor submission in response to Agency Information Request, sNDA 021830, supporting document 282, dated April 10, 2013)

The low dose group received doses of Asacol ranging from 27.0 – 59.3 mg/kg/day and the high dose group received doses of Asacol ranging from 56.2 – 117.0 mg/kg/day. As discussed in Section 6.1.1 Methods, the high dose group more closely resembles the recommended dose range used in clinical practice (60 – 80 mg/kg/day).

6.1.3 Subject Disposition

Table 12 and Figure 2 below describe the subject disposition. The modified intent to treat (mITT) population included all randomized subjects who took at least one dose of the study drug, based on dose group to which he/she was randomized. Protocol deviations were documented and stored in the database, and a per-protocol population was identified. However, per protocol analysis on this population was not performed. Eighty-three patients were randomized and each dose level group contained 41 subjects included in the mITT analysis. There were 17 screening failures that were excluded before randomization. The majority of the randomized patients completed the study. The mITT analysis included ten patients who discontinued from the trial (7 for adverse events, 2 for treatment failure, and 1 voluntary withdrawal).

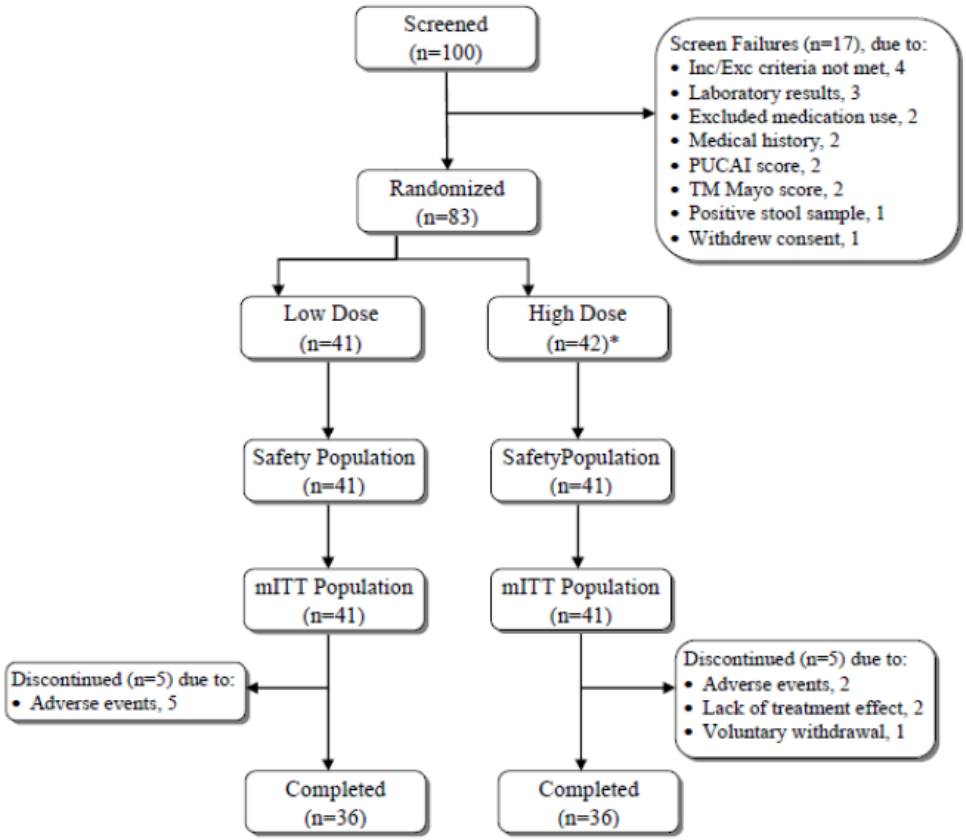
Table 12: Subject Disposition

Parameter Category	Low Dose (N=41) n (%)	High Dose (N=42) n (%)	Overall (N=83) n (%)
Randomized to Treatment			
Completed	36 (87.8%)	36 (85.7%)	72 (86.7%)
Discontinued	5 (12.2%)	6 (14.3%)	11 (13.3%)
Reason for Discontinuation			
Adverse Events	5 (12.2%)	2 (4.8%)	7 (8.4%)
Lack of Treatment Effect	0 (0.0%)	2 (4.8%)	2 (2.4%)
Voluntary Withdrawal	0 (0.0%)	2 (4.8%)	2 (2.4%)

Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day. Dosage was dependent on body weight.
Subject 1048641004 in High Dose group was randomized but not dosed.
Subject data can be found in Appendix 16.2.1.
/ASACOL/PEDS/2007017/ANAL/disp_dev_scrn.sas; SAS 8.2 26JUL11 10:01 f12jul11 TI3565.

(Source: Sponsor Study Report- Study 2007017, dated December 21, 2012, page 43/3086)

Figure 2: Study Subject Disposition- Study 2007017



* Subject 1048641004 in High Dose group was randomized but not dosed and discontinued due to voluntary withdrawal.

(Source: sponsor study report- Study 2007017, dated December 21, 2012, page 42/3086)

Refer to Table 2a for a description of protocol deviations.

6.1.4 Analysis of Primary Endpoint(s)

Efficacy Endpoints:

Primary Endpoint: proportion of patients who achieved treatment success (TS) measured by PUCAI (PUCAI-TS). Treatment success included complete and partial responders. The definition of complete and partial response is shown in Table 13. The sponsor's definition of complete responder corresponds to what is often considered clinical remission and partial response is often categorized as clinical response. Table 14 shows the overall proportion of patients with treatment success at week 6 as measured by the PUCAI, Amended PUCAI, and modified Mayo (TM-Mayo). In addition, the proportion of patients determined to be complete and partial responders are shown.

Table 13: Efficacy Endpoint Definitions (evaluated at Week 6)

Scoring System	Complete Response (-CR)	Partial Response (-PR)	Treatment Success (-TS)	Treatment Failure (-TF)
PUCAI Amended PUCAI	< 10	reduction of score ≥ 20 points and PUCAI score ≥ 10	Patients with CR or PR	Failure to achieve CR or PR
TM-Mayo	0: Stool Frequency AND 0: Rectal Bleeding	Improvement from baseline in stool frequency OR rectal bleeding with no worsening in the other	Patients with CR or PR	Failure to achieve CR or PR

(Source: reviewer's own table based on sponsor definitions from study report- Study 2007017, dated December 21, 2012)

The definitions follow what is published in the literature on interpreting these scoring systems. A PUCAI change of 20 was considered the minimal clinically significant difference.[17]

The proportion of patients with PUCAI-TS were similar between two dosing arms: 23 (56.1%) TS in the low dose arm and 22 (55%) TS in the high dose arm. Of the patients who achieved complete response, 19 (46%) were in the low dose group and 17 (43%) were in the high dose group. Four (10%) in the low dose and 5 (13%) in the high dose group were in partial remission. Table 14 below shows the remission and response rates for the overall dose levels (high vs. low) and by weight category for the primary, secondary, and tertiary endpoints.

[17] Turner, D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study Gastroenterology. 2007 Aug;133(2):423-32.

Table 14: Proportion of Subjects Meeting the Primary Endpoint (PUCAI treatment success), and Secondary Endpoints (Amended PUCAI Treatment Success, and TM-Mayo Treatment Success)

Parameter	Low Dose				High Dose			
	Total (N=41)	17-<33 kg (N=5)	33-<54 kg (N=17)	54-90 kg (N=19)	Total (N=41)	17-<33 kg (N=7)	33-<54 kg (N=17)	54-<90 kg (N=17)
Total Daily Asacol Dose (g/day)		1.2	2.0	2.4		2.0	3.6	4.8
Body Weight Based Dose Range (mg/kg/day)		36 - 71	37 - 61	27 - 44		61 - 118	67 - 109	53 - 89
Number of Subjects Included in the Analysis[1]	41	5	17	19	40	7	16	17
Primary Endpoint PUCAI-Treatment Success (complete + partial remission)	**23 (56%)**	**3 (60%)**	**11 (65%)**	**9 (47%)**	**22 (55%)**	**3 (43%)**	**10 (63%)**	**9 (53%)**
PUCAI Complete Response (Remission)	19 (46%)	2 (40%)	9 (53%)	8 (42%)	17 (43%)	2 (29%)	9 (56%)	6 (35%)
PUCAI Partial Response	4 (10%)	1 (20%)	2 (12%)	1 (5%)	5 (13%)	1 (14%)	1 (6%)	3 (18%)
Amended PUCAI-Treatment Success (complete + partial remission)	**23 (56%)**	**3 (60%)**	**11 (65%)**	**9 (47%)**	**23 (58%)**	**2 (29%)**	**10 (63%)**	**11 (65%)**
Amended PUCAI Complete Response (Remission)	21 (51%)	2 (40%)	10 (59%)	9 (47%)	19 (48%)	2 (29%)	9 (56%)	8 (47%)
Amended PUCAI Partial Response	2 (5%)	1 (20%)	1 (6%)	0	4 (10%)	0	1 (6%)	3 (18%)
TM-Mayo-Treatment Success (complete + partial remission)	**30 (73%)**	**4 (80%)**	**14 (82%)**	**12 (63%)**	**28 (70%)**	**4 (57%)**	**11 (69%)**	**13 (76%)**
TM-Mayo Complete Response (Remission)	14 (34%)	2 (40%)	8 (47%)	4 (21%)	17 (43%)	1 (14%)	9 (56%)	7 (41%)
TM-Mayo Partial Response	16 (39%)	2 (40%)	6 (35%)	8 (42%)	11 (28%)	3 (43%)	2 (13%)	6 (35%)

The Amended PUCAI is similar to the PUCAI (but with the PUCAI 3-level Abdominal Pain question replaced by a 5-level Abdominal Pain question). The Amended PUCAI is the same as the Amended Endpoint used in the CSR.
(1) Includes subjects who completed the study and subjects who dropped due to Adverse Event or Lack of Treatment Effect. These numbers are used as the denominator.
S:\Projects\WC3045\FDA_2007017_Mar2013\Program\Anal\t_trtsucc.sas SAS 9.2 03APR2013 20:14 FINAL

(Source: sponsor submission in response to Agency Information Request, sNDA 021830, supporting document 282, dated April 10, 2013)

For the patients who achieved TS based on PUCAI and Amended PUCAI scores at Week 6, a higher percentage of patients were in complete response (remission) compared to partial response. In contrast, when the TM-Mayo was used as the measurement tool, the differences between complete and partial response were not as large.

There are some challenges with assessing disease severity using the PUCAI. PUCAI score relies on the patient's ability to accurately report symptoms. Children may have difficulty accurately reporting symptoms such as rectal bleeding. PUCAI also requires input from a physician, which may vary between treating physicians. In addition, there is no endoscopic score built into the tool.

Efficacy was extrapolated from adult clinical trials. Partial extrapolation requires the comparison of a PD measure in children that can be used to determine efficacy. We determined that the stool frequency and rectal bleeding scores from the TM-Mayo could be compared to the same components from Mayo Score used to measure efficacy in the adult Asacol trials. Through an information request to the sponsor, we asked that the sponsor provide a summary of the efficacy

data from the two adult trials, C3 and C14, using the same endpoints as were used pediatric Study 2007017 (stool frequency and rectal bleeding scores from the Mayo Score). Table 15 shows the pooled study data from the adult trials and compares the proportion in remission, rectal bleeding, and stool frequency individual component scores of the Mayo Score to the pediatric Study 2007017.

Table 15: Pooled Analysis from Adult Studies (C3 and C14) and Comparison to Study 2007017

	Adult Study C3			Adult Study C14			Pediatric	
Asacol Dose (g/day)	Placebo	1.6	4.8	Placebo	1.6	2.4	Low Dose	High Dose
Proportion Remission n (%)	4/38 (11)	2/11 (18)	12/38 (32)	5/52 (11)	12/53 (27)	14/53 (33)	14/41 (34)	17/40 (43)
Rectal Bleeding n	21	8	36	29	41	39	36	36
Mean (SD) Median Min, Max	-0.3(1.2) 0.0 (-3, 2)	-0.9(1.2) 0.0 (-3, 0)	-1.3(1.1) -1.5 (-3, 1)	-0.4(0.6) 0.0 (-2, 1)	-0.6(1.1) -1.0 (-2, 3)	-0.5(0.6) 0.0 (-2, 0)	-0.8(0.8) -1.0 (-2, 1)	-1.0(0.9) -1.0 (-2, 0)
Stool Frequency n	21	8	36	29	41	39	36	36
Mean (SD) Median Min, Max	-1.2(1.0) 0.0 (-3, 2)	-1.0(0.9) -1.0 (-2, 1)	-1.2(1.1) -1.0 (-3, 1)	-0.5(0.9) 0.0 (-3, 1)	-0.3(1.1) 0.0 (-3, 3)	-0.8(0.9) -1.0 (-3, 1)	-0.8(1.0) -1.0 (-3, 1)	-0.7(1.1) -1.0 (-3, 2)

(Source: reviewer's table adapted from sponsor submission in response to Agency Information Request, sNDA 021830, supporting document 282, dated April 10, 2013)

The proportion of pediatric patients in complete response (remission) at week 6 was approximately 30% and was similar to what was seen in the adult trials. Additionally, there are large variations in changes for rectal bleeding and stool frequency scores between all three trials. The rectal bleeding scores for the low dose pediatric trial are similar to the rectal bleeding scores in the C14 adult trial (2.4 g/day). The stool frequency scores are most consistent between the C14 adult trial (2.4 g/day) and both pediatric dose levels (high and low).

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoint of Amended Endpoint- TS by weight category is shown above in Table 14. Treatment success as measured by this Amended Endpoint was achieved in 23 (56.1%) of

patients in the low dose level group and 23 (57.5%) of patients in the high dose level group. The Amended endpoint uses the PUCAI scoring system but replaces the 3-level abdominal pain questions with a 5-level abdominal pain question. The percentage of patients with treatment success, complete response, and partial response were similar between the PUCAI and Amended PUCAI.

The overall change in scores from baseline to Week 6 assessment are shown below in Table 16. The PUCAI and Amended PUCAI encompass a wider range of scores in the high dose group. The overall range of scores on the TM-Mayo was similar between the low and high dose groups.

Table 16: Overall Score Change from Baseline to Week 6 Assessment: PUCAI, Amended Endpoint, and TM-Mayo

	Low Dose N = 36	High Dose N = 36
PUCAI Score Mean (SD) Median Min, Max	 -17 (16.5) -20 (-45, 20)	 -18.8 (23.3) -22.5 (-55, 45)
Amended PUCAI Score Mean (SD) Median Min, Max	 -17.4 (16.7) -18.8 (-45.0, 22.5)	 -18.5 (22.8) -22.5 (-52.5, 47.5)
TM-Mayo Score Mean (SD) Median Min, Max	 -1.6 (1.6) -2.0 (-5, 2)	 -1.7 (1.8) -1.5 (-4, 1)

(Source: reviewer's own table adapted from sponsor submission in response to Agency Information Request, sNDA 021830, supporting document 282, dated April 10, 2013)

All three assessment tools demonstrate improvement of scores that reflect an improvement in disease activity at the Week 6 assessment. The individual components of each measurement tool were reviewed. The overall score did not appear to be driven by any one component. The overall change from baseline to week 6 for each individual component of the PUCAI and Amended Endpoint is shown below in Table 17.

Table 17: Overall Change from Baseline to Week 6 for Individual Components of the PUCAI and Amended Endpoint

PUCAI Individual Component Score Change Baseline to Week 6	Low Dose N = 36	High Dose N = 36
Abdominal Pain: 3-level Mean (SD) Median (Min, Max)	 -1.9 (3.6) 0.0 (-10, 5)	 -2.9 (4.5) -5.0 (-10. 5)
Abdominal Pain: 5-level (Amended PUCAI)	-1.7 (3.3) -1.3 (-7.5, 7.5)	-2.7 (3.8) -2.5 (-10, 7.5)
Rectal Bleeding	-7.5 (10.2) -10.0 (-30, 20)	-9.4 (10.7) -10.0 (-30, 20)
Stool Consistency of Most Stools	-2.8 (3.5) -5.0 (-10, 5)	-2.9 (3.7) -2.5 (-10, 5)
# Stools per 24 Hours	-2.4 (3.5) -5.0 (-10, 5)	-0.8 (4.1) 0.0 (-10, 10)
Nocturnal Bowel Movement (any diarrhea episode causing wakening)	-1.4 (3.5) 0.0 (-10, 0)	-0.8 (3.7) 0.0 (-10, 10)
Activity Level	-1.7 (2.7) 0.0 (-5, 5)	-1.8 (4.2) 0.0 (-10, 10)

(Source: reviewer's own table adapted from sponsor submission in response to Agency Information Request, sNDA 021830, supporting document 282, dated April 10, 2013)

The change in rectal bleeding and stool frequency individual scores from TM- Mayo from baseline to week 6 is shown below in Table 18.

Table 18: Overall Change from Baseline to Week6 for Individual Components of the TM-Mayo Score

TM-Mayo Individual Component Score Change Baseline to Week 6	Low Dose N = 36	High Dose N = 36
Rectal Bleeding Mean (SD) Median Min, Max	 -0.8 (0.8) -1.0 (-2, 1)	 -1.0 (0.9) -1.0 (-2, 0)
Stool Frequency Mean (SD) Median Min, Max	 -0.8 (1.0) -1.0 (-3, 1)	 -0.7 (1.1) -1.0 (-3, 2)

(Source: reviewer's own table adapted from sponsor submission in response to Agency Information Request, sNDA 021830, supporting document 282, dated April 10, 2013)

6.1.6 Other Endpoints

Change in disease activity and fecal biomarkers were assessed at baseline and week 6. Disease activity was determined by the investigator on a 7-point scale ranging from significantly improved (1) to significantly worsened (7). Nineteen (46.3%) subjects in the Low Dose group and 22 (55.0%) in the High Dose group were characterized as significantly improved. Mild to significant worsening was noted in 8 (19.5%) of subjects in the Low Dose group and 4 (10.0%) in the High Dose group. (b) (4) The change from baseline to week 6 in disease activity is summarized below in Table 19.

Table 19: Change in Disease Activity from Baseline to Week 6

Change in Disease Activity	Low Dose (N = 41) n (%)	High Dose (N = 41) n (%)	Total (N = 82) n (%)
1: Significantly Improved	19 (46.3%)	22 (55.0%)	41 (50.6%)
2: Moderately Improved	8 (19.5%)	4 (10.0%)	12 (14.8%)
3: Mildly Improved	4 (9.8%)	6 (15.0%)	10 (12.3%)
4: No Change	2 (4.9%)	4 (10.0%)	6 (7.4%)
5: Mildly Worse	4 (9.8%)	1 (2.5%)	5 (6.2%)
6: Moderately Worse	2 (4.9%)	1 (2.5%)	3 (3.7%)
7: Significantly Worse	2 (4.9%)	2 (5.0%)	4 (4.9%)
Total	41	40	81

(Source: reproduced from sponsor study report volume 1- Study 2007017 , dated December 21, 2012, page 60/392)

Although fecal biomarkers are being used more frequently in clinical practice, the relationship of these biomarkers to disease severity remains unclear. Fecal biomarkers (lactoferrin and calprotectin) were measured at baseline, week 3, week 6 and final assessment. Overall, fecal lactoferrin and calprotectin showed little improvement from baseline to week 6. The shift table for the fecal biomarkers is shown below in Table 20.

Table 20: Fecal Biomarker Shift Table (mITT population)- Study 2007017

Biomarker Visit	Baseline	Post-baseline					
		Low Dose (N=41)			High Dose (N=41)		
		Total	Normal n (%)	High n (%)	Total	Normal n (%)	High n (%)
Calprotectin (ug/g)							
Final Assessment	Normal	8	5 (62.5%)	3 (37.5%)	4	3 (75.0%)	1 (25.0%)
	High	28	2 (7.1%)	26 (92.9%)	30	4 (13.3%)	26 (86.7%)
Lactoferrin (ug/g)							
Final Assessment	Normal	8	7 (87.5%)	1 (12.5%)	5	4 (80.0%)	1 (20.0%)
	High	28	4 (14.3%)	24 (85.7%)	30	4 (13.3%)	26 (86.7%)

Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day. Dosage was dependent on body weight.
Total = number of subjects within specified Biomarker, Visit, Treatment and Baseline value.
n = number of subjects within specified Biomarker, Visit, Treatment and Baseline value.
% = percent of subjects within specified Biomarker, Visit, Treatment and Baseline value: (n/Total) X 100
Final Assessment = last post-baseline visit.

(Source: Sponsor Submission, Study Report, volume 1- Study 2007017, dated December 21, 2012, page 62/392)

6.1.7 Subpopulations

No subpopulations were evaluated in this study.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Results from the phase 3 pediatric trial suggested lack of dose-response with respect to the efficacy endpoints, as no additional therapeutic benefit was noted at the high dose level compared to the low doses (up to 2.4 g/day). In addition, exposure-response analyses involving systemic as well as predicted gut concentrations of mesalamine against probability of treatment success suggested a lack of correlation in both pediatric patients as well as in adults, (b) (4) . Although dose cannot be extrapolated from adult trials, this pediatric trial demonstrated similar response to treatment when compared to the same measures of disease improvement in adult trials (rectal bleeding and stool frequency). The proportion of pediatric patients in complete response (remission) at week 6 was approximately 30% and was similar to what was seen in the adult trials. Additionally, there is not a large variation between changes in the rectal bleeding and stool frequency scores between all three trials. The rectal bleeding scores for the low dose pediatric trial are similar to the rectal bleeding scores in the C14 adult trial (2.4 g/day). The stool frequency scores are most consistent between the C14 adult trial (2.4 g/day) and both pediatric dose levels (high and low).

The pediatric clinical trials were completed to fulfill a PREA PMR requirement under Asacol HD (NDA 021830). Asacol 400 mg was determined to be the pediatric formulation of Asacol HD. The recommended pediatric dosing is shown below. Please see PeRC PREA Subcommittee Meeting Minutes, dated April 9, 2008.

The recommended total daily dose of Asacol is weight-based, up to a maximum daily dose of 2.4 g/day (see table below).

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (mg/day)
17 to < 33	36 – 71	1200
33 to < 54	37 – 61	2000
54 to 90	27 - 44	2400

(b) (4)

7 Review of Safety

Brief Summary of Adverse Events

Asacol 400 mg delayed release tablets were approved for (b) (4) and maintenance of remission in adult patients with mild to moderate UC in 1992. Asacol is widely used off label for these indications in the pediatric UC population. The safety results from this analysis was overall similar to safety results from trials in adult patients with UC.

The same three trials were used to evaluate safety, efficacy and PK (studies 2007017, 2008085, and 2005018). Safety data from these trials were evaluated separately because the duration of treatment and indication (b) (4) differed between the three studies. In addition, Study 2005018 (PK study) included a different dosing regimen from Studies 2007017 and 2008185.

The table below is copied from Section 5- Table 7: mITT population - Treatment Groups (Study 2007017 and Study 2008085).

Study 2007017				Study 2008085		
	Asacol Dose (g/day)	**Number of patients N = 82**			**Asacol Dose (g/day)**	**Number of patients N = 39**
High Dose (N =41)	2.0	7		**High Dose (N =19)**	2.0	1
	3.6	17			3.6	6
	4.8	17*			4.8	12
Low Dose (N = 41)	1.2	5		**Low Dose (N = 20)**	1.2	1
	2.0	17			2.0	7
	2.4	19			2.4	12

*N = 17 for mITT analysis. Patient 1048641001 was randomized but voluntarily withdrew and was never dosed.
(Source: reviewer's own table adapted from sponsor study report- Study 2007017 and Study 2008085, dated December 21, 2012)

Study 2007017:

Forty-four patients reported 91 adverse events (AEs). There were no deaths and 7 nonfatal, serious adverse events (SAEs), including one report of pancreatitis. There were no changes in baseline creatinine. Overall, the types of adverse events reported in the pediatric study population were similar to the known adverse events associated with Asacol and similar to adverse events observed in adult ulcerative colitis trials.

Nasopharyngitis, fatigue, pyrexia, worsening ulcerative colitis, abdominal pain, headache, dizziness, rash, cough, diarrhea, and sinusitis were the AEs observed in at least 2 patients in Study 2007017. Seven patients (5 in the low dose and 2 in the high dose) withdrew due to AEs. All five patients in the low dose group withdrew because of AEs. In the high dose group, 2 patients withdrew due to AEs, 2 withdrew due to lack of treatment effect, and there was 1 voluntary withdrawal.

Table 21: **Summary of Types of Adverse Events- Study 2007017**

Type of adverse event	**Low dose group N (%)**	**High dose group N (%)**
Treatment Emergent AEs (TEAEs)	23 (56.1%)	21 (51.2%)
TEAEs occurring in ≥ 5% subjects	ulcerative colitis, nasopharyngitis, headache, dizziness, sinusitis, and (abdominal pain)*	nasopharyngitis, fatigue, and pyrexia
Subjects who withdrew due to AEs	5 (12.2%)	2 (4.9%)
Incidence of serious adverse events	5 (12.2%)	2 (4.9%)

(SAEs)		
Deaths	0	0

(Source: reviewer's own table adapted from sponsor study report- Study 2007017, dated December 21, 2012)

*Abdominal pain was not included in the sponsor's submission. This reviewer recoded "abdominal pain upper" as "abdominal pain" for this safety review, which increased the percentage to 9.8% of subjects in the low dose group.

7.1 Methods:

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The same three clinical trials were reviewed to evaluate efficacy and safety (Study 2007017, 2008085, and 2005018). The reader is referred to Section 5, Table 3: Summary of Studies/Clinical trials for details on the individual studies. All patients who received at least one dose of the study drug were included in the safety population. The results were compared to previously conducted trials in adults with UC (Studies C3 and C14).

7.1.2 Categorization of Adverse Events

The sponsor defined adverse events (AEs) as any unfavorable or unintended sign, symptom, or disease that appeared or worsened in a subject during the period of observation for the clinical study. The AE could be a new sign or symptom or an exacerbation of a sign or symptom of the underlying condition under treatment. All treatment-emergent AEs (TEAEs) were collected. Non-treatment-emergent adverse events were defined as AEs that occurred after written consent was obtained but before the first dose of the study drug was administered. Only serious non-treatment- emergent AEs that were related to study procedures were collected. If reported events were not serious and procedure related, they were documented by updating the medical history eCRF.

The sponsor acknowledges and defines the differences between serious and severe adverse events and states that seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The definitions below are adapted from the sponsor's study report pages 25- 26).

Serious Adverse Event:

- Results in death
- Life threatening defined as any AE that puts the patient at immediate risk of death
- Results in hospitalization or prolongation of current hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient

- Medically significant defined as an AE that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the outcomes listed above

Severity of Adverse Event:

- Mild: Normal activities unaltered
- Moderate: Normal activities altered
- Severe: Unable to undertake normal activities.

Causality of Adverse Event:

- Doubtful: There is no medical evidence to suggest that the AE may be related to study drug usage, or there is another more probable medical explanation.
- Possible: There is medical evidence to suggest that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause.
- Probable: There is strong medical evidence to suggest that the AE is related to study drug usage.
- AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT). Overall, the coding was appropriate. Table 22 and Table 23 below describe the terms that this reviewer recoded for the safety analysis.

Table 22: **Recoded Adverse Event Terms (Study 2007017)**

AETERM	AEDECOD	Recoded Term
Bloody Diarrhea	Diarrhoea haemorrhagic	Hematochezia
Drowsiness	Somnolence	Fatigue
Left And Right Ear Infection	Ear infections	Otitis media
Stomach Ache	Abdominal pain upper	Abdominal pain
Stomach Pain	Abdominal pain upper	Abdominal pain
Upper Respiratory Infection	Upper respiratory tract infection	Nasopharyngitis
Upper Respiratory Tract Infection	Upper respiratory tract infection	Nasopharyngitis
Upper Respiratory Tract Viral Infection	Viral upper respiratory tract infection	Nasopharyngitis

Table 23: Recoded Terms (Study 2008085)

AETERM	AEDECOD	Recoded Term
Abdominal Cramps	Abdominal discomfort	Abdominal pain
Upper abdominal pain	Abdominal pain upper	Abdominal pain
Rectal bleeding	Rectal haemorrhage	Hematochezia
Sinus congestion	Sinus congestion	Nasopharyngitis
Upper respiratory tract infection	Upper respiratory tract infection	Nasopharyngitis
Positive Lactoferrin Stool	Stool analysis abnormal	Positive Lactoferrin Stool

7.1.3 Pooled Safety Data from Clinical Trials to Compare Incidence

The three pediatric clinical trials submitted to NDA 021830 as this pediatric (b) (4) supplement were reviewed separately. The data are limited for study 2008085, due to small numbers of patients who enrolled (39 patients) and completed (21 patients), on the maintenance of remission of mildly to moderately active UC in pediatric patients.

7.2 Adequacy of Safety Assessments

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

Study 2007017:

The duration of the study (6 weeks) was appropriate (b) (4) Eighty-two patients received at least one dose of Asacol in study 2007017. In both dose arms, the median days of exposure was 43 days and 87.8% of patients were exposed to the drug for ≥ 5 weeks. Study drug exposure is summarized in Table 24 below.

Table 24: Study Drug Exposure for the Safety Population of Study 2007017

Parameter Statistic	Low Dose (N=41)	High Dose (N=41)	Overall (N=82)
Subject days of exposure			
n	41	41	82
Mean (SD)	39.8 (9.4)	40.4 (7.8)	40.1 (8.6)
Median	43.0	43.0	43.0
Min-Max	12-47	16-50	12-50
Exposure by Category			
< 1 week	0 (0.0%)	0 (0.0%)	0 (0.0%)
1 <= weeks < 3	4 (9.8%)	1 (2.4%)	5 (6.1%)
3 <= weeks < 5	1 (2.4%)	4 (9.8%)	5 (6.1%)
>= 5 weeks	36 (87.8%)	36 (87.8%)	72 (87.8%)

Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day. Dosage was dependent on body weight.
N=number of intent-to-treat subjects within specified treatment.
n(%) = number (percent) of subjects within specified category and treatment.

(Source: Sponsor's submission- Study 2007017, dated December 21, 2012, page 68/3086)

The mean and median durations of exposure were similar between the two dose groups. The number of patients who discontinued the study drug before 5 weeks is small and probably does not contribute to the interpretation of the safety analysis.

The age range of pediatric patients included in Study 2007017 is representative of the pediatric population with UC. One natural history study of pediatric UC reported a median age of diagnosis of 14 years (11-16 years).[18] Therefore, we expect smaller numbers of patients to be enrolled in the younger age groups. The reader is referred to Table 7: mITT population - Treatment Groups (Study 2007017 and Study 2008085) and Table 8: Demographic and Baseline Characteristics by Dose Group (mITT population) in Section 6.1.2 of this NDA review.

Study 2008085:

The sponsor did not provide a description of drug exposure for Study 2008085. The sponsor terminated the study prematurely due to challenges with enrollment and 21 patients completed the planned 26 week study duration.

7.2.2 Explorations for Dose Response

Patients in Study 2007017 remained on the dose to which they were randomized throughout the study duration. If they continued into the 30 day run-in phase for Study 2008085, they remained

[18] Gower-Rousseau, C., et al. The Natural History of Pediatric Ulcerative Colitis: A Population-Based Cohort Study. *Am J Gastroenterol* 2009; 104:2080–2088

on the dose given in Study 2007017. Patients who met inclusion criteria for the treatment phase of Study 2008085 were re-randomized to a fixed dose and remained on that dose for the duration of the trial.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

The routine clinical testing in Studies 2007017 and 2008085 appear adequate. Inquires about adverse events were made at each visit (baseline, week 3 and week 6) and at one week follow up telephone calls. Safety monitoring included adverse events (including tinnitus), subject withdrawals, vital signs, compliance, standardized and replicated weight and height, and laboratory parameters. Laboratory testing included complete blood count, liver enzymes, serum creatinine, BUN, and urinalysis. Patients with serious AEs, such as renal, hepatic, cardiac, pancreatic, gastritis, and cholecystitis, were monitored until resolution or until a new, stable baseline was established. Patients with persistent or significant elevations of AST, ALT, or LDH underwent further evaluation that included serum ammonia for Reye's Syndrome. Salicylate levels were obtained for any patient who experienced an AE suggestive of salicylate toxicity, including tinnitus.

7.2.5 Metabolic, Clearance, and Interaction Workup

The drug is thought to act locally in the colon and systemic exposures (BA ~ 20%) are relevant primarily from a safety perspective. High fat meals do not affect the bioavailability; however, the C_{max} is decreased 47% and delayed 14 hours. The C_{max} occurs between 10 – 16 hours post dose. Asacol is metabolized to N-acetyl-mesalamine in liver and gut prior to excretion in kidney. The apparent half-life is 12 h for mesalamine and 23 hr for its major metabolite (N-acetyl-mesalamine), however, these values are driven by the delayed release of the product and flip-flop pharmacokinetics. The reader is referred to the Clinical Pharmacology review by Dr. Sandhya Apparaju and Dr. Justin Earp, dated 9/13/2012.

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

No new or unexpected adverse events occurred during these three pediatric trials.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in Study 2007017, 2005018, or 2008085.

7.3.2 Nonfatal Serious Adverse Events

Study 2007017:

Seven (8.5%) patients reported 11 serious adverse events (SAEs). The SAEs included anemia/syncope, sinusitis, worsening abdominal pain/weight loss, worsening ulcerative colitis, adenovirus infection/worsening ulcerative colitis, bloody diarrhea/primary sclerosing cholangitis, and pancreatitis. Worsening UC and adenovirus, bloody diarrhea and PSC, and pancreatitis all required hospitalization. The patient with PSC has ongoing disease. The patients with worsening UC/adenovirus and pancreatitis recovered. Table 25 describes the SAEs for Study 2007017.

Table 25: Description of Serious Adverse Events (SAEs) Study 2007017

Patient ID	Treatment Group (dose)	Disposition	Type Of SAE	Onset (Study Day)	SAE Details
1048741002	Low (2.0 g/day)	Complete	Sinusitis	18	None provided
1048871007	High (3.6 g/day)	Complete	Ulcerative colitis	28	None Provided
1048881002	High (2.0 g/day)	Complete	Anemia	25	Patient transfused 1 Unit of red blood cells
			Syncope	25	Probably secondary to anemia
1048871001	Low (2.0 g/day)	Complete	Abdominal Pain	36	Admitted to clinical with persistent abdominal pain, likely due to UC
			Weight Loss	22	Hospitalization due to for weight loss
1048871005	Low (2.4 g/day)	Dropout	Adenovirus Infection	14	Hospitalization: (b) (6) Worsening UC likely due to Adenovirus Infection
			Ulcerative colitis	14	Hospitalized due to worsening Ulcerative Colitis: 5-10 loose, bloody stools daily
1048881003	Low (2.4 g/day)	Dropout	Sclerosing Cholangitis	6	Ultrasound findings: changes in bile ducts and enlargement of abdominal lymph nodes
			Hematochezia	15	Persistent Diarrhea, Blood In Stools, Sideropenia
1049551005	Low (2.4 g/day)	Dropout	Pancreatitis	12	Local Labs Collected: Amylase 121, Lipase 911, CRP 3.3

(Source: reviewer's own table adapted from sponsor's data- Study 2007017, dated December 21, 2012)

The sponsor determined that sclerosing cholangitis, hematochezia, and pancreatitis were possibly related to the study drug. (b) (4) Hematochezia is likely a symptom of

active UC but could also be due to mesalamine. Causality is difficult to establish given the small sample size. Pancreatitis is probably related to the study drug, as well as elevation of pancreatic enzymes without clinical symptoms (chemical pancreatitis). Pancreatitis and primary sclerosing cholangitis (PSC) are well-known extra-intestinal complications of inflammatory bowel disease.[19] Many of these adverse events are also symptoms of active UC, making it difficult to establish definite causality. Due to the small number of reports, data are insufficient to make conclusions on the relationship of time to a serious adverse event.

Study 2008085:

There were no deaths during Study 2008085. Two patients experienced a serious adverse event.

- Patient 1048503001 (Asacol dose 2.0 g/day) withdrew from the study on day 62 (3 days after onset of worsening UC, requiring hospitalization) and the study drug was discontinued.

- Patient 1048893002 (Asacol dose 4.8 g/day) was hospitalized for anemia requiring transfusion (hemoglobin 6.8 g/dL (normal 12.0 – 15.5 g/dL)). A sigmoidoscopy showed vascular changes in the distal colon. The mesalamine dose was changed to Mesalazine (2 x 500 mg) and the drug was continued at the new dose. EGD and colonoscopy were scheduled for approximately one month after hospital discharge. The patient withdrew from the study at the time of study termination.

Study 200518:

One patient in the 60 mg/kg/day dose group (Patient 88522008) withdrew due to worsening UC, which was considered a SAE. This patient started the study drug on April 25, 2006 and stopped the drug on May 17, 2006.

7.3.3 Dropouts and/or Discontinuations

Study 2007017:

Seven patients withdrew from the study because of an AE. Five patients in the low dose and 2 in the high dose group withdrew due to AEs. Three of those patients had a SAE. All SAEs were considered resolved except for Patient 1048881003 who has ongoing primary sclerosing cholangitis.

[19] Pitchumoni, et al. Pancreatitis in Inflammatory Bowel Diseases. J Clin Gastroenterol 2010;44:246–253

Table 26: **Study Withdrawals due to Adverse Events (N=7) Study 2007017**

Patient ID#	Weight group Treatment group (dose)	Observed AE	Onset of AE Study Day
1048701002	17- < 33 kg Low (1.2 g/day)	Worsening UC#	14
		Headache	5
1048891006	33- < 54 kg Low (2.0 g/day)	Worsening UC	28
1048561001	33- < 54 kg High (3.6 g/day)	Elevated amylase/ elevated lipase	20
1048711001	33- < 54 kg High (3.6 g/day)	Abdominal pain#	25
		Generalized Rash	31
1048871005**	54 - 90 kg Low (2.4 g/day)	Worsening UC	14
		Adenovirus infection	
1048881003**	54 - 90 kg Low (2.4 g/day)	Sclerosing Cholangitis#	15
		Hematochezia	6
1049551005**	54 - 90 kg Low (2.4 g/day)	Pancreatitis#	12
		Sinusitis	7

** Patient required hospitalization for Serious Adverse Event (SAE)
# Primary reason for study withdrawal in patients who reported > 1 AE
(Source: adapted from sponsor data submitted in study report- Study 2007017, appendix 16.2.7, page 23-29)

Run in phase- Study 2008085: Disposition and Adverse Events

Fourteen patients entered the 30 day run in phase from Study 2007017. Three patients dropped out of the run in phase. Patient 1048603001 was a voluntary withdrawal (low dose 2.0 g/day). Two patients withdrew due to disease relapse: patient 1049043001 in the low dose (2.4 g/day) and patient 1049053005 in the high dose (4.8g/day). Table 42 in Section 9.4 shows the disposition of patients during the Run-in phase. The ages of the patients range from 8 years to 17 years of age. Younger patients tended to be included in the lower dose groups and older children were in the higher dose groups because of the weight categories.

Concomitant medications during the run in phase included allergy medications, vitamins, reflux medication, or antibiotics for a throat infection. Two patients reported taking medications used in the treatment of UC (metronidazole and mesalazine enemas/Rowasa). The patient taking mesalazine enemas dropped out due to relapse and the patient taking metronidazole completed the run in phase. These medications were not taken concomitantly with the study drug and the dates of these medications were not provided.

Adverse Events during the 30 day run in phase:
There were 5 AEs reported from 3 patients during the run in phase. One patient (4.8 g/day) dropped out because of a relapse of UC with increased rectal bleeding and diarrhea. The two other patients completed the run in phase. One patient reported pharyngitis (low dose 1.2 g/day) and another patient reported influenza and seasonal allergies (low dose 2.4 g/day). None of these

were classified as severe and there were no deaths. The sponsor determined rectal bleeding and diarrhea were possibly related to the study drug. These symptoms could also be a result of active underlying disease. Symptoms indicating a relapse of UC more accurately represent a treatment failure rather than an adverse reaction.

Treatment Phase- Study 2008085:

Two patients (Subject ID #1048503001 and #1050203003) withdrew due to adverse events, both reported worsening of ulcerative colitis. Patient #1048503001 withdrew from the study on day 62 (3 days after onset of worsening UC, requiring hospitalization) and the study drug was discontinued. Patient #1050203003 reported worsening of UC on study day 91.

Study 2005018:

The disposition of patients for Study 2005018 is show in Table 27 below. Thirty-one patients completed the study. Two patients withdrew voluntarily and one patient withdrew due to a serious adverse event. Description of the SAE leading to study withdrawal is located in section 7.3.2 Nonfatal Serious Adverse Events.

Table 27: Disposition of Patients: Study 2005018

Category	30 mg/kg/day (N = 10) n (%)	60 mg/kg/day (N = 12) n (%)	90 mg/kg/day (N = 12) n (%)	Overall (N = 34) n (%)
Randomized To Treatment				
Completed	9 (90%)	11 (92%)	11 (92%)	31 (91%)
Discontinued	1 (10%)	1 (8%)	1 (8%)	3 (9%)
Reason For Discontinuation				
Adverse Event	0 (0%)	1 (8%)	0 (0%)	1 (3%)
Voluntary Withdrawal	1 (10%)	0 (0%)	1 (8%)	2 (6%)

(Source: Sponsor study report- Study 2005018, dated December 21, 2012, page 25)

7.3.4 Significant Adverse Events

Study 2007017:

In Study 2007017, there were two events that were possibly related to the study drug. Both events occurred in the same patient. Pancreatitis and bloody diarrhea were considered serious adverse events. The study drug was discontinued due to pancreatitis. Narrative from the sponsor's study report (page 159) is summarized below.

Subject 1049551005 was a 15 year-old Caucasian female, of Hispanic or Latino ethnicity, who

experienced a SAE of pancreatitis that resulted in hospitalization and withdrawal from the study. Her medical history is significant for pancolitis, seasonal allergies, tonsillectomy and adenoidectomy, occasional headache, and gastroesophageal reflux disease. Her total daily Asacol dose was 2.4 g/day from 11-Nov-2010 to 22-Nov-2010.

The patient presented to an urgent care center with severe abdominal pain on (b) (6) where she was found to have an elevated lipase 911 U/L (normal range: 25-120 U/L), amylase 121 (normal range: 23-85), and C-reactive protein 3.3 (normal range: 0-1.0). She was discharged home and continued to have pain. On (b) (6) she was seen in an outpatient clinic where physical exam was significant for severe epigastric pain and bloody diarrhea. She was admitted to the hospital for further evaluation and management, and withdrew from the study. Upon admission, her lipase was 516 and amylase was 101. Abdominal magnetic resonance imaging was negative for primary sclerosing cholangitis but was suggestive of pancreatitis. Her pancreatitis was felt to be secondary to Asacol and the study drug was discontinued. Her bloody diarrhea was treated with intravenous methylprednisolone and transitioned over to prednisone 40 mg per day with improvement of stool output. Upon discharge on (b) (6), her lipase and amylase were trending down and the abdominal pain resolved. The event was considered to be resolved on December 6, 2010. Mercaptopurine 50 mg was started on December 10, 2010. The investigator deemed the pancreatitis to be possibly related to the study drug.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 2007017:

There were a total 44 patients reporting 91 adverse events. Common adverse events were similar between Study 2007017 and Study 2008085. The total number of patients enrolled in these studies was small so the percentage of patients experiencing an adverse event appears high when compared to studies in adults with ulcerative colitis who are treated with Asacol.

Nasopharyngitis was the most common AE occurring in 14.6% of patients in the low dose group and 12.2% of patients in the high dose group. Increased frequency of nasopharyngitis and sinusitis are expected in a pediatric population. Abdominal pain, diarrhea, and fever are common symptoms associated with UC, therefore these events are probably not related to the study drug. The common adverse events occurring in at least 2 patients for Study 2007017 are shown below in Table 28.

Table 28: Common Adverse Events Observed in at Least 2 Patients in Study 2007017

Adverse Event	Study 2007017	
	Low Dose N= 41 n (%)	High Dose N= 41 n (%)
Nasopharyngitis	6 (14.6)	5 (12.2)
Fatigue	1 (2.4)	4 (9.8)
Pyrexia	0 (0)	3 (7.3)
Ulcerative Colitis	5 (12.2)	2 (4.9)
Headache	4 (9.8)	2 (4.9)
Lipase increased	0 (0)	2 (4.9)
Abdominal pain	4 (9.8)	1 (2.4)
Dizziness	3 (7.3)	1 (2.4)
Rash	2 (4.9)	2 (4.9)
Cough	2 (4.9)	0 (0.0)
Diarrhea	2 (4.9)	0 (0.0)
Sinusitis	3 (7.3)	0 (0.0)

(Source: reviewer's own table created using sponsor study data- Study 2007017, dated December 21, 2012)

The numbers and percentages differ slightly from the sponsor's submission in the Study Report-Study 2007017 (pages 134-135) because some terms were recoded for this review. For example, abdominal pain upper was recoded as abdominal pain and diarrhea hemorrhagic was recoded as hematochezia. Refer to Table 22 for a listing of recoded terms.

Twenty three (56.1%) of patients in the low dose and 21(51.2%) of the patients in the high dose group reported at least one treatment emergent adverse event (TEAE). Table 29 below shows the adverse events for each dose arm reported during Study 2007017.

Table 29: All Adverse Events by Treatment Group - Study 2007017

Body System/Event	Low Dose (N =41) n (%)	High Dose (N= 41) n(%)
Number of patients with ≥ 1 TEAE	23 (56.1%)	21 (51.2%)
Gastrointestinal disorders		
Abdominal pain	4 (9.8)	2 (4.9)
Ulcerative Colitis	5 (12.2)	2 (4.9)
Constipation	1 (2.4)	0 (0)
Diarrhea	2 (4.9)	0 (0)
Fecal incontinence	1 (2.4)	0 (0)
Hematochezia	1 (2.4)	1 (2.4)
Pancreatitis	1 (2.4)	0 (0)
Vomiting	0 (0)	1 (2.4)
Infections and infestations		
Adenovirus infection	1 (2.4)	0 (0)
Bacteriuria	1 (2.4)	0 (0)
Nasopharyngitis	6 (14.6)	5 (12.2)
Otitis media	1 (2.4)	1 (2.4)
Pharyngitis	0 (0)	1 (2.4)
Sinusitis	3 (7.3)	0 (0)
Investigations		
Blood amylase increased	0 (0)	1 (2.4)
Body mass index decreased	1 (2.4)	0 (0)
Hepatic enzyme increased	0 (0)	1 (2.4)
Lipase increased	0(0)	2 (4.9)
Nervous system disorders		
Dizziness	3 (7.3)	1 (2.4)
Headache	4 (9.8)	2 (4.9)
Syncope	0 (0)	1 (2.4)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (4.9)	0 (0)
Dysphonia	1 (2.4)	0 (0)
Rhinorrhea	1 (2.4)	1 (2.4)
Throat irritation	1 (2.4)	0 (0)
General disorders and administration site conditions		
Fatigue	1 (2.4)	4 (9.8)
Asthenia	0 (0)	1 (2.4)
Pyrexia	0 (0)	3 (7.3)
Injury, poisoning and procedural complications		
Hand fracture	0 (0)	1 (2.4)
Limb injury	0 (0)	1 (2.4)
Sunburn	1 (2.4)	0 (0)
Reproductive system and breast disorders		
Dysmenorrhea	0 (0)	1 (2.4)

Menorrhagia	1 (2.4)	0 (0)
Testicular pain	0 (0)	1 (2.4)
Renal and urinary disorders		
Bilirubinuria	0 (0)	1 (2.4)
Proteinuria	1 (2.4)	0 (0)
Blood and lymphatic system disorders		
Anemia	0 (0)	1 (2.4)
Hepatobiliary disorders		
Sclerosing Cholangitis	1 (2.4)	0 (0)
Musculoskeletal and connective tissue disorders		
Neck pain	0 (0)	1 (2.4)
Skin and subcutaneous tissue disorders		
Rash	2 (4.9)	2 (4.9)

(Source: reviewer's own table created using sponsor study data- Study 2007017, dated December 21, 2012)

To further explore the relationship of dose to the observed adverse events, the total daily Asacol dose was calculated for each subject in milligrams per kilogram (mg/kg) and divided into commonly used dose ranges in clinical practice (< 50 mg/kg, 50 – 80 mg/kg, > 80 mg/kg). In clinical practice, the upper limit for total daily Asacol dose is around 100 mg/kg/day. In Study 2007017, only three patients were dosed above 100 mg/kg/day (101.7 mg/kg, 102.9 mg/kg, and 117 mg/kg). The observed adverse events for Study 2007017 are described in Table 30 below.

Table 30: All Observed Adverse Events by Asacol Dose Range (mg/kg)- Study 2007017

Body System/Event	Asacol dose range (mg/kg/day)		
	< 50	50 - 80	> 80
	n (%)	n(%)	n(%)
Number of patients in each group	36	12	34
Gastrointestinal disorders			
Abdominal pain	4 (11.1)		1 (2.9)
Hematochezia	1 (2.8)	1(8.3)	
Ulcerative Colitis	4 (11.1)	3 (25.0)	
Constipation	1 (2.8)		
Diarrhea	2 (5.6)		
Fecal incontinence	1 (2.8)		
Pancreatitis	1 (2.8)		
Vomiting		1 (8.3)	
Infections and infestations			
Nasopharyngitis	6 (16.7)	3 (25.0)	2 (5.9)
Adenovirus infection	1 (2.8)		
Bacteriuria	1 (2.8)		
Otitis Media	1 (2.8)	1 (8.3)	
Pharyngitis		1 (8.3)	
Sinusitis	3 (8.3)		
General disorders and administration site conditions			
Fatigue	1 (2.8)	2 (16.7)	2 (5.9)
Pyrexia		1 (8.3)	2 (5.9)
Asthenia		1 (8.3)	
Nervous system disorders			
Dizziness	3 (8.3)	1 (8.3)	
Headache	4 (11.1)	2 (16.7)	
Syncope		1 (8.3)	
Investigations			
Lipase increased		1 (8.3)	1 (2.9)
Blood amylase increased			1 (2.9)
Body mass index decreased	1 (2.8)		
Hepatic enzyme increased		1 (8.3)	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	1 (2.8)	1 (8.3)	
Cough	2 (5.6)		
Dysphonia	1 (2.8)		
Throat irritation		1 (8.3)	
Injury, poisoning and procedural complications			
Hand fracture		1 (8.3)	

Limb injury			1 (2.9)
Sunburn	1 (2.8)		
Reproductive system and breast disorders			
Dysmenorrhea			1 (2.9)
Menorrhagia	1 (2.8)		
Testicular pain		1 (8.3)	
Skin and subcutaneous tissue disorders			
Rash	1 (2.8)	2 (16.7)	1 (2.9)
Renal and urinary disorders			
Bilirubinuria			1 (2.9)
Proteinuria	1 (2.8)		
Blood and lymphatic system disorders			
Anemia		1 (8.3)	
Hepatobiliary disorders			
Sclerosing Cholangitis	1 (2.8)		
Musculoskeletal and connective tissue disorders			
Neck pain		1 (8.3)	

(Source: reviewer's own table created using sponsor study data- Study 2007017, dated December 21, 2012)

The number of patients in each dose arm and the number of adverse events reported for each body system and AE are small. The most commonly reported AE was nasopharyngitis with 6 (16.7%) in the lowest dose range of < 50 mg/kg/day, 3 (25%) in 50 - 80 mg/kg/day range, and 2 (5.9%) in the > 80 mg/kg/day range. As described earlier in this review, other commonly reported adverse events could also be symptoms of active underlying disease. These include hematochezia, ulcerative colitis (the disease for this drug indication), diarrhea, abdominal pain and vomiting. These adverse events are most frequently reported the lowest dose range (< 50 mg/kg/day). The exception is fatigue, which is more evenly distributed across all three dose ranges. However, it is difficult to determine if these symptoms are related to the underlying disease or to the drug. Mesalamine-induced acute intolerance syndrome has been described and symptoms are similar to that of a flare of UC (abdominal pain, hematochezia, fever, headache, and rash).[20]

The types of adverse events were similar between Study 2007017 and Study 2008085. The total number of patients in each dose arm for Study 2008085 is approximately half of the total number per dose arm in Study 2007017.

Study 2008085:

Adverse Events during the 30-day run in phase: There were 5 AEs reported from 3 patients during the run in phase. One patient (4.8 g/day) dropped out because of a relapse of UC with increased rectal bleeding and diarrhea. The sponsor determined rectal bleeding and diarrhea to be

[20] Delzicol label, last updated February 1, 2013, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204412s000lbl.pdf

possibly related to the study drug. The two other patients completed the run in phase. One patient reported pharyngitis (low dose 1.2 g/day) and another patient reported influenza and seasonal allergies (low dose 2.4 g/day). None of these were classified as severe and there were no deaths.

During the treatment phase of Study 2008085, the most common AEs that occurred in at least 2 patients during Study 2008085 were abdominal pain, diarrhea, headache, nasopharyngitis, sinusitis, and vomiting and are shown below in Table 31.

Table 31: Common Adverse events observed in at least 2 patients in Study 2008085

Adverse Event	Study 2008085 (treatment phase)	
	Low Dose N= 20 n (%)	High Dose N= 19 n (%)
Abdominal pain	3 (15.0)	2 (10.5)
Diarrhea	3 (15.0)	1 (5.3)
Headache	1 (5.0)	3 (15.8)
Nasopharyngitis	1 (5.0)	3 (15.8)
Sinusitis	1 (5.0)	2 (10.5)
Vomiting	2 (10.0)	1 (5.3)

(Source: reviewer's own table using sponsor study data- Study 2008085, dated December 21, 2012)

The number and percentages differ slightly from what the sponsor reported in the Study Report for Study 2008085 (page 13) because this reviewer recoded terms. For example, abdominal pain was recoded to include abdominal discomfort, abdominal pain, and abdominal pain upper, where the sponsor listed these as separate events. Refer to Table 23 for a listing of recoded terms.

Abdominal pain, diarrhea, and vomiting are all associated symptoms of ulcerative colitis and may not be related to the study drug. Headache is a labeled adverse reaction for Asacol and possibly related to the study drug. Headache occurred more frequently in the high dose group (15.8%). In adult trials evaluating Asacol 2.4 g/day (N = 732) compared to Asacol HD 4.8 g/day (N= 727), headache occurred in 4.9% and 4.7% of adult patients, respectively.

Compared to Study 2007017, the percentage of patients in the low dose group who experienced a TEAE were similar, 56.1% in Study 2007017 and 55.0% in Study 2008085. The high dose group in Study 2008085 had a slightly higher percentage of patients who experienced a TEAE (68.4%) compared to 51.4% in the high dose group in Study 2007017.

Table 32 below shows the adverse events for each dose arm reported during Study 2008085.

Table 32: All Adverse Events by Treatment Group- Study 2008085 treatment phase

Body System/Event	Low Dose (N= 20) n (%)	High Dose (N = 19) n (%)
Number of patients with ≥ 1 TEAE	11 (55.0)	13 (68.4)
Gastrointestinal disorders		
Abdominal pain	3 (15.0)	2 (10.5)
Constipation	0 (0)	1 (5.3)
Diarrhea	3 (15.0)	1 (5.3)
Dyspepsia	0 (0)	1 (5.3)
Gastroesophageal reflux disease	1 (5.0)	0 (0)
Hematochezia	1 (5.0)	1 (5.3)
Lip blister	1 (5.0)	0 (0)
Nausea	1 (5.0)	1 (5.3)
Ulcerative colitis	1 (5.0)	1 (5.3)
Vomiting	2 (10.0)	1 (5.3)
Infections and infestations		
Campylobacter gastroenteritis	1 (5.0)	0 (0)
Orbital Cellulitis	1 (5.0)	0 (0)
Infectious mononucleosis	0 (0)	1 (5.3)
Nasopharyngitis	1 (5.0)	3 (15.8)
Otitis media	0 (0)	1 (5.3)
Sinusitis	1 (5.0)	2 (10.5)
Viral infection	0 (0)	1 (5.3)
Respiratory, thoracic and mediastinal disorders		
Asthma	0 (0)	1 (5.3)
Epistaxis	0 (0)	1 (5.3)
Oropharyngeal pain	1 (5.0)	1 (5.3)
Sinus congestion	0 (0)	1 (5.3)
Skin and subcutaneous tissue disorders		
Dermatitis	0 (0)	1 (5.3)
Dry skin	1 (5.0)	0 (0)
Rash	2 (10.0)	0 (0)
Skin erosion	1 (5.0)	0 (0)
Injury, poisoning and procedural complications		
Contusion	0 (0)	1 (5.3)
Muscle strain	0 (0)	1 (5.3)
Skin laceration	1 (5.0)	0 (0)
Investigations		
Lipase increased	1 (5.0)	1 (5.3)
Positive Lactoferrin Stool	1 (5.0)	0 (0)
Urinary sediment present	0 (0)	1 (5.3)
General disorders and administration site conditions		
Axillary pain	0 (0)	1 (5.3)
Cyst	1 (5.0)	0 (0)
Musculoskeletal and connective tissue disorders		

Arthralgia	0 (0)	1 (5.3)
Pain in extremity	1 (5.0)	1 (5.3)
Blood and lymphatic system disorders		
Anemia	0 (0)	1 (5.3)
Metabolism and nutrition disorders		
Dehydration	1 (5.0)	0 (0)
Nervous system disorders		
Headache	1 (5.0)	3 (15.8)
Renal and urinary disorders		
Proteinuria	0 (0)	1 (5.3)

(Source: reviewer's own table using sponsor study data- Study 2008085, dated December 21, 2012)

Study 2005018:

The observed adverse events during Study 2005018 are described in Table 33 below. The type of event and frequency is consistent with what is observed in Studies 2007017 and 2008085. The numbers of patients reporting AEs were small with no more than 2 in each dose group. The percentages appear high, however, because the total number of patients in each dose group was small. The 30 mg/kg/day group included 9 patients; the 60 mg/kg/day and 90 mg/kg/day groups included 12 patients each.

Table 33: All Adverse Events by Treatment Group- Study 2005018

Body System/Event	Asacol dose group (mg/kg/day)		
	30	60	90
	N = 9	N = 12	N = 12
	n (%)	n (%)	n (%)
Gastrointestinal disorders			
Ulcerative Colitis		1 (8.3)	1 (8.3)
Hematochezia	2 (22.2)	1 (8.3)	
Nausea		1 (8.3)	2 (16.7)
Vomiting		1 (8.3)	1 (8.3)
Abdominal pain			1 (8.3)
Borborygmi			1 (8.3)
Constipation	1 (11.1)		
Painful defecation	1 (11.1)		
Stomatitis			1 (8.3)
Infections and infestations			
Nasopharyngitis	1 (11.1)		1 (8.3)
Influenza		1 (8.3)	
Viral infection		1 (8.3)	
Injury, poisoning and procedural complications			
Contusion	1 (11.1)		1 (8.3)
Abrasion		1 (8.3)	
Skin laceration			1 (8.3)
Nervous system disorders			
Headache	1 (11.1)		1 (8.3)
Migraine	1 (11.1)		
Syncope	1 (11.1)		
Respiratory, thoracic and mediastinal disorders			
Cough	2 (22.2)	2 (16.7)	
Sinus congestion	1 (11.1)		
Throat pain		1 (8.3)	
General disorders and administration site conditions			
Vessel puncture site bruise		2 (16.7)	1 (8.3)
Pyrexia			1 (8.3)
Investigations			
Blood calcium decreased			1 (8.3)
Blood phosphorus increased			1 (8.3)
Musculoskeletal and connective tissue disorders			
Arthralgia			1 (8.3)
Pain in extremity		1 (8.3)	
Ear and labyrinth disorders: Ear pain	1 (11.1)		
Eye disorders: Conjunctivitis	1 (11.1)		
Other: Oral pain from braces		1 (8.3)	
Reproductive system and breast disorders: Dysmenorrhea	1 (11.1)		

(Source: Reviewer's own table using sponsor data from Study 2005018, dated December 21, 2012)

Comparison to Adverse Events from Adult Trials

The nature of adverse events observed in adult trials are similar to the adverse events reported in these pediatric studies. The Table below compares pooled data from three studies in adult subjects with mild to moderate UC, leading to the approval of Asacol HD 800 mg.

Table 34: Adverse Reactions occurring in > 1% of All Treated Adult Patients treated with Asacol (three studies combined: Intent-to-treat population)

MedDRA Preferred Term	Asacol* 2.4g/day (400 mg Tablet) (N=732)	Asacol HD* 4.8g/day (800 mg Tablet) (N=727)
Headache	4.9 %	4.7 %
Nausea	2.9 %	2.8 %
Nasopharyngitis	1.4 %	2.5 %
Abdominal pain	2.3 %	2.3 %
Ulcerative Colitis	2.7 %	2.3 %
Diarrhea	1.9 %	1.7 %
Dyspepsia	0.8 %	1.7 %
Vomiting	1.6 %	1.4 %
Flatulence	0.7 %	1.2 %
Influenza	1.2 %	1.0 %
Pyrexia	1.2 %	0.7 %
Cough	1.4 %	0.3 %

N = number of patients within specified treatment group
% = percentage of patients in category and treatment group
*One Asacol HD 800 mg tablet has not been shown to be bioequivalent to two Asacol 400 mg tablets *[see Clinical Pharmacology (12.3)]*.

(Source: Asacol HD 800 mg FDA approved label, last updated 5/24/2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021830s005lbl.pdf)

When comparing this pediatric trial to the adult trials, it is important to note that Asacol HD 800 mg (used for 4.8 g/day dosing) is not bioequivalent to Asacol 400 mg. Asacol dosing for adults is a fixed dose whereas children received weight based dosing (mg/kg). This pediatric trial includes a range of doses in the low and high dose groups. The low dose group ranges from 1.2 g/day to 2.4 g/day and the high dose group ranges from 2.0 g/day to 4.8 g/day. In the pediatric trial, the percentage of patients reporting ulcerative colitis (12.2% in the low dose and 4.9% in the high dose) was higher than in the adult studies (2.7% in the 2.4 g/day group and 2.3% the 4.8 g/day group). The higher percentage of ulcerative colitis in the lower dose group may be a result of decreased efficacy rather than an adverse drug reaction since ulcerative colitis is the primary disease of interest in the study.

The types of AEs from studies in adult patients with UC are similar to the types of AEs reported from the pediatric studies. The most common adverse events included nasopharyngitis, fatigue, pyrexia, ulcerative colitis, headache, increased lipase, abdominal pain. dizziness, rash, cough, diarrhea, and sinusitis. Nasopharyngitis (14.6% in low dose and 12.2% in high dose group) and sinusitis (7.3% in low dose group) are slightly higher in the pediatric studies but this is expected for a pediatric population. The pediatric studies had a significantly smaller sample size than the adult studies. The total per dose group in the pediatric studies was 41 patients compared to 732 patients in one dose group for the adult studies.

7.4.2 Laboratory Findings

Study 2007017:

Serum chemistry was measured at baseline, week 6, and final assessment. There were no changes in serum sodium, albumin, alkaline phosphatase, or chloride. There were no patients with hyperkalemia. Two patients, with normal baseline potassium, in the low dose group had potassium in the low range at week 6 and final assessment. One patient in the high dose group had normal baseline AST, ALT, and bilirubin that were elevated at week 6 and final assessment. Lab values that are related to the toxicity of mesalamine products are described below.

Creatinine:
Renal impairment (minimal change nephropathy, acute and chronic interstitial nephritis and rarely renal failure) has been reported in patients taking mesalamine products. In nonclinical animal studies, the principle organ for toxicity was the kidney.

Creatinine values were reported for 34 patients at week 6. All 34 patients had normal baseline creatinine and remained normal at week 6. One patient in the high dose group had a high baseline creatinine value that remained high at final assessment.

Lipase:
Pancreatitis has been associated with mesalamine use, as well as with inflammatory bowel disease. Twenty-six patients had elevated lipase levels at week 6 evaluation, however, a minority of these were clinically relevant. Some patients were reported with elevated values for lipase values that were only a few points outside of the normal range. The shift table below summarizes the changes in lipase values for the safety population.

Table 35: Shift Table of Serum Lipase Values- Study 2007017 Safety Population

Lab Test Visit	Baseline	Post-baseline							
		Low Dose (N=41)				High Dose (N=41)			
		Total	Low n (%)	Normal n (%)	High n (%)	Total	Low n (%)	Normal n (%)	High n (%)
Lipase (Triaclglycerol Lipase)									
Week 6	Low	N/A	N/A (N/A)	N/A (N/A)	N/A (N/A)	N/A	N/A (N/A)	N/A (N/A)	N/A (N/A)
	Normal	21	N/A (N/A)	19 (90.5%)	2 (9.5%)	23	N/A (N/A)	21 (91.3%)	2 (8.7%)
	High	13	N/A (N/A)	2 (15.4%)	11 (84.6%)	11	N/A (N/A)	3 (27.3%)	8 (72.7%)
Final Assessment	Low	N/A	N/A (N/A)	N/A (N/A)	N/A (N/A)	N/A	N/A (N/A)	N/A (N/A)	N/A (N/A)
	Normal	22	N/A (N/A)	20 (90.9%)	2 (9.1%)	25	N/A (N/A)	23 (92.0%)	2 (8.0%)
	High	14	N/A (N/A)	2 (14.3%)	12 (85.7%)	13	N/A (N/A)	3 (23.1%)	10 (76.9%)

(Source: sponsor submission- Study Report- 2007017, dated December 21, 2012, page 284)

Table 36 below shows the patients who had a recorded increase in lipase value of ≥100% from baseline at week 6.

Table 36: Lipase values (U/L) for Patients with ≥ 100% Change from Baseline to Week 6

Subject	Asacol Dose Group (g/day)	Baseline Lipase (u/L)	Lipase Week 6 (u/L)	Change from Baseline (u/L)	% Change From Baseline	Disposition (dropout reason)
1048561001	High (3.6)	161	688	527	327.3	dropout- AE
1048721004	Low (2.4)	40	211	171	427.5	complete
1049051004	High (3.6)	37	90	53	143.2	complete
1049331001	High (4.8)	31	77	46	148.4	complete

(Source: reviewer's own table using sponsor study data- Study 2007017, dated December 21, 2012)

For a full list of patients with elevated lipase during Study 2007017, refer to Table 41 in Section 9: Appendix.

Elevations in amylase and lipase can be associated with inflammatory bowel disease, however, not all of the elevated lab values occurred in patients with symptoms of clinical pancreatitis. Four patients had elevations that exceeded 100% change from baseline. Patient 1048561001 withdrew from the trial due to elevated amylase/lipase. Patient 1048721004 completed the study but reported an adverse event of worsening UC. Patient 1049051004 reported elevated lipase, fatigue and vomiting which could be symptoms of pancreatitis. Patient 1049331001 did not report a GI related adverse event. One patient (1049551005), not shown in the above table, withdrew from the trial because of pancreatitis (amylase: 211, lipase 911). The labs were collected at a local lab, not during a scheduled blood draw. Therefore, the values were not included in the sponsor's dataset that was used to create Table 36.

Hematology:
Hematologic measures included platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), absolute erythrocyte count, and absolute leukocyte count. There were no patients with

thrombocytopenia. Patients, who started with normal platelet counts, remained with normal counts at week 6 and final assessment.

Of the patients with normal baseline hemoglobin at baseline, 3 had low values at Week 6 in the low dose group and 2 had low values in the high dose group. Of the patients with low hemoglobin values at baseline, 1 out of 6 patients normalized in the low dose group and 3 out of 7 normalized in the high dose group. The shift table below summarizes the changes in hematocrit and hemoglobin for the safety population of Study 2007017.

Table 37: Shift Table of Hematocrit and Hemoglobin Values- Study 2007017 Safety Population

		Post-baseline							
		Low Dose (N=41)				High Dose (N=41)			
Lab Test Visit	Baseline	Total	Low n (%)	Normal n (%)	High n (%)	Total	Low n (%)	Normal n (%)	High n (%)
Hematocrit									
Week 6	Low	5	4 (80.0%)	1 (20.0%)	0 (0.0%)	6	3 (50.0%)	3 (50.0%)	0 (0.0%)
	Normal	22	1 (4.5%)	20 (90.9%)	1 (4.5%)	26	2 (7.7%)	24 (92.3%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Final Assessment	Low	6	5 (83.3%)	1 (16.7%)	0 (0.0%)	7	4 (57.1%)	3 (42.9%)	0 (0.0%)
	Normal	23	1 (4.3%)	21 (91.3%)	1 (4.3%)	28	2 (7.1%)	26 (92.9%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hemoglobin									
Week 6	Low	6	5 (83.3%)	1 (16.7%)	0 (0.0%)	7	4 (57.1%)	3 (42.9%)	0 (0.0%)
	Normal	24	3 (12.5%)	21 (87.5%)	0 (0.0%)	25	2 (8.0%)	23 (92.0%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Final Assessment	Low	7	6 (85.7%)	1 (14.3%)	0 (0.0%)	9	6 (66.7%)	3 (33.3%)	0 (0.0%)
	Normal	25	3 (12.0%)	22 (88.0%)	0 (0.0%)	27	2 (7.4%)	25 (92.6%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)

(Source: sponsor submission- Study Report- 2007017, dated December 21, 2012, page 288)

Study 2008085:

Laboratory measurements were documented at week 12, week 26, and final assessment for patients in this 26 week trial evaluating longer term use of Asacol in pediatric patients with UC. There were no significant changes in serum chemistry or urinalysis values. Baseline liver function remained stable at a normal value or lower than normal reference range value without any documented elevations at the pre-determined safety assessments.

Creatinine:
One patient in the low dose group was reported to have elevated creatinine at the post-baseline final assessment. The shift table below summarizes the changes in creatinine values for the safety population of Study 2008085.

Table 38: Creatinine Values at Baseline and Post-baseline Assessments- Safety Population Study 2008085

Lab Test Visit	Baseline	Post-baseline							
		Low Dose (N=20)				High Dose (N=19)			
		Total	Low n (%)	Normal n (%)	High n (%)	Total	Low n (%)	Normal n (%)	High n (%)
Creatinine									
Week 12	Low	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	11	0 (0.0%)	10 (90.9%)	1 (9.1%)	14	0 (0.0%)	14 (100.0%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 26	Low	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	11	0 (0.0%)	10 (90.9%)	1 (9.1%)	10	0 (0.0%)	10 (100.0%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Final Assessment	Low	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	17	0 (0.0%)	16 (94.1%)	1 (5.9%)	19	0 (0.0%)	19 (100.0%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)

(Source: sponsor submission in response to information request, dated 7/1/2013, page 17)

Lipase:

Eleven patients had documented lipase values at week 12 and week 26, and 17 patients had documented lipase values post-baseline assessment. Two patients in the low dose group had normal baseline lipase values and elevated lipase values at week 12. Of the patients with normal baseline lipase in the high dose group, none had elevated lipase at Week 12. At Week 26, one patient in the low dose group and one in the high dose group had elevated lipase from normal baseline values. These elevations were not necessarily clinically relevant. Increased lipase was reported as a treatment-emergent-adverse-event by only one patient in both the low dose and high dose groups. The shift table below summarizes the changes serum lipase values for study 2008085.

Table 39: Lipase Values at Baseline and Post-baseline Assessments- Safety Population Study 2008085

Lab Test Visit	Baseline	Post-baseline							
		Low Dose (N=20)				High Dose (N=19)			
		Total	Low n (%)	Normal n (%)	High n (%)	Total	Low n (%)	Normal n (%)	High n (%)
Lipase (Triaclglycerol Lipase)									
Week 12	Low	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Normal	9	N/A	7 (77.8%)	2 (22.2%)	12	N/A	12 (100.0%)	0 (0.0%)
	High	2	N/A	0 (0.0%)	2 (100.0%)	2	N/A	0 (0.0%)	2 (100.0%)
Week 26	Low	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Normal	9	N/A	8 (88.9%)	1 (11.1%)	9	N/A	8 (88.9%)	1 (11.1%)
	High	2	N/A	1 (50.0%)	1 (50.0%)	1	N/A	0 (0.0%)	1 (100.0%)
Final Assessment	Low	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Normal	14	N/A	13 (92.9%)	1 (7.1%)	15	N/A	14 (93.3%)	1 (6.7%)
	High	3	N/A	1 (33.3%)	2 (66.7%)	4	N/A	0 (0.0%)	4 (100.0%)

(Source: sponsor submission in response to information request, dated 7/1/2013, page 25)

Hematology:

Of the patients with normal baseline hemoglobin, there were few decreases from baseline. One patient in the high dose group had a low hemoglobin at Week 26 and one patients had a low hemoglobin at final assessment, where both patients had normal baseline values. Three patients

in each of the low dose and high dose groups with low baseline values had normal values at week 12 or 26. The table below describes the changes in hemoglobin for the safety population.

Table 40: Hemoglobin at Baseline and Post-baseline Assessments- Safety Population Study 2008085

		Post-baseline							
		Low Dose (N=20)				High Dose (N=19)			
Lab Test Visit	Baseline	Total	Low n (%)	Normal n (%)	High n (%)	Total	Low n (%)	Normal n (%)	High n (%)
Hemoglobin									
Week 12	Low	3	2 (66.7%)	1 (33.3%)	0 (0.0%)	2	1 (50.0%)	1 (50.0%)	0 (0.0%)
	Normal	7	0 (0.0%)	7 (100.0%)	0 (0.0%)	12	0 (0.0%)	12 (100.0%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 26	Low	3	2 (66.7%)	1 (33.3%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	7	0 (0.0%)	7 (100.0%)	0 (0.0%)	10	1 (10.0%)	9 (90.0%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)
Final Assessment	Low	4	3 (75.0%)	1 (25.0%)	0 (0.0%)	4	2 (50.0%)	2 (50.0%)	0 (0.0%)
	Normal	12	0 (0.0%)	12 (100.0%)	0 (0.0%)	15	1 (6.7%)	14 (93.3%)	0 (0.0%)
	High	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)	0 (0.0%)	0 (0.0%)

(Source: sponsor submission in response to information request, dated 7/1/2013, page 3)

Study 2005018:

There were no clinically relevant changes in the baseline labs during the study for all three dose groups.

7.4.3 Vital Signs

There were no significant changes in vital signs reported by the sponsor.

7.4.4 Electrocardiograms (ECGs)

No ECG evaluations were performed.

7.4.5 Special Safety Studies/Clinical Trials

Study 2007017:

A safety concern regarding the use of dibutyl phthalate (DBP) as an excipient in the formulation of Asacol 400 mg tablets (b) (4). DBP is an inactive ingredient in Asacol (b) (4) (b) (4), and in animal studies at doses >190 times the human dose based on body surface area, maternal DBP was associated with external and skeletal malformations and adverse effects on the male reproductive system. Given the safety concerns of DBP urine phthalate was measured in the Study 2007017, however, it is difficult to make conclusions about clinical significance based on these results. Limited data presented (at screening and at week 6) suggests increased urinary output of phthalates following treatment with Asacol DR formulation suggesting systemic uptake of the plasticizer excipient. Data were highly variable and did not

suggest a trend for higher uptake with higher Asacol dose. Please see clinical pharmacology review by Dr. Justin Earp and Dr. Sandhya Apparaju, dated 9/13/2013. Delzicol, a phthalate-free 400 mg mesalamine formulation, was recently approved on February 1, 2013. Pediatric trials may need to be performed on the new drug once an age appropriate formulation is available. Please refer to clinical review by Dr. Aisha Johnson, dated December 26, 2012, for details.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There did not appear to a dose response relationship to adverse events that were possibly related to the study drug.

7.5.2 Time Dependency for Adverse Events

The sponsor did not assess the time dependency of AEs. In this reviewer's own analysis of the 91 reported AEs, there were no significant differences between the high and lose dose groups with respect to time to AEs.

7.5.3 Drug-Demographic Interactions

There were no differences in treatment success as measured by the primary endpoint with respect to gender, weight category, or disease severity. See statistical review by Shahla Farr for more details.

7.5.4 Drug-Disease Interactions

No specific studies were done to assess drug-disease interactions in this trial.

7.5.5 Drug-Drug Interactions

No specific studies were done to assess drug-drug interactions in this trial.

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

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

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

None submitted in this pediatric efficacy supplement.

7.6.2 Human Reproduction and Pregnancy Data

None submitted in this pediatric efficacy supplement.

7.6.3 Pediatrics and Assessment of Effects on Growth

An assessment of growth was not performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

To date, there is no abuse or dependency potential. There are two reported cases of overdose with Asacol tablets, which are described in the current Asacol label. A 3 year old male ingested 2 grams of Asacol, treated with ipecac and activated charcoal and no adverse events occurred. Another 3 year old male ingested an unknown amount, maximum 24 grams crushed in solution. He was treated with activated charcoal and experienced no adverse events.

8 Post-market Experience

Asacol (400 mg tablets) was marketed in the United States in January 1992, and Asacol HD was released in the United States in May 2008. The post-marketing experience is described in the labels for these products. The Asacol and Asacol HD labels were both updated May 24, 2010. Since that last label update, a periodic safety update report (PSUR) was submitted and reviewed for both Asacol (NDA19651) and Asacol HD (NDA 21830) covering dates July 1, 2011 to June 30, 2013. During this reporting period, there were 265 adverse event reports: 109 from health care professionals (HCP), 10 from the medical literature, and 146 from consumers. The majority of the reports were non-serious (230/265, 87%). Of the 109 HCP reports, the greatest number of reports were received for the General disorders and administration site conditions SOC: 53 reports (49%), of which 44 reports (83%) were unlisted (tablet in stool). Other commonly reported events were in the Gastrointestinal disorders category (24 reports, 22%), respiratory, thoracic and mediastinal disorders and Skin and subcutaneous tissue disorders (5 reports, 5% each), investigations and Renal and urinary disorders (4 reports, 4% each). The majority of frequently reported HCP reports were most commonly medication residue (‘tablet in stool’). Other frequently reported events included listed events of diarrhea (6 reports, 1 serious), unlisted events of general signs and symptoms NEC (4 reports, 3 serious), therapeutic and non-

therapeutic responses (3 reports of drug ineffective, all non-serious), colitis (3 reports, 2 serious), and abdominal pain (3 reports, all non-serious).

The overall reporting rate for the serious HCP reports was 7.69 reports per 100,000 patient-years (one report per 13,004 patient-years), a slight decrease compared to the range of rates observed in three of the four preceding periods. No significant increase in reporting rate compared to the previous periods was noted in any organ system. There were 20 serious HCP reports. Gastrointestinal disorders was the most common (6, 2.31%). Serious reports included severe anemia, hematuria, pericarditis, abdominal pain and hemorrhagic diarrhea, Crohn's flare (2), pancreatitis, ulcerative colitis flare (2), reports of tablets in the stool, sepsis, pneumonia, elevated creatinine with hydronephrosis, renal failure, mesalamine-induced eosinophilic pneumonia (2), aortic aneurism, deep vein thrombosis. No new, serious adverse reactions were identified in the most recent post-marking update that are not included in the current labeling for Asacol and Asacol HD.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

This reviewer recommends revisions to the proposed Asacol and Asacol HD labels. This reviewer agrees with the sponsor's proposal to revise sections 1, 2, 6, 8.4, 12, and 14 of the Asacol label. (b) (4)
the review team proposes to revise sections 1 and 8.4 of the Asacol HD label to include a summary of the pediatric trials as required by PREA. (b) (4)

Please refer to finalized Asacol and Asacol HD labels for detailed revisions.

9.3 Advisory Committee Meeting-

None

9.4 Supplementary Tables

Table 41: Lipase values (U/L) for Patients with Elevated Lipase* at Week 6 Evaluation

Subject	Asacol Dose Group (g/day)	Baseline Lipase (u/L)	Lipase Week 6 (u/L)	Change from Baseline (u/L)	% Change From Baseline	Disposition (dropout reason)
1048561001	High (3.6)	161	688	527*	327.3	dropout- AE
1048711001	High (3.6)	63	57	-6	-9.5	dropout- AE
1048871005	Low (2.4)	36	40	4	11.1	dropout- AE
1048721004	Low (2.4)	40	211	171*	427.5	complete
1048471001	Low (2.4)	29	33	4	13.8	complete
1048531001	Low (2.4)	33	37	4	12.1	complete
1048531002	Low (2.4)	50	52	2	4.0	complete
1048561002	High (2.0)	43	41	-2	-4.7	complete
1048581007	Low (2.4)	35	36	1	2.9	complete
1048641001	High (4.8)	33	35	2	6.1	complete
1048641005	Low (2.0)	303	163	-140	-46.2	complete
1048681002	Low (2.0)	45	38	-7	-15.6	complete
1048721002	Low (2.0)	92	40	-52	-56.5	complete
1048731001	Low (2.0)	200	67	-133	-66.5	complete
1048771001	High (3.6)	90	38	-52	-57.8	complete
1048871007	High (3.6)	32	40	8	25.0	complete
1048881002	High (2.0)	89	48	-41	-46.1	complete
1049001002	Low (2.4)	43	42	-1	-2.3	complete
1049041002	High (2.0)	37	40	3	8.1	complete
1049041005	Low (2.4)	26	33	7	26.9	complete
1049041008	Low (2.4)	37	40	3	8.1	complete
1049051002	High (4.8)	44	41	-3	-6.8	complete
1049051004	High (3.6)	37	90	53*	143.2	complete
1049331001	High (4.8)	31	77	46*	148.4	complete
1049331002	High (3.6)	95	105	10	10.5	complete
1049551001	Low (2.4)	33	47	14	42.4	complete

(Source: reviewer's own table using sponsor study data- Study 2007017, dated December 21, 2012)
*The normal reference range (0 - 32 U/L) for males and females ages 1 – 17 years (listed in sponsor submission clinical study report Appendix 16.2.8 Listing 8, page 195/267).

Table 42: Disposition of Patients in 30 day run in phase to Study 2008085

Treatment Group/ Asacol Dose (g/day)	Age (years)/ Sex	Disposition	Reason for dropout	Weight Stratification (Kg)	Time on Study Drug (Days)
Low 1.2	8 Male	Complete		17 - < 33	31
Low 2.0	11 Male	Dropout	Voluntary withdrawal	33 - < 54	32
Low 2.4	11 Female	Complete		54 - 90	38
	16 Female	Complete		54 - 90	39
	9 Female	Complete		54 - 90	38
	16 Male	Dropout	Relapse	54 - 90	42
High 3.6	9 Female	Complete		33 - < 54	37
	12 Male	Complete		33 - < 54	36
	13 Female	Complete		33 - <5 4	36
	14 Male	Complete		33 - < 54	34
High 4.8	13 Female	Complete		54 - 90	35
	16 Male	Complete		54 - 90	35
	17 Male	Complete		54 - 90	34
	16 Male	Dropout	Relapse	54 - 90	32

(Source: reviewer's own table created using sponsor's data - Study 2008085, dated December 21, 2012)

Pediatric UC Activity Index

Pediatric UC Activity Index	
Item	**Points**
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only in < 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal bowel movement (any diarrhea episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Total PUCAI Score	**0-85**
Final PUCAI: <10 = Remission 10-34 = Mild 35-64 = Moderate 65-85 = Severe	
Reference: Turner et al. 2007	

Abdominal Pain Score for Amended Endpoint

5-level Abdominal Pain for Amended Endpoint	
No abdominal pain	0
Very mild pain	2.5
Mild pain	5
Moderate pain	7.5
Severe pain	10

Truncated Mayo Score (TM-Mayo)

Rectal Bleeding Scale	
0	No blood seen
1	Streaks of blood with stool less than half of the time
2	Obvious blood with stool most of the time
3	Blood alone passed
Stool Frequency Scale	
0	Normal stool frequency per day
1	1-2 stools greater than normal per day
2	3-4 stools greater than normal per day
3	5 or more stools greater than normal per day

9.5 Summary of Study 2008085

Study 2008085 (CAMP II)- Run In Phase

Study 2008085 enrolled new patients and patients who previously completed Study 2007017. Patients from Study 2007017 who were in remission at the end of the 6 week study were eligible to continue to the 30 day run in phase for Study 2008085. Patients continued on the same dose of Asacol during the 30 days but were re-randomized at baseline for Study 2008085. Fourteen patients entered the 30 day run in phase from Study 2007017. Three patients dropped out of the run in phase. Patient 1048603001 was a voluntary withdrawal (low dose/2.0 g/day). Two patients withdrew due to disease relapse. Patient 1049043001 in the low dose 2/4g/day and Patient 1049053005 in the high dose 4.8g/day. The ages of the patients range from 8 years to 17 years of age. Younger patients were in the lower dose groups and older children were in the higher dose groups.

Concomitant medications during the run in phase included allergy medications, vitamins, reflux medication, or antibiotics for a throat infection. Two patients reported taking medications for the treatment of UC (metronidazole and mesalazine enemas/Rowasa). The patient taking mesalazine enemas dropped out due to a relapse of UC. The other patient completed the run in phase. The dates of these medications were not provided but the sponsor reported that the medications were not taken along with the study drug.

Table 1A: Disposition of Patients in 30 day run in phase to Study 2008085

Treatment Group Asacol Dose (g/day)	Age (years) Sex	Disposition	Reason for dropout	Weight Stratification (Kg)	Time on Study Drug (Days)
Low 1.2	8 Male	Complete		17 - < 33	31
Low 2.0	11 Male	Dropout	Voluntary withdrawal	33 - < 54	32
Low 2.4	11 Female	Complete		54 - 90	38
	16 Female	Complete		54 - 90	39
	9 Female	Complete		54 - 90	38
	16 Male	Dropout	Relapse	54 - 90	42
High 3.6	9 Female	Complete		33 - < 54	37
	12 Male	Complete		33 - < 54	36
	13 Female	Complete		33 - <5 4	36
	14 Male	Complete		33 - < 54	34
High 4.8	13 Female	Complete		54 - 90	35
	16 Male	Complete		54 - 90	35
	17 Male	Complete		54 - 90	34
	16 Male	Dropout	Relapse	54 - 90	32

Study: 2008085 (CAMP III)

Title: A randomized, double-blind, parallel-group study to assess the safety and efficacy of Asacol (1.2 g/day to 4.8 g/day) 400mg delayed-release tablets given twice daily for 26 weeks to children and adolescents for the maintenance of remission of ulcerative colitis.

Study design: Study was a randomized, double blind, parallel group study
Study Drug: Asacol (mesalamine) 400mg delayed release tablets
Population: Pediatric patients 5-17 years of age with mildly to moderately active UC
Dates: October 6, 2009 to March 31, 2011
Study centers: 18 centers in United States, Canada, and Poland

Objectives: To assess the efficacy and safety of a high and low doses of delayed-release mesalamine (Asacol) given twice daily for 26 weeks in maintenance of remission of ulcerative colitis in children and adolescents.

Efficacy Endpoints:
Primary end point: Proportion of patients who have maintained complete remission through Week 26 as determined by a PUCAI score < 10 during the entire study period. Patients withdrawn prior to the Week 26 visit were considered as failures to maintain complete remission.

Secondary endpoint: Proportion of patients who maintained complete remission through Week 26 as determined by an Amended Endpoint score of < 10 during the entire study.

Safety endpoints:
Adverse events (AEs), tolerability (withdrawals, AEs), vital signs, clinical labs, compliance, standardized and replicated weight and height were assessed as safety measures.

Randomization:
Patients were randomized to low dose or high dose, and then stratified by weight into three categories (17 to < 33 kg, 33 to < 54 kg, 54-90 kg). The doses were based on results from a pediatric PK study (Study 2005018), and weight-based dosing used in clinical practice (< 120 mg/kg/day). The trial was designed to randomize 100 patients with the expectation that about 80 would complete the study (40 in each dose arm). The doses arms, weight groups, Asacol doses, and number of pills were the same as described in Table 6: Treatment Groups and Treatments Administered - Study 2007017.

Number of subjects:
Thirty-nine patients were randomized (20 in Low dose group, 19 in high dose group). The mean age of the patients was 13.1 years of age (range 8 – 17 years) with one patient in the 5-8 year age range and 38 patients in the 9 -17 year age range. Fourteen entered run-in phase from Study

2007017 (6 in low dose, 8 in high dose). Eleven completed run-in phase (4 in low dose, 7 in high dose). All randomized subjects were included in the modified intent to treat (mITT) and safety populations. Table 2A below shows disposition of patients in Study 2008085.

Table 2A: Number (%) of Patients Randomized and Discontinued- Study 2008085

Parameter Statistic / Category	Low Dose (N = 20) n (%)	High Dose (N = 19) n (%)	Overall (N = 39) n (%)
Randomized to Treatment			
Completed	11 (55.0%)	10 (52.6%)	21 (53.8%)
Discontinued	9 (45.0%)	9 (47.4%)	18 (46.2%)
Reason for Discontinuation			
Adverse Events	1 (5.0%)	1 (5.3%)	2 (5.1%)
Lost to Follow-up	1 (5.0%)	0	1 (2.6%)
Lack of Treatment Effect	1 (5.0%)	2 (10.5%)	3 (7.7%)
Sponsor Terminated Study	5 (25.0%)	4 (21.1%)	9 (23.1%)
Voluntary Withdrawal	1 (5.0%)	2 (10.5%)	3 (7.7%)

Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day. Dosage was dependent on body weight.
All subjects randomized received at least one dose of study medication.
Subject data are listed in Appendix 16.2.1.
/ASACOL/PEDS/2008085/ANAL/disp_dev_scrn.sas; SAS 8.2 10AUG11 11:43 f14jul11 BG4157.

(source: sponsor's study report- Study 2008085, dated December 21, 2012, page 8)

Safety population: All randomized subjects were included in the modified intent to treat (mITT) and safety populations.

Inclusion criteria:

- Male or female
- Ages 5 to 17 years
- Documented history of UC and maintained in complete remission for at least 1 month prior to study entry
- Baseline PUCAI score < 10
- Generally in good health (other than the diagnosis of UC)
- Able to swallow Asacol 400 mg tablets
- Body weight ≥ 17 kg and ≤ 90 kg
- History of at least 1 active episode or relapse in the last 12 months
- Stable oral mesalamine or equivalent oral 5-ASA dose at least 1 month prior to study entry
- Patients who complete Study 2007017 at week 6 in remission and immediately roll-over to the 30-day run-in phase must maintain complete remission throughout the 30-day run-in phase

- Female patients who are pre-menarchal or have a negative urine pregnancy test and, if sexually active, practice acceptable contraception \
- Able and willing to participate in the study and follow study procedures

Exclusion criteria:

- Allergy to salicylates
- Co-morbidities: malabsorption, short gut syndrome, co-existing illness
- Current abuser of drugs or alcohol
- History of HIV infection or AIDS
- History of co-existing chronic illness or other condition(s)
- Current renal disease, or a screening blood urea nitrogen (BUN) or creatinine value that is > 1.5 times the upper limit of the age appropriate normal
- Documented history of or current hepatic disease, or liver function tests (alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin) that are > 2 times the upper limit of normal
- History of pancreatitis
- Any other screening laboratory test values that the Investigator or Sponsor considers clinically significant that would impact the outcome of the study or the safety of the patient
- Previously participated in this study
- Currently participating or have participated in any other clinical study (except Study 2007017) within 30 days prior to the screening visit
- Any oral, intravenous, intramuscular, or rectally administered corticosteroids (including budesonide) within 30 days prior to the screening visit
- Rectal mesalamine therapy within 30 days prior to the screening visit
- Immunomodulatory therapy and/or biologic therapy within 90 days of the Screening visit
- Metronidazole within 7 days prior to the screening visit
- Aspirin or other non-steroidal anti-inflammatory drugs NSAIDs) within 7 days prior to the screening visit
- Antidiarrheal and/or antispasmodic within 30 days of the screening visit
- Stool examination positive for *Clostridium difficile (C. difficile)*, bacterial pathogens, or ova and parasites.

Dose: Asacol 400mg delayed-release tablets were dispensed to subjects in fourteen, 4-day blister cards with a day and a night dose. The 14 blister cards were packed in moisture resistant bags. Each bag contained an 8-week supply of drug.
Kits: 400mg Asacol tabs. Lots 426920, 431881 and the matching placebo tablets were from lot

number 416049. Placebo tabs were given with active tabs to blind between number of tablets in the low and high dose groups. Table 3A below shows the treatments administered.

Table 3A: Treatments Administered

Dose group	Weight group (kg)	Asacol dose (g/day)	Dose range (mg/kg)	Number of Tablets			
				Asacol 400 mg	Placebo	Asacol 400 mg	Placebo
High Dose	17-<33	2.0	61 – 118	3	0	2	0
	33-<54	3.6	67 – 109	5	0	4	0
	54-90	4.8	53 – 89	6	0	6	0
Low Dose	17-<33	1.2	36 – 71	2	1	1	1
	33-<54	2.0	37 – 61	3	2	2	2
	54-90	2.4	27 – 44	3	3	3	3

(Source: sponsor study report- Study 2007017, dated December 21, 2012, page 7)

Dose groups, weight groups, total daily Asacol dose, dose rang (mg/kg), and number of tablets was the same for Study 2007017 and Study 2008085.

Duration: The study consisted of a 30 day run-in phase for patients continuing directly from Study 2007017 and a 26 week treatment phase. Study center visits occurred at Screening, Baseline, Week 12, and Week 26. Patients and their parents/legal guardians were contacted by phone at Week 6, Week 18, and at a 1 week follow up visit.

The study was terminated due to difficulty in recruiting subjects. Fewer than half of the target number were randomized and no formal analyses were performed by the sponsor.

Table 4A: Schedule of Study Events- Study 2008085

	Visits							
Study Procedures	**30-Day Run-in Phase (+ 7 days)**	**Screening Day -7 to -1**	**Baseline[a]** Day 1	**Week 6 Phone Visit ±7 days**	**Week 12 ±7 days**	**Week 18 Phone Visit ± 7 days**	**Week 26 /WD ±7 days**	**1-week Follow-up Visit ± 3 days**
Informed consent/assent	X	X						
Medical history		X	X[d]					
Medication history		X	X[d]	X[d]	X[d]	X[d]	X[d]	
Personal/demographic data		X						
Physical examination		X					X	
Body weight/height (replicated)		X	X		X		X	
Vital Signs (heart rate, blood pressure temperature)		X	X		X		X	
Hematology / Serum Chemistry		X	X[e]		X		X	
Serum pregnancy test – CANADA ONLY		X						
Urine pregnancy test		X	X		X		X	
Urine collection for urinalysis, urinary creatinine and assessment of phthalate		X	X[e]				X	
Stool sample for bacterial pathogens, ova and parasites, and *C. difficile*			X[f]					
AE monitoring	X	X[g]	X[g]	X	X	X	X	X
Distribute PUCAI Diary Cards[b]		X	X		X			
IVRS Contact	X[h,i]	X[j]	X[k]		X[i]			
Remind subject/legal guardian that subject should avoid protocol-excluded medications	X	X	X	X	X	X		
Review dosing instructions/ compliance/return of study medication with subject/legal guardian	X		X	X	X	X	X	
Subjects/legal guardian(s) to assess subject compliance and well-being				X		X		X
Clinical Assessments[c]			X		X		X	

a Baseline Visit to occur within 7 days after Screening Visit.
b PUCAI Diary Cards to be completed 2 days prior AND 1 day prior to Baseline, Week 12 and Week 26/withdrawal visit.
c Includes review of PUCAI Diary Cards and completion of PUCAI and 5-level abdominal pain scale.
d Update only.
e Not repeated if drawn at Screening.
f If a previous stool sample collected within the past 30 days of this visit was negative for bacterial pathogens, ova and parasites, and *C. difficile*, the stool sample collection was not required at this visit.
g Only serious study procedure-related non-treatment-emergent AEs were collected (only for subjects who did not enter the 30-day Run-in phase).
h Call to obtain subject number.
i Call to obtain kit number(s) to dispense a 3-month supply of study medication.
j Call to obtain subject number (for those subjects who did not participate in the 30-day Run-in phase).
k Call to randomize subject and obtain kit numbers to dispense a 3-month supply of study medication.

Note: A blood sample for PK was also to be collected if subject had a SAE, had an AE of tinnitus, or at the request of the Sponsor.

(Source: sponsor's study report, dated December 21, 2012, page 7)

Statistical Analysis: No formal analysis was performed.

Efficacy Results:
Study 2008085 evaluated safety and efficacy in patients who maintained remission of UC for one month prior to study start. This trial was terminated prematurely due to lack of enrollment. A brief summary of the results from Study 2008085 is shown below.

Thirty-nine patients were enrolled in Study 2008085 with 20 patients in the low dose group and 19 patients in the high dose group. The definition of the dose arms, weight categories, disease severity were the same as those described for Study 2007017. PUCAI and Amended PUCAI were used to evaluate disease activity at Week 12 and Week 26. A score of <10 was considered complete remission as measured by the PUCAI and amended PUCAI.

Table 5A: Disease Activity as Measured by PUCAI at Week 12, Week 26, and Final Assessment- Study 2008085 (mITT population)

Visit	Complete Remission	Low Dose (N = 20) n (%)	High Dose (N = 19) n (%)	Total (N = 39) n (%)
Week 12	Complete Remission	[redacted] (b) (4)		
	Mildly Active Disease			
	Active Disease			
	Total			
Week 26	Complete Remission			
	Mildly Active Disease			
	Active Disease			
	Total			
Final Assessment	Complete Remission			
	Mildly Active Disease			
	Active Disease			
	Total			

MITT: Modified Intent-to-treat includes subjects who took at least one dose of study medication and did not have baseline stool examination positive for C. difficile, bacterial pathogens, or ova and parasites.

Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day. Dosage was dependent on body weight.

For Weeks 12 and 26: complete remission is defined as a score < 10 at the specified timepoint, mildly active disease is a change from baseline < 20 points with a score >= 10 at the specified timepoint, and active disease is >= 20 point change from baseline at the specified timepoint based on observed data.

Final Assessment: complete remission is defined as a score < 10 during the entire study period, mildly active disease is a change from baseline < 20 points with a score >= 10 at any time during the study, and active disease is >= 20 point change from baseline at any time during the study or subjects who discontinued from study for reason other than Study Terminated by Sponsor. Those terminating due to Study Terminated by Sponsor are not included in the Final Assessment.

Total = number of subjects in dose group with treatment outcome.

(Source: sponsor study report- Study 20080085, dated December 21, 2012, page 10)

Table 6A: Disease Activity as Measured by Amended PUCAI at Week 12, Week 26, and Final Assessment- Study 2008085 (mITT population)

Table 5 Summary of Amended Endpoint Complete Remission (Modified Intent-to-treat Population) - Study 2008085

Visit	Complete Remission	Low Dose (N = 20) n (%)	High Dose (N = 19) n (%)	Total (N = 39) n (%)
Week 12	Yes	(b) (4)		
	No			
	Total			
Week 26	Yes			
	No			
	Total			
Final Assessment	Yes			
	No			
	Total			

MITT: Modified Intent-to-treat includes subjects who took at least one dose of study medication and did not have baseline stool examination positive for C. difficile, bacterial pathogens, or ova and parasites.

Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day. Dosage was dependent on body weight.

For Weeks 12 and 26: complete remission is defined as a score < 10 at the specified timepoint based on observed data.

Final Assessment: complete remission is defined as a score < 10 during the entire study. Subjects who terminated early for any reason other than Study Terminated by Sponsor are set to no for complete remission. Those terminating due to Study Terminated by Sponsor are not included in the Final Assessment.

Total = number of subjects in dose group with treatment outcome.

n (%) = number and percentage (n/Total x 100) of subjects in dose group with specified treatment response.

Subject data can be found in Appendix 16.2.6.

/ASACOL/PEDS/2008085/ANAL/pucai.sas; SAS 8.2 28JUL11 11:27 f14jul11 BG4157.

(Source: sponsor study report- Study 2008085, dated December 21, 2012, page 11)

The study was terminated due to difficulty in recruiting subjects. Fewer than half of the target number of subjects were actually randomized and no formal analyses were performed. PUCAI complete remission was achieved in (b) (4) subjects in the low-dose group and (b) (4) subjects in the high-dose group at week 26. At the final assessment, PUCAI complete remission was achieved in (b) (4) subjects in the Low-dose group and (b) (4) subjects in the high-dose group. The results of the Amended PUCAI Endpoint of complete remission at week 26 were similar to those for the PUCAI. Conclusions on efficacy and safety for long term treatment of pediatric patients with UC cannot be made without supporting information because of the small numbers of patients who completed the trial.

Safety Analysis for Study 2008085 are included in Section 7 of this clinical review.

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/s/

JULI A TOMAINO
09/16/2013

ANIL K RAJPAL
09/16/2013
I concur with Dr. Tomaino.