

CLINICAL REVIEW

Application Type	Pediatric efficacy supplement for NDA 204412 (Delzicol)
Application Number(s)	sNDA 204412/3
Priority or Standard	Standard
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Division / Office	DGIEP
Reviewer Name(s)	Juli Tomaino, MD, Medical Officer Anil Rajpal, MD, Team Leader
Review Completion Date	February 13, 2014
Established Name	Mesalamine
(Proposed) Trade Name	Delzicol
Therapeutic Class	5-aminosalicylic acid (5-amino-2-hydroxybenzoic acid)
Applicant	Warner Chilcott
Formulation(s)	400 mg 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 12 -17 years old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, sNDA 204412/3 is acceptable to support recommendation for approval of Delzicol 400 mg for the treatment of mildly to moderately active ulcerative colitis in patients ages 12 years and older, after agreement with revised labeling for Delzicol.

1.2 Risk Benefit Assessment

Based on a safety concern regarding the use of dibutyl phthalate (DBP), an excipient in the outer shell of Asacol, Asacol 400 mg tablets were reformulated to Delzicol. For this reformulation, the (b) (4) dibutyl phthalate (DBP) was replaced with dibutyl sebacate. Bioequivalence and dissolution studies established that Delzicol was bioequivalent to Asacol 400 mg. Delzicol was approved on February 1, 2013. Please refer to Delzicol NDA 204412 Clinical Review by Dr. Aisha Peterson Johnson, dated December 26, 2012, for further details on the approval of Delzicol.

The current pediatric efficacy supplement was submitted in response to PREA PMR 2011-1 under Delzicol (NDA 204412). This submission did not contain new data and cross-referenced data from an efficacy supplement submitted to NDA 19651/24 for Asacol. The efficacy supplement for Asacol (NDA 19651/24) was approved on October 18, 2013; the indicated population was altered to include pediatric patients ages 5 to 17 years old, and dosing information for this patient population was added to the Asacol label. The data to support approval were generated from two adult clinical trials and one pediatric clinical trial, which evaluated the safety and efficacy of Asacol 400 mg delayed release tablets over a 6 week trial duration for 82 pediatric patients ages 5 to 17 years old for the treatment of mildly to moderately active ulcerative colitis. Efficacy was extrapolated from adequate and well-controlled trials in adults. The safety data were collected from that trial and two additional pediatric, uncontrolled clinical trials. The safety profile of Asacol 400 mg delayed-release tablets in pediatric patients ages 5 to 17 years old was found to be similar to the known safety profile of Asacol 400 mg delayed-release tablets in adults.

This reviewer recommends approval of Delzicol for the treatment of mildly to moderately active ulcerative colitis (UC) in pediatric patients ≥ 12 years of age. Delzicol is a larger capsule (size 0, 21.7 mm) compared to Asacol (size 2, 14 mm) and young children may not be able to swallow the larger capsule.

Since no new data were submitted, a summary of the data from the Asacol pediatric efficacy supplement will be provided in this review. Please refer to Asacol (NDA 19651/24) for the complete clinical review by Dr. Juli Tomaino, dated September 17, 2013. The same data from the three pediatric trials using Asacol were also submitted as an efficacy supplement to the Asacol HD NDA (NDA 21830/6) to fulfill a PREA PMR. Refer to NDA 21830/6 Clinical Review, dated September 16, 2013.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A REMS is not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The Division does not agree that the PMR is fulfilled since young children are unlikely to have the ability to swallow the size 0 Delzicol capsule. Other medications, such as Strattera and Trokendi XR, are available in size 0 capsules and are approved for pediatric patients as young as 6 years of age. In contrast to Delzicol, both Strattera and Trokendi XR are approved in smaller sized tablets/capsules, which provide patients and prescribers with additional options. Development of an age-appropriate formulation for Delzicol is ongoing. Currently, there is no available information on the swallowability of the current Delzicol formulation in pediatric patients.

Since the PMR is only partially fulfilled for children ≥ 12 years of age, the PMR is considered ongoing and not fulfilled at this time. Once the sponsor develops the age-appropriate formulation for Delzicol (4 x 100 mg Delayed Release Tablets, Encapsulated), the Division will consider whether the PMR is fulfilled.

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 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

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.

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.

Based on a safety concern regarding the use of dibutyl phthalate (DBP), an excipient in the outer shell of Asacol, Asacol 400 mg tablets were reformulated to Delzicol. For this reformulation, the ^{(b) (4)} dibutyl phthalate (DBP) was replaced with dibutyl sebacate. Bioequivalence and dissolution studies were done and Delzicol was found to be bioequivalent to Asacol 400 mg. Delzicol was approved on February 1, 2013.

The current pediatric efficacy supplement did not contain new clinical data. It was submitted in response to PREA PMR 2011-1 for Delzicol (NDA 20412) with cross-reference to data from an efficacy supplement submitted to NDA 19651/24 for Asacol. The efficacy supplement for Asacol (NDA 19651/24) was approved on October 18, 2013; the indicated population was altered to include pediatric patients ages 5 to 17 years old, and dosing information for this patient population was added to the Asacol label. Delzicol is the phthalate-free formulation of Asacol 400 mg delayed-release tablets.

Since no new data were submitted, this review includes a high-level summary of the Asacol pediatric efficacy supplement (NDA 19651/24) Please refer to the Asacol (NDA 19651/24) clinical review dated September 17, 2013, for the full clinical review.

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

⁶ Kornbluth A. 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=ddb69f3-bd55-45f3-a64f-f60226c744c4#nmlm34067-9>

2.1 Product Information

Delzicol 400 mg capsule and Asacol (mesalamine) 400 mg delayed-release tablets are in the pharmacologic class of aminosalicylates. Mesalamines are thought to act as topical anti-inflammatory medications in the intestine by inhibition of prostaglandin and leukotriene synthesis.

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 Colitis⁹

Drug name	Indication	Approved Pediatric indication (yes/no)
Apriso (mesalamine)	<ul style="list-style-type: none"> Maintenance of remission of UC in adults 	No
Asacol (mesalamine)	<ul style="list-style-type: none"> Treatment of mildly to moderately active UC and for the maintenance of remission of UC 	Yes
Asacol HD (mesalamine)	<ul style="list-style-type: none"> Treatment of moderately active UC 	No
Lialda (mesalamine)	<ul style="list-style-type: none"> Induction of remission in adults with mild to moderately active UC and for maintenance of remission of UC 	No
Pentasa (mesalamine)	<ul style="list-style-type: none"> Induction of remission and for treatment of patients with mildly to moderately active UC 	No
Canasa (mesalamine rectal suppository)	<ul style="list-style-type: none"> Treatment of adult patients with ulcerative proctitis 	No
Rowasa (mesalamine rectal enema and suppository)	<ul style="list-style-type: none"> Treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis 	No
Colazal (balsalazide sodium)	<ul style="list-style-type: none"> Treatment of mildly to moderately active UC in patients 5 years and older 	Yes
Azulfidine (sulfasalazine)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Inducing and sustaining clinical remission in adults with moderately to severely active Ulcerative colitis 	No

⁹ <http://www.accessdata.fda.gov>

Remicade (infliximab)	<ul style="list-style-type: none"> • 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. • 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. 	Yes
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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.

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 used less frequently in clinical practice for short term treatment of severe pediatric UC.¹⁰ 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. Error! Bookmark not defined.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Regulatory timeline:

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

August 1997: Asacol 400 mg (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.

¹⁰ Rufo P, Bousvaros A. Current Therapy of Inflammatory Bowel Disease in Children. *Pediatr Drugs*. 2006; 8(5): 279-302

May 29, 2008: Asacol HD 800 mg 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.

The original Asacol HD NDA approval contained a PREA PMR for a study using Asacol 400 mg tablets as an age appropriate formulation. However, two Asacol 400 mg tablets have not been shown to be bioequivalent to one Asacol HD 800 mg tablet.

January 20, 2011: In response to the WR for Asacol 400 mg (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 (1.2 g 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”, was being terminated early due to enrollment challenges (b) (4). A final study report was submitted under IND 26093. The sponsor planned (b) (4).

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.

December 21, 2012 and May 2, 2013: Efficacy supplement (SE5) for addition of pediatric use and dosing information was submitted under NDA 21830/6 (December 2, 2012) and under NDA 19651/24 (May 2, 2013). 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 26093 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 26093 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 26093 on March 2, 2012.

January 15, 2013: A Type C meeting (minutes filed under IND 26093) was held to discuss an age appropriate formulation and pediatric studies for WC3045 capsules (phthalate-free formulation submitted under NDA 204412). Key conclusions of this meeting were: 1) a palatability/swallow study is needed to determine if this formulation is acceptable; 2) a bridging program should include a comparative bioavailability assessment in adult subjects; 3) the potential to leverage existing data to (b) (4); and 4) a dissolution study for the individual 100 mg tablets compared to the (b) (4) WC3079 prototype formulation is needed.

February 1, 2013: NDA 204412 for WC3045 (Delzicol 400 mg) 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

October 18, 2013: Approval action was taken for both the Asacol efficacy supplement (NDA 19651/24) and the Asacol HD efficacy supplement (NDA 21830/6). The indicated population was altered to include pediatric patients ages 5 to 17 years old in the Asacol label, but not in the Asacol HD label. The efficacy supplement was determined to fulfill the PREA PMR for Asacol HD.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No new data were submitted. 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.

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.

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

In a dose-ranging PK study evaluating 30, 60 and 90 mg/kg/day doses of Asacol administered twice daily for four weeks, the mean C_{avg} values of mesalamine in pediatric ulcerative colitis patients ranged from approximately 400 ng/mL to 2100 ng/mL based on data from all dose levels. PK data were also collected during the pediatric trial (study 2007017). The mean plasma concentrations of mesalamine (based on sparse sampling) were 820 to 988 ng/mL at the low dose level (that is, 1.2, 2.0 or 2.4 g/day based on body weight strata of 17 to greater than 33 kg, 33 to less than 54 kg, and 54 to less than 90 kg, respectively). Additional information can be found in the Asacol label, last updated 10/18/2013.¹¹

For a full clinical pharmacology review, please refer to Asacol (NDA 19651/24) and Asacol HD (NDA 21830/6), Clinical Pharmacology reviews by Dr. Justin Earp and Dr. Sandhya Apparaju, dated September 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.

4.4.2 Pharmacodynamics

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. 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

The clinical pharmacology reviewer, Dr. Sandhya Apparaju, and the biopharmaceutics reviewer, Dr. John Z. Duan, agreed that the study results confirm the bioequivalence of

¹¹ Asacol approved label, last updated 10/18/2013, accessed 2/7/2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019651s023lbl.pdf

Delzicol (WC3045) and Asacol 400 mg tablets. For further information see the full discipline reviews (NDA 204412).

5 Sources of Clinical Data

There were three pediatric clinical trials submitted as part of the Asacol pediatric efficacy 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 2: 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 and reviewed in detail. Study 2007017 was the primary trial to evaluate efficacy and safety of Asacol 400 mg 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.^{12,13}

We determined that the stool frequency and rectal bleeding scores from the modified Mayo score (TM-Mayo), used as an efficacy endpoint in pediatric study 2007017, 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 ulcerative colitis. In the pediatric clinical trial, the proportion of 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 also comparable between the adult and pediatric trials. The safety data of three pediatric trials (study 2007017, 2008085, and 2005018) were reviewed for an integrated safety evaluation.

Study 2008085 evaluated safety and efficacy of Asacol in pediatric 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 numbers 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. However, safety data from study 2008085 are included in the safety review, section 7.

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

5.3 Discussion of Individual Studies/Clinical Trials

¹² 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.

¹³ Presentation from Dr. Skip Nelson from the Office of Pediatric Therapeutics available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM361846.pdf>.

Please refer to Asacol (NDA 19651/24) and Asacol HD (NDA 21830/6), clinical review by Dr. Juli Tomaino, dated September 16, 2013. A high-level summary is provided in Section 6 of this review.

6 Review of Efficacy- Study 2007017

Efficacy Summary

A randomized, double blinded, parallel group trial 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 was small between the low dose and high dose groups, as measured by the PUCAI score. 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 and 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).

The current pediatric efficacy supplement was submitted in response to PREA PMR 2011-1 under Delzicol (NDA 204412). Since this Delzicol pediatric efficacy supplement did not contain new data and cross-referenced data from an efficacy supplement submitted to NDA 19651/24 for Asacol, a summary of the data from the Asacol pediatric efficacy supplement will be provided in this review. Please refer to the complete clinical review by Dr. Juli Tomaino, dated September 17, 2013 (NDA 19651/24) for the comprehensive review of the Asacol pediatric efficacy supplement data.

6.1 Indication

The efficacy supplement for Asacol (NDA 19651/24) was approved on October 18, 2013; the indicated population was altered to include pediatric patients ages 5 to 17 years old, and dosing information for this patient population was added to the Asacol label. The data to support approval were generated from two adult clinical trials and one pediatric clinical trial (study 2007017), which evaluated the safety and efficacy of Asacol 400 mg delayed release tablets over

a 6 week trial duration for 82 pediatric patients ages 5 to 17 years old for the treatment of mildly to moderately active ulcerative colitis. Efficacy was extrapolated from adequate and well-controlled trials in adults. The safety data were collected from study 2007017 and two additional pediatric, uncontrolled clinical trials. The safety profile of Asacol 400 mg delayed-release tablets in pediatric patients ages 5 to 17 years old was found to be similar to the known safety profile of Asacol 400 mg delayed-release tablets in adults. The three pediatric trials using Asacol were also submitted as an efficacy supplement to the Asacol HD NDA (NDA 21830/6).

6.1.1 Methods:

The study design is a randomized, double blind, parallel group trial evaluating safety and efficacy of high and low dose Asacol using 400 mg 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 ≤ 90 kg.
- 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 3 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 400 mg delayed release tablets, divided every 12 hours for 6 weeks duration. The total daily dose increments were restricted by the Asacol 400 mg tablets, which cannot be cut or crushed.

Table 3: 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, dated December 21, 2012, located in Asacol (NDA 19651/24) and Asacol HD (NDA 21830/6))

6.1.2 Demographics

Table 4 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. Conclusions on efficacy and safety for long term treatment of pediatric patients with UC cannot be made at this time based on the data collected from study 2008085 alone because of the small numbers of patients who completed the trial. However, as previously discussed, all three submitted pediatric studies are included in the safety review, Section 7.

Table 4: 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)

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.¹⁴ Of note, the youngest patient in Study 2008085 (26 week duration) was 8 years of age.

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.

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 5 below describes the low dose and high dose groups by the three weight categories and by daily weight-based dose of Asacol.

¹⁴ 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.

Table 5: 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)

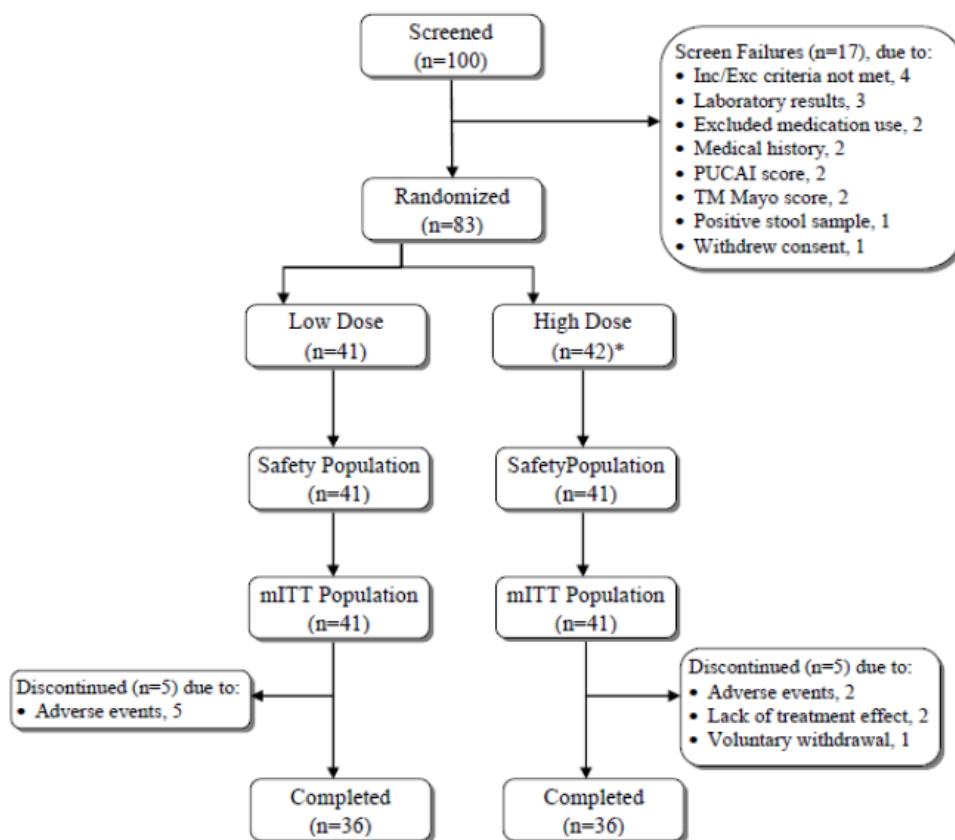
(Source: sponsor submission in response to Agency Information Request, sNDA 021830, supporting document 282, dated April 10, 2013)

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. For additional details, please refer to Asacol (NDA 19651/24) ,clinical review by Dr. Juli Tomaino, dated September 17, 2013.

6.1.3 Subject Disposition

Figure 1 below describes 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. Eighty-three patients were randomized and each dose level group contained 41 subjects included in the mITT analysis. Seventeen screening failures 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).

Figure 1: 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)

Protocol Deviations

Twenty-nine patients in the Low Dose and 25 in the High Dose group had a protocol deviation. The protocol deviations were balanced between the low dose and high dose groups and would not be expected to influence the efficacy results. For further details, please refer to Asacol (NDA 19651/24) clinical review by Dr. Juli Tomaino, dated September 17, 2013.

6.1.4 Analysis of Primary Endpoint(s)

Efficacy Endpoints:

A summary of the data is provided below. Please refer to the Asacol (NDA 19651/24) for a complete review of the pediatric efficacy supplement by Dr. Juli Tomaino, dated September 17, 2013.

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 6. 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 7 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 6: 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.¹⁵

The proportions of patients with PUCAI-TS were similar between the 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 7 below shows the remission and response rates for the overall dose levels (high vs. low) and by weight category for the efficacy endpoints.

¹⁵ 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 7: 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\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 with 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.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoint of Amended Endpoint- TS by weight category is shown above in Table 7. The percentage of patients with treatment success, complete response, and partial response were similar between the PUCAI and Amended PUCAI.

For further efficacy analysis, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

6.1.6 Other Endpoints

Change in disease activity and fecal biomarkers were assessed at baseline and week 6. Please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013, for details.

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, thus supporting approval of only the low dose level. 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 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

7 Review of Safety

Brief Summary of Adverse Events

A summary of the data is provided below. Please refer to the Asacol (NDA 19651/24) for a complete review of the pediatric efficacy supplement by Dr. Juli Tomaino, dated September 17, 2013.

The three pediatric trials described in Section 5 of this review (studies 2007017, 2008085, and 2005018) were used to evaluate safety. Safety data from these trials were evaluated separately because the duration of treatment and indication (induction of remission or maintenance of remission) differed between the three studies. In addition, study 2005018 (PK study) included a different dosing regimen from studies 2007017 and 2008185.

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 8: 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 \geq 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 (SAEs)	5 (12.2%)	2 (4.9%)
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

Three pediatric clinical trials were reviewed to evaluate safety (study 2007017, 2008085, and 2005018).

7.1.2 Categorization of Adverse Events

For the full clinical review, please refer to Asacol (NDA 19651/24) clinical review by Dr. Juli Tomaino, dated September 17, 2013.

7.1.3 Pooled Safety Data from Clinical Trials to Compare Incidence

Safety data from the three pediatric trials were evaluated separately because the duration of treatment and indication (induction of remission or maintenance of remission) differed between the three studies. In addition, study 2005018 (PK study) included a different dosing regimen from studies 2007017 and 2008185.

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 to evaluate induction of remission in pediatric patients with mildly to moderately active UC. 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.

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).¹⁶ Therefore, we expect smaller numbers of patients to be enrolled in the younger age groups.

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 on the dose given in study 2007017. Patients who met inclusion criteria for the treatment phase

¹⁶ Gower-Rousseau, C., et al. The Natural History of Pediatric Ulcerative Colitis: A Population-Based Cohort Study. *Am J Gastroenterol* 2009; 104:2080–2088

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. For additional details, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to Asacol (NDA 19651/24) and Asacol HD (NDA 21830/6), clinical pharmacology reviews by Dr. Sandhya Apparaju and Dr. Justin Earp, dated September 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

A high-level safety summary is provided below. For additional details, please refer to Asacol (NDA 19651/24) and Asacol HD (NDA 21830/6), clinical review by Dr. Juli Tomaino, dated September 16, 2013.

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.

Study 2008085:

There were no deaths during Study 2008085. Two patients experienced a serious adverse event; onset of worsening UC that required hospitalization, and anemia requiring hospitalization and transfusion.

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 two 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.

Study 2008085: Disposition and Adverse Events

Two patients (subject ID #1048503001 and #1050203003) withdrew due to adverse events, both reported worsening of ulcerative colitis.

Study 2005018:

Thirty-one patients completed the study. Two patients withdrew voluntarily and one patient withdrew due to a serious adverse event.

7.3.4 Significant Adverse Events

Study 2007017:

In Study 2007017, two events 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.

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 particular adverse events may appear 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.

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 9 below shows the adverse events for each dose arm reported during study 2007017.

Table 9: 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)

For additional discussion, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

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 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. For additional details, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

Study 2005018:

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. For additional details, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

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.

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. For additional details, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

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. For additional details, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

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 led to a reformulation. DBP is an inactive ingredient in Asacol's enteric coating, 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 approved on February 1, 2013. Please refer to clinical review by Dr. Aisha Johnson, dated December 26, 2012, for details of the approval of Delzicol. Asacol 400 mg delayed-release tablets are not currently being marketed. Approval of this pediatric efficacy supplement, with cross-reference to data submitted to Asacol (NDA 19651/24) and Asacol HD (NDA 21830/6), supports pediatric labeling information to the Delzicol label for pediatric patients ≥ 12 years of age.

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 Asacol (NDA 19651/24), statistical review by Shahla Farr, dated October 7, 2013, 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.

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

Post-marketing adverse reactions described in the Delzicol label include adverse reactions for mesalamine delayed-release tablets and mesalamine-containing products.

The following post-marketing updates for Delzicol were reviewed: Periodic Adverse Drug Experience (ADE) Report (reporting period July 1, 2013 - September 30, 2013) and Periodic ADE Report (reporting period October 1, 2013-December 31, 2013). In the July 1, 2013 - September 30, 2013 submission, 266 events were reported. In the October 1, 2013-December 31, 2013 submission, 110 events were reported. No new serious adverse reactions were identified. The majority of the reported adverse reactions are included in the current labeling for Delzicol, with the exception of issues swallowing the medication.

There were multiple reports that appeared to be related to difficulty swallowing the medication. In the July 1, 2013 - September 30, 2013 submission: "product size issue" (9 reports; all nonserious), "product physical issue" (3 reports; all nonserious), and "foreign body" (13 reports; nonserious). In the October 1, 2013 - December 31, 2013 submission: "product size issue" (3 reports; all nonserious), "product physical issue" (6 reports; all nonserious), and "foreign body" (4 reports; all nonserious).

However, a signal for adverse events related to difficulty swallowing the Delzicol capsules was not found in the review of the relative bioavailability study conducted in healthy adult subjects in support of the Delzicol approval (study PR-08210; n=251 in Delzicol group, and n=249 in the Asacol group). Refer to Clinical Review by Dr. Aisha Peterson Johnson, dated December 26, 2012.

Therefore, based on the postmarketing reports of difficulty swallowing Delzicol, this reviewer recommends that information about any adverse events related to difficulty swallowing from the relative bioavailability study should be requested from the applicant. For comparison, we plan to also request postmarketing data on patient reports with difficulty swallowing Asacol and Asacol HD.

9 Appendices

9.1 Literature Review/References

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

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Delzicol label, last updated February 1, 2013, available at:
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9.2 Labeling Recommendations

After the sponsor submitted their proposed Delzicol label, the Division requested that the sponsor make further revisions to the label to include all pediatric information that was agreed upon and included in the currently approved Asacol label.

- 1) Since Delzicol was approved based on bioequivalence to Asacol 400mg delayed-release tablets, the Division proposes to add the following language to the relevant sections of the label to clarify why data from trials conducted with Asacol are contained in the label.
 - The data presented in Section [XX] are from clinical trials conducted with mesalamine 400 mg delayed-release tablets. Delzicol is bioequivalent to these mesalamine delayed-release tablets.
- 2) Data from trials conducted with Asacol are discussed in the Delzicol label. Since Asacol and Delzicol are indicated for different ages of pediatric patients, the division proposes to add the following language to the Section 8.4.
 - However, for patients less than 12 years of age, there is no age-appropriate formulation available. Therefore, Delzicol is indicated for the treatment of mildly to moderately active ulcerative colitis for patients 12 years of age and older.

For final labeling agreements, see the updated label for Delzicol.

9.3 Advisory Committee Meeting-

None

9.4 Supplementary Tables

For additional details, please refer to Asacol (NDA 19651/24), clinical review by Dr. Juli Tomaino, dated September 17, 2013.

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

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/s/

JULI A TOMAINO
02/14/2014

ANIL K RAJPAL
02/14/2014
I concur with Dr. Tomaino.