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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES -PEDIATRICS

NDA #: 21-830

Supplement #: Pediatrics Supplement

Drug Name: Asacol HD (mesalamine) Delayed-Release 400 mg Tablets/bid

Indication(s): Pediatric Ulcerative Colitis

Applicant: Warner Chilcott

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1 EXECUTIVE SUMMARY

Warner Chilcott has submitted one pivotal randomized, double-blind, parallel-group, 6-week study of 2 dose levels of Asacol 400mg in 83 pediatric subjects 5-17 years of age for treatment of mild to moderate Ulcerative Colitis (Study 2007017). A total of 27 investigators from 5 countries participated in this study. All subjects were randomly assigned to receive a low or high dose of Asacol, with randomization stratified by weight (17 to 33 kg, 33 to 54 kg, and 54 to 90 kg) and by disease severity (mild and moderate).

Study 2007017 failed to show a statistical difference in treatments success rates between the mesalamine high dose group (22/40, 55.0%) and the low dose group (23/41, 56.1%) for the primary efficacy endpoint ($p = 0.924$). The treatment difference was -1.1% with 95% confidence interval (-22.7%, 20.6%).

This reviewer conducted a post-hoc sensitivity analysis assuming subjects with partial success or with missing data were treatment failures. This sensitivity analysis resulted in a numerically higher treatment success rate for the low dose group (46.3%) versus the high dose group (40.5%); the difference in success rates was -5.9% with 95% confidence interval (-27.2%, 15.4%).

From a statistical perspective, efficacy of Asacol administered as 400 mg delayed-release tablets in pediatric subjects was not demonstrated in this study. Neither dose was shown superior to the other, and it is not known if either dose would have been superior to a placebo control. The study however was not powered to show a treatment effect less than 30% which might be considered unrealistic for the doses studied. Moreover, a dose-response trend was not evident, although the lower dose showed numerically better success rates compared to the higher dose.

The study was not designed to compare treatment success to those previously seen in adult studies. Extrapolation of adult response rates to this pediatric study population is a clinical determination, but at this juncture, any comparison to an historical control would be exploratory and not solely supportive of a an efficacy claim.

2 INTRODUCTION

Asacol® (mesalamine) delayed-release tablets, 400-mg (NDA 19-651, approved in January 1992) is indicated for treatment in adults of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC. Asacol HD (mesalamine) delayed-release tablets, 800mg (NDA 21-830; approved in May 2008) is indicated for treatment in adults of moderately active UC.

To fulfill the pediatric assessment for NDA 21-830 in accordance with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), a study (Study No.2007017) was conducted as a post-marketing commitment.

The Agency had requested the Sponsor to conduct a study in pediatric patients ages 5 to 17 years with ulcerative colitis using an age-appropriate formulation (i.e., an oral mesalamine formulation appropriate for pediatric dosing), such as their approved drug, Asacol®. 5-Aminosalicylic acid (5-ASA) products like Asacol® are used off-label as first-line therapy to treat children with UC.

In 2007, the Sponsor had completed their clinical protocol for the pediatric indication. The applicant proposed a randomized and double-blind study (Study # 2007017), comparing two different dose-levels of mesalamine. The study would enroll at least 83 pediatric patients from multiple countries and

centers and would evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy.

2.1 Overview

(b) (4), the applicant conducted Study 2007017 which evaluated the safety and efficacy of a low and a high dose of Asacol tablets in subjects aged 5-17 years for remission of mild or moderate UC. In addition, the sponsor initiated a second Phase 3 study (Study 2008085) for maintenance of remission. This trial was terminated early due to slow recruitment. Therefore, the focus of this review is mainly on the completed trial (study 2007017). Table 1 lists some information regarding these trials.

Table 1: List of Controlled Clinical Trials and a Brief Summary

Study #	Design	Treatment arms/ Sample size	Primary Endpoint /Analysis
2007017	Randomized, double-blind, parallel-group, 6-week study of 2 dose levels in pediatric subjects ages 5-17 years. 27 Investigators	N= 83 Asacol tablets, 400 mg Low Dose: 1.2 g /day 2.0 g/day 2.4 g/day High Dose: 2.0 g/day 3.6 g/day 4.8 g/day Total daily dose based on body weight and dose Level Dosage split across am and pm using 400 mg tablets oral	Pediatric UC Activity Index (PUCAI) The primary, secondary, and other exploratory categorical efficacy endpoints are analyzed using the Cochran-Mantel-Haenszel (CMH) test to compare dose levels (high vs. low), adjusting for weight group and disease severity.
2008085*	Randomized, double-blind, parallel-group, multi-center, multinational, 26-week study of 2 dose levels of Asacol 400 mg tablet consisting of a high dose and a low dose in pediatric subjects aged 5-17 years with documented history of ulcerative colitis successfully maintained in remission for at least 1 month prior to study entry	Asacol tablets, 400 mg Low Dose: 1.2 g/day 2.0 g/day 2.4 g/day High Dose: 2.0 g/day 3.6 g/day 4.8 g/day Total daily dose based on body weight and dose Level Dosage split across am and pm using 400 mg tablets oral	Pediatric UC Activity Index (PUCAI)

*Study 2008085 was terminated early for insufficient enrollment.

Study 2007017 (Remission):
This was a randomized, double-blind, parallel-group, 6-week study of 2 doses of Asacol (1.2 to 4.8 g/day) administered as 400 mg delayed-release tablets given every 12 hours in 83 pediatric subjects, ages 5-17 years with mildly to moderately active ulcerative colitis. A total of 27 investigators from five countries took part in this study.

The primary efficacy endpoint was based on the Pediatric UC Activity Index (PUCAI).

Study 2008085 (Maintenance of Remission):
Study 2008085 was a randomized, double-blind, parallel-group study to assess the safety and efficacy of Asacol (1.2 to 4.8g/day) 400 mg delayed-release tablets, given twice daily for 26 weeks to children and adolescents for the maintenance of remission of ulcerative colitis. The study required at least 40 patients at age 5 to 17 years in each dose cohort complete the study and at least 5 patients per arm at 5 to 10 years old.

On January 20, 2011, the applicant t notified the Agency that enrollment was terminated for this study before reaching the required number of subjects due to lack of eligible subjects and a very slow recruitment.

2.2 Data Sources

This NDA was submitted electronically. The data appeared to have been captured, assessed and organized adequately, consistent with CDISC format.

The submission is located at:

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In this review, the ADaM data formats were used for analyses. Some of the main datasets used for review of this submission were:

Dataset BLSUB (Baseline and Subgroup), COMP (Treatment Compliance), DMSTA (Demographics), DSCDM (Disposition), PEENCDM (Endoscopy) MEDS (Concomitant Medications), PUCAI (PUCAI), TREAT (Treatment Un-blinding), DISCHAR (Disease Characteristics) and TRUNMAYO (Truncated Mayo).

The applicant had submitted the SAS programming codes they used for the analysis of the data.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data submitted by the applicant was fairly organized and was easy to use and similar to the ADaM format. It was possible to reproduce the primary analysis dataset, and in particular the primary endpoint, from the original data source. The applicant's statistical analysis plan (SAP) was finalized prior to data base lock.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

This was a randomized, double-blind, parallel-group, 6-week study of 2 dose levels of Asacol 400mg in 83 pediatric subjects 5-17 years of age for treatment of mild to moderate UC. Twenty-seven investigators from 5 countries participated in this study. All subjects were randomly assigned to receive a low or high dose of Asacol, with randomization stratified by weight (17 to 33 kg, 33 to 54 kg, and 54 to 90 kg) and by disease severity (mild and moderate). Baseline and screening visits were followed by a treatment period of six weeks, during which subjects received high or low doses of Asacol as defined in Table 2.

Table 2: Asacol Dose Groups, Study 2007017

Weight Range (kg)	Low Dose	High Dose
17 to 33	1.2 g/day	2.0 g/day
33 to 54	2.0 g/day	3.6 g/day
54 to 90	2.4 g/day	4.8 g/day

Study Objective

The overall objective was to assess the safety and efficacy of high dose and low dose Asacol administered as 400 mg delayed-release tablets given every 12 hours for 6 weeks to children and adolescents with mild to moderately active ulcerative colitis (UC).

The study was designed to randomize 100 subjects with the expectation that about 80 (40 in High Dose group and 40 in Low Dose group) would complete the study.

Screening (Day -7 to -1) – At the Screening visit, a subject's potential eligibility for the study was determined by the PUCAI score, subject medical and medication history, physical examination findings, and body weight/height; by safety measures including vital signs and clinical laboratory tests (hematology, serum chemistry, urinalysis); and by pregnancy test results. Urine samples were taken for determination of creatinine and phthalate levels. In subjects for whom permission was given, blood samples were taken for optional serum biomarker assessments. Serious, study procedure-related non-treatment-emergent AEs were recorded. Subjects or parents/legal guardians were given PUCAI Diary Cards for at-home use and reminded that subjects should avoid protocol-excluded medications.

Baseline – Day 1 of Treatment Period – Subjects who met the inclusion criteria were randomized to the High Dose or Low Dose group. Medical and medication histories were updated, body weight/height was measured, and vital signs were assessed. Samples were taken for clinical laboratory tests (hematology, serum chemistry, urinalysis) and determination of urinary creatinine and phthalate levels if the Baseline visit had occurred > 7 days after Screening, and for pregnancy testing (post-menarchal females). Additional blood samples were taken from subjects for whom consent was given for analysis of optional serum biomarkers if the Baseline visit had occurred > 7 days after Screening. Stool samples were obtained for analysis of calprotectin and lactoferrin levels and for evaluation of bacterial pathogens, ova and parasites, and C. difficile. In addition, subjects underwent Clinical Assessment, including review of PUCAI Diary Cards, completion of PUCAI and 5-level abdominal pain scale, and assessment per the TM-Mayo Score of stool frequency and rectal bleeding. Serious, study-procedure-related, non-treatment-emergent AEs were recorded. Study medication was dispensed, and dosing instructions were reviewed with the subject/parent or legal guardian and the importance of compliance was stressed. Subjects/parents or legal guardians were reminded that subjects should avoid protocol-excluded medications.

Week 1 Phone Visit – Subjects or parents/legal guardians were contacted by telephone to assess compliance and well-being of the subject during Week 1.

Week 3 Visit – Medication histories were updated, and blood samples were taken for pharmacokinetic analyses. Additional blood samples were taken from subjects for whom consent was given for analysis of optional serum biomarkers. Stool samples were obtained for analysis of calprotectin and lactoferrin levels, and AEs were recorded. Subjects/parents or legal guardians were given PUCAI Diary Cards for at-home use. Study medication was returned and counted, additional study medication was dispensed, and dosing instructions were reviewed with the subject/parent or legal guardian and the importance of

compliance was stressed. Subjects/parents or legal guardians were reminded that subjects should avoid protocol-excluded medications.

Week 6 Visit – Medication histories were updated, physical examination was done, body weight/height was measured, and vital signs were assessed. Samples were taken for clinical laboratory tests (hematology, serum chemistry, urinalysis), pregnancy testing (post-menarchal females only), determination of levels of urinary creatinine and phthalate and fecal calprotectin and lactoferrin, and pharmacokinetic analyses. Additional blood samples were taken from subjects for whom consent was given for assessment of optional serum biomarkers. Adverse events were recorded. In addition, subjects underwent Clinical Assessment, as described above, and the Final Investigator Assessment. Study medication was returned and counted.

1-week Follow-up Visit – Subjects who did not continue into the follow-up Study 2008085 received a telephone follow-up visit for adverse event evaluations and assessment of compliance and subject well-being.

Main Criteria for Inclusion
Subjects were males and females, 5-17 years of age (inclusive), with a history of biopsy- and endoscopy-confirmed UC; mildly-to-moderately active UC (relapsed or newly diagnosed) as defined clinically by a PUCAI score ≥ 10 and ≤ 55; baseline scores of ≥ 1 for both rectal bleeding and stool frequency, as defined by the TM-Mayo Score; and a body weight ≥ 17 kg and ≤ 90 kg; subjects were generally in good health and able to swallow Asacol tablets.

Additionally, female subjects were pre-menarchal or had a negative urine pregnancy test; if sexually active; they must have practiced acceptable contraception and must not have been breast-feeding.

Removal of Subjects from Therapy or Assessment
Withdrawn subjects were those who did not complete all evaluations and procedures outlined in the protocol. Subjects who discontinued taking study drug for any reason must also have been withdrawn from the study. Subjects may have been withdrawn from the study because of one of the following:

- Adverse Event: AEs that, in the opinion of the Investigator or Sponsor, suggested that continued participation in the study was not in the subject's best interest.

- Subject Request/Withdrawal of Consent: Subject or parent/legal guardian requested that the subject be withdrawn or withdrew his/her consent

- Pregnancy: Subject became pregnant; positive pregnancy test. If any pregnancy test was positive, the subject was referred to an obstetrician and followed throughout the remainder of her pregnancy

- Protocol Violation: A subject could be withdrawn from the study at the discretion of the Investigator or Sponsor due to poor compliance with protocol requirements, especially when subject safety was concerned.

- Other, including, but not limited to: Investigator decision that it was in the subject's best interest to be withdrawn, administrative reasons, relocation of subject, etc.

If a subject was withdrawn from the study following the start of study drug, all Week 6 assessments should have been completed. Subjects withdrawn from the study were not replaced.

Blinding

Double-blind kits for the 2 treatment groups within a weight group were identically packaged. The treatment each subject received was not disclosed to the Investigator, study center personnel, subjects, contracted monitors, contracted vendors, or the Sponsor (except for selected Clinical Supplies, Clinical Pharmacovigilance, and Regulatory personnel, as necessary). The treatment codes were controlled by the Clinical Supplies Department of the Sponsor.

Placebo tablets were administered to maintain the blind. The maximum absolute dose was capped at 4.8 g/day mesalamine for all patients.

The medication code for a particular subject could be broken via the IVRS only for situations in which the Investigator felt the subject could not be adequately treated without knowing the dose of the study medication. Every effort was to be made to contact the Sponsor's Medical Monitor prior to breaking the code. The site would then call the IVRS and use the code to break the blind. Pertinent information regarding the un-blinding of a subject's treatment code was to be documented in the subject's source documents and the eCRF. If a subject and/or Investigator was un-blinded during the course of the study, the subject was to be immediately discontinued from further participation.

Handling of Dropouts or Missing Data

Subjects withdrawn from the study for safety or efficacy reasons were included in the efficacy analyses as treatment failures.

Post-baseline visits were determined based on the labels provided in the clinical database. For clinical lab summaries, post-baseline values obtained at the original visit were used when time-point data were summarized. Repeat values were not used in time-point summaries.

Primary Efficacy Endpoint

The primary efficacy endpoint was treatment success (TS) based on the Pediatric Ulcerative Colitis Activity Index (PUCAI) as assessed by the investigator. Treatment Success was defined as achieving either a PUCAI Complete Response (PUCAI-CR) or a PUCAI Partial Response (PUCAI-PR). CR was defined as achieving a PUCAI total score of < 10 at Week 6, and PR was defined as achieving a reduction of the PUCAI score of ≥ 20 points from Baseline to Week 6, with an PUCAI total score ≥10 at Week 6.

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	

PUCAI Total Score= Sum of 6 individual symptom scores.

Secondary Efficacy Endpoints
The secondary efficacy endpoints included the following:

1. Complete response (CR)
2. Partial response (PR)
3. Treatment failure (TF) based on the PUCAI
4. TS based on the Amended Endpoint
5. Truncated Mayo Score (TM-Mayo)
6. TS based on the TM-Mayo.

The Amended Endpoint was a pre-specified endpoint similar to the PUCAI (but with the PUCAI 3-level Abdominal Pain question replaced by a 5-level Abdominal Pain question). In this review, however, we only discuss CR and PR based on PUCAI. We also show the frequency distributions for each individual component of the PUCAI.

3.2.2 Statistical Methods

The protocol and SAP stated the primary endpoint would be analyzed using the Cochran-Mantel-Haenszel (CMH) test to compare the dose levels (High vs. Low) adjusting for the weight group and disease severity, using a two-sided test at α=0.05. The Sponsor indicated that a Zelen's test would be used to check for homogeneity of the odds ratio across the weight and disease severity strata. The odds ratio would be assessed in the event that it is not homogeneous across the two strata. Depending on the outcome of Zelen's test, the two dose levels within a weight and/or disease severity stratum would be compared.

The applicant stated that the descriptive statistics would be generated for the primary endpoint for each weight group (17-33 kg, 33-54 kg and 54-90 kg), disease severity (mild and moderate) and dose level (High vs. Low) combination.

As requested by the FDA (Meeting Preliminary Comments, 24 February 2012), each component of the investigator-scored PUCAI and the patient-completed PUCAI Diary Card was to be analyzed. The analyses were to be conducted on the change from baseline score at Week 6 for each component using the Cochran-Mantel-Haenszel (CMH) test to compare dose levels (high vs. low), adjusting for weight group and baseline disease severity. For subjects who withdrew from the study prior to Week 6, the scores at the withdrawal visit were to be used in place of the Week 6 values. Each test was conducted at the α=0.05 significance level.

For the investigator-scored PUCAI, the change from baseline for each component was to be calculated as the difference between the Week 6 (or Withdrawal) score and the baseline score.

The patient-completed PUCAI Diary Card was to be completed in the 2 days prior to the visit day. For each PUCAI Diary Card component, the maximum score recorded on the 2 diary cards prior to each visit was obtained. The change from baseline for the PUCAI was to be calculated as the difference between the maximum score at Week 6 (or Withdrawal) and the maximum score at baseline, i.e.,

$$[\text{PUCAI Diary}]_{\text{Bsl,i}} = \text{maximum of } ([\text{Diary Card 1}]_{\text{Bsl,i}} , [\text{Diary Card 2}]_{\text{Bsl,i}})$$

$$[\text{PUCAI Diary}]_{\text{Post,i}} = \text{maximum of } ([\text{Diary Card 1}]_{\text{Post,i}} , [\text{Diary Card 2}]_{\text{Post,i}})$$

Change from baseline for $[\text{PUCAI Diary}]_i = [\text{PUCAI Diary}]_{Post,i} - [\text{PUCAI Diary}]_{Bsl,i}$

where Bsl = baseline visit
Post = post-baseline visit (Week 6 or the Withdrawal visit)
i = the i^{th} component of the PUCAI Diary Card

All the above analyses were to be conducted on the modified Intent-to-Treat (mITT) population defined as all subjects randomized and having at least one dose of study drug.

Power and Sample Size Considerations
A total of about 100 patients would be enrolled in the study with the expectation that about 80 patients (40/dose level) will complete. The applicant had anticipated that the number of 5-8 year olds enrolled will be proportional to the pediatric UC patient population at large. Therefore, a minimum of 9 patients in the 5-8 year old age range would be enrolled, 4-5 per dose level (High vs. Low). A two-sided α=0.05 Fisher's Exact test has an estimated power of 0.74 to detect a .30 difference between response rates assuming Low dose response rate = 0.20 and High dose response rate = 0.50.

Changes in the Planned Analyses
The following list details deviations from the planned analyses identified in the Statistical Methods section of the Protocol:

- The Per- Protocol population was specified in the protocol as the analysis population to be used for primary and secondary efficacy analyses; however, the mITT population was used to maximize the number of subjects included in the efficacy/end of treatment analyses. The Per-Protocol population analysis was not performed.
- Changes in each of the 6 components of the PUCAI and the 5-level abdominal pain score were to be compared with the overall change in the PUCAI and Amended Endpoint total scores. This comparison was not performed.
- The PUCAI 3-level abdominal pain score was to be correlated with the Amended Endpoint 5-level abdominal pain score. This analysis was not performed.
- The subject-completed diary cards were to be compared to the interviewer's scored PUCAI. This comparison was not performed.
- The final Investigator Assessment of change in disease activity was to be compared to individual constructs of the PUCAI and 5-level abdominal pain score. This comparison was not performed.
- Collection of serum biomarker was optional in this study. These biomarkers were not analyzed.
- Though not specified in the protocol, all safety summaries were based on the Safety Population. The Safety Population was defined as all subjects who were randomized and took at least one dose of study medication. Subjects were summarized according to the treatment they actually received.
- The statistical methods section of the protocol states that the AEs will be tabulated using MedDRA System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT); instead, AEs were summarized by SOC and PT only.

- The statistical methods section of the protocol stated that stool samples collected more than 24 hours after the most recent dose were to be excluded from analysis; however, samples collected more than 12 hours after the most recent dose were excluded from analysis to be consistent with the sampling time periods (0-6 hours post-dose and 6-12 hours post-dose). No samples were collected between 12 and 24 hours post-dose, so both criteria provided the same summary.

The applicant asserts that all deviations were planned in advance of database lock and therefore in advance of breaking the treatment blind.

3.2.3 Study Results

Patient Disposition, Demographic and Baseline Characteristics

Table 3 shows the number of subjects who discontinued early and the reason.

Table 3: Disposition of Subjects (Randomized Population) - Study 2007017

Parameter Category	Low Dose (N=41) n (%)	High Dose (N=42) n (%)	Overall (N=83) n (%)
Completers	36 (87.8%)	36 (85.7%)	72 (86.7%)
Drop-Outs with the Reason for discontinuation:			
Adverse events	5 (12.2%)	2 (4.8%)	7 (8.4%)
Lack of treatment effect	0	2 (4.8%)	2 (2.4%)
Voluntary withdrawal	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.
One subject (#1048641004) in the High Dose group was randomized but not dosed.
Source: Sponsor's Study Report Page 43

It is noted that 5 (12.2%) of the discontinuations due to an adverse event were from the Low Dose and 2 (4.8%) were from the High Dose group. Seven out of the 11 drop-outs were from USA, 3 from Poland and 1 from Croatia. (See Table 11 for subject disposition by country.)

Table 4 shows demographic and baseline characteristics.

Table 4: Demographic and Baseline Characteristics (MITT) – Study 2007017

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%)
Gender			
Female	22 (53.7%)	23 (56.1%)	45 (54.9%)
Male	19 (46.3%)	18 (43.9%)	37 (45.1%)
Race			
Black	2 (4.9%)	2 (4.9%)	4 (4.9%)
Caucasian	37 (90.2%)	39 (95.1%)	76 (92.7%)
Multi-Racial	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 Study Report Page 46

Analysis populations

A total of 83 subjects were randomized (41 to the Low Dose group and 42 to the High Dose group). One subject (#1048641004) was randomized to the High Dose group but voluntarily withdrew and was not dosed. Another subject (#1048501001) was randomized to the High Dose group, voluntarily withdrew and had no post-baseline observations. The sponsor excluded both these patients from their mITT population which resulted in efficacy analyses based on 41 subjects in the Low Dose group and 40 subjects in the High Dose group

The Safety population consisted of 41 subjects in each dose group.

Analysis of the Primary Efficacy Endpoint
Primary and secondary endpoints and other exploratory categorical efficacy endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test to compare dose levels (high vs. low), adjusting for weight group and disease severity.

The sponsor's primary analysis was based on the mITT population, which included subjects who were randomized and took at least one dose of study medication and had post-baseline data. The drug dosage taken depended on body weight; for Low Dose = Asacol 1.2 - 2.4 g/day; High Dose = Asacol 2.0 - 4.8 g/day.

The Total Success (TS) rate was defined as a PUCAI total score < 10 at Week 6 (complete success) or a reduction of >=20 points from baseline to Week 6 with Week 6 score >= 10 (partial success). A subject's result would be a failure if a success was not achieved or the subject had dropped out due to AE or lack of efficacy. If a subject's score was missing at Week 6, treatment failure was assumed.

Table 5 shows the sponsor's results of the primary efficacy endpoint analysis.

Table 5: Analysis of the Primary Efficacy – Study 2007017

	High Dose (n=40)	Low Dose (n=41)	Difference 95% CI
Success	22 (55.0%)	23 (56.1%)	-1.1% (-22.7%, 20.6%) (p=0.924)
Failure	18 (45.0%)	18 (43.9%)	

Analysis of PUCAI Treatment Success (Modified Intent-to- treat Population)
Endpoint is total success based on investigator PUCAI total score.
Source: Sponsor's Study Report Page 51

Table 5 shows that, although not statistically significant, the low dose success rate (56.1%) is numerically larger than the high dose success rate (55%), with a difference in success rate of -1.1% and 95% CI (-22.7, 20.6). The reviewer's analysis produced the same results. Inclusion of subject #1048501001 (who withdrew early but was dosed) as a treatment failure would lower the High Dose success rate to 53.6% and the difference in rates to -2.5%.

Table 6 breaks down the success group into Complete Response and Partial Response using the sponsor's analysis population..

Table 6: Reviewer's Analysis of Secondary Efficacy – Study 2007017

	High Dose (n=40)	Low Dose (n=41)	Difference 95% CI
Complete Success	17 (42.5%)	19 (46.3%)	-3.8% (-24.9%, 17.6%)
Partial Success	5 (12.5%)	4 (9.8%)	2.8% (-12.1%, 18.0%)

Below, Table 7 lists the number and percentage of subjects in each category for each individual component of the PUCAI.

Table 7: Frequency of Each Individual Component

	Baseline		Week 6		Change from Baseline		
	High Dose (n=42)	Low Dose (n=41)	High Dose (n=36)	Low Dose (n=36)	Score	High Dose (n=36)	Low Dose (n=36)
Abdominal Pain					-5	4 (11%)	3 (8%)
0	7 (16.7%)	13 (31.7%)	17 (47.2%)	23 (63.9%	0	13 (36%)	18 (50%)
5	22 (52.4%)	24 (58.5%)	16 (44.4%)	11 30.6%)	5	13 (36%)	13 (36%)
10	13 (31%)	4 (9.8%)	3 (8.3%)	2 (5.6%)	10	6 (17%)	2 (5.6%)
Rectal Bleeding					-20	2 (5.6%)	1 (2.8%)
0	1 (2.4%)	1 (2.4%)	24 (66.7%)	22 (61.1%)	-10	1 (2.8%)	3 (8.3%)
10	20 (47.6%)	24 (58.5%)	6 (16.7%)	7 (19.4%)	0	5 (13.9%)	7 (19.4%)
20	19 (45.2%)	12 (29.3%)	4 (11.1%)	4 (11.1%)	10	18 (50%)	20 (55.6%)
30	2 (4.8%)	4 (9.8%)	2 (5.6%)	3 (8.3%)	20	9 (25%)	3 (8.3%)
					30	1 (2.8%)	2 (5.6%)
Stool Consistency					-5	1 (2.8%)	2 (5.6%)
0	6 (14.3%)	11 (26.8%)	22 (61.1%)	28 (77.8%)	0	17 (47.2%)	14 (38.9%)
5	30 (71.4%)	25 (61%)	12 (33.3%)	8 (22.2%)	5	14 (38.9%)	18 (50%)
10	6 (14.3%)	5 (12.2%)	2 (5.6%)	0 (0%)	10	4 (11.1%)	2 (5.6%)
Number of Stools					-10	2 (5.6%)	0
0	13 (31%)	9 (22%)	22 (61.1%)	23 (63.9%)	-5	2 (5.6%)	3 (8.3%)
5	22 (52.4%)	28 (68.3%)	9 (25%)	12 (33.3%)	0	21 (58.3%)	14 (38.9%)
10	4 (9.5%)	3 (7.3%)	2 (5.6%)	0	5	10 (27.8%)	18 (50%)
15	3 (7.1%)	1 (2.4%)	3 (8.3%)	1 (2.8%)	10	1 (2.8%)	1 (208%)
Nocturnal B.M.					-10	1 (208%)	0
0 (No)	31 (73.8%)	33 (80.5%)	31 (86.1%)	35 (97.2%)	0	31 (86.1%)	31 (86.1%)
10 (Yes)	11 (26.2%)	8 (19.5%)	5 (13.9%)	1 (2.8%)	10	4 (11.1%)	5 (13.9%)
Activity Level					-10	1 (2.8%)	0
0	17 (40.5%)	24 (58.5%)	27 (75%)	34 (94.4%)	-5	3 (8.3%)	1 (2.8%)
5	23 (54.8%)	17 (41.5%)	6 (16.7%)	2 (5.6%)	0	16 (44.4%)	22 (61.1%)
10	2 (4.8%)	0	3 (8.3%)	0	5	14 (38.9%)	13 (36.1%)
					10	2 (5.6%)	0

Source: Reviewer's analyses

This reviewer notes that there appears to be a treatment imbalance at baseline for the abdominal pain scores as well as stool consistency.

Sensitivity Analyses
We conducted a sensitivity analysis by varying the criteria that defined patient response. We considered all subjects with partial success or with missing data as treatment failures.

Table 8 summarizes the results of this analysis. .

Table 8: Reviewer's Results of Sensitivity Analysis

	High Dose (n=42)	Low Dose (n=41)	Difference 95% CI
Success	17 (40.5%)	19 (46.3%)	-5.9%
Failure	25 (59.5%)	22 (53.7%)	(-27.2%, 15.4%)

The sensitivity analysis shows that the low dose (46.3%) has a higher response rate than the high dose (40.5%); with a difference in success rate of -5.9% and 95% CI (-27.2, 15.4). The numerically larger success rate for the low dose is consistent with the results for the primary analysis.

3.3 Evaluation of Safety

The focus of this review is efficacy. Therefore, for safety evaluation, refer to the Medical Officer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The Sponsor did not submit results of subgroup analyses. In this review, however, we conducted some subgroup analyses where reasonable.

The number of subjects in each center was small (between 1 and 7). Therefore, no analysis by investigator was done.

4.1 Gender, Race, Age, and Geographic Region

Tables 9 through 12 show the reviewer's efficacy results (Total Success rates based on PUCAI) by weight, disease severity, country and gender, respectively. These tables are based on the sponsor's mITT population (40 High Dose subjects and 41 Low Dose subjects). No apparent differences between dose groups were indicated, consistent with the overall analysis. However, the small sample sizes of the subgroups preclude any clear interpretation.

Table 9: Success Rate by Weight Category

Weight Category in KG	High Dose	Low Dose
17 to < 33 n=12	3 (42.9%) n=7	3 (60.0%) n=5
33 to < 54 n=33	10 (62.5%) n=16	11 (64.7%) n=17
54 to 90 n=36	9 (52.9%) n=17	9 (47.4%) n=19

Table 10: Success Rate by Disease Severity

Disease Severity	High Dose	Low Dose
Mild N=41	10 (50%) N=20	12 (57.1%) N=21
Moderate N=40	12 (60.0%) N=20	11 (55.0%) N=20

Table 11: Success Rate by Country

Country	High Dose	Low Dose
Canada (n=4)	2 (50%) (n=4)	0 (n=0)
Croatia (n=6)	1 (50%) (n=2)	2 (50%) (n=4)
Poland (n=19)	5 (50%) (n=10)	6 (67%) (n=9)
Romania (n=5)	2 (67%) (n=3)	2 (100%) (n=2)
USA (n=47)	12 (57%) (n=21)	13 (50%) (n=26)

Table 12: Response by Gender

Gender	High Dose	Low Dose
Female (n=45)	12 (52%) (n=23)	13 (59%) (n=22)
Male (n=36)	10 (59%) (n=17)	10 (53%) (n=19)

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

Warner Chilcott has submitted one pivotal randomized, double-blind, parallel-group, 6-week study of 2 dose levels of Asacol 400mg in 83 pediatric subjects 5-17 years of age for treatment of mild to moderate Ulcerative Colitis (Study 2007017). A total of twenty-seven investigators from 5 countries participated in this study. All subjects were randomly assigned to receive a low or high dose of Asacol, with randomization stratified by weight (17 to 33 kg, 33 to 54 kg, and 54 to 90 kg) and by disease severity (mild and moderate).

Study 2007017 failed to show a statistical difference between treatment success for the mesalamine high dose (22/40, 55.0%) and the low dose (23/41, 56.1%) for the pre-specified primary efficacy endpoint (p=0.942). The treatment difference was -1.1% with 95% Confidence Interval (-22.7%, 20.6%).

This reviewer conducted a post-hoc sensitivity analysis assuming subjects with partial success or with missing data were treatment failures. This sensitivity analysis resulted in a numerically higher success rate for the low dose (46.3%) versus the high dose (40.5%); with a difference in success rates of -5.9% and 95% CI (-27.2%, 15.4%).

From a statistical perspective, efficacy of Asacol administered as 400 mg delayed-release tablets in pediatric subjects was not demonstrated in this study. The study however was not powered to show a treatment effect less than 30% which might be considered unrealistic for the doses studied. Moreover, a dose-response trend was not evident, although the lower dose showed numerically better success rates compared to the higher dose.

The study was not designed to compare treatment success to those previously seen in adult studies, and any such comparison would need to reconcile the differences in study endpoints. Extrapolation of adult response rates to this pediatric study population is a clinical determination but would be exploratory at this point and not clearly supportive of an efficacy claim.

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/s/

SHAHLA S FARR
10/07/2013

MICHAEL E WELCH
10/07/2013
Concur with review.