Clinical Pharmacology Review

NDA/Supplement	021830/ SE6
Submission Date	12/21/2012
Brand Name	Asacol HD®
Generic name	Mesalamine
Type/Category	Pediatric supplement/ priority
Dosage Form and Strength	400 mg tablet
Route of Administration	oral
Proposed Indication	Induction of remission in pediatric patients 5 – 17 years of age, with mildly to moderately active ulcerative colitis (UC)
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TABLE OF CONTENTS

1 Executive Summary 3

1.1 Recommendations 3

1.2 Post-Marketing Requirement and Post-Marketing Commitment 3

1.3 Summary of Important Clinical Pharmacology Findings 3

2.1 General Attributes of the Drug 9

2.2 General Clinical Pharmacology 10

2.3 Intrinsic Factors 20

2.4 Extrinsic Factors 24

2.5 General Biopharmaceutics 24

2.6 Analytical Section 25

3 Detailed Labeling Recommendations 33

3 Detailed Labeling Recommendations 33

Appendices (Supporting Materials) 34

LIST OF FIGURES

(b) (4)

Figure 3. Predicted mesalamine exposures in pediatrics are comparable to those in adults after the sponsor's proposed dosing based on the individuals body weight (left panel) and their daily dose (right panel). *7*

Figure 4. Individual estimated mesalamine exposures in pediatrics are comparable to those in adults based on the individuals body weight (left panel) and their daily dose (right panel). *8*

Figure 7. Box and whisker plots suggesting lack of a trend for dose-response (change from baseline in PUCAI score) in the three body weight cohorts of study 2007017 ..... *13*

Figure 8. Percentage reduction from baseline PUCAI presented by extent of disease. *22*

Figure 9. Average plasma mesalamine concentrations (ng/mL) by extent of disease. *23*

LIST OF TABLES

Table 1. Proposed Pediatric Dosing in patients 5- 17 years of age *3*

14

14

Table 4: Biomarker baseline information and treatment effects with low and high doses. *15*

Table 5. Treatment emergent adverse events (safety population) for study 2007017. ..... *16*

Table 6: Summary of baseline and change from baseline in urinary phthalates *16*

Table 7. Sponsor's non-compartmental analysis of the pharmacokinetic data from the dose-ranging study in pediatric (Study 2005018). *18*

Table 8: Urinary excretion data for parent mesalamine and metabolite in pediatric UC patients (Study 2005018). *18*

Table 9: Dose linearity and proportionality assessment for mesalamine in pediatric UC patients of study 2005018 20
Table 10. Responder analyses in pediatric patients by UC disease severity (mild vs. moderate) 21
Table 11. Baseline and % change from baseline in PUCAI by extent of disease. 21
Table 12. Responder analyses by extent of disease (pediatric UC). 23
Table 13. Summary of Validation Data for 5 ASA in Human Plasma 25
Table 14. Summary of Validation Data for N Ac 5 ASA in Human Plasma: 26
Table 15. Summary of Validation Data for 5 ASA in Human Urine. 26
Table 16. Summary of Validation Data for N Ac 5 ASA in Human Urine 27
Table 17. Summary of validation data for mono-n-butylpthalate in human urine is presented: 31

1 EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this application and found it to be acceptable for (b) (4) in pediatric UC. We recommend the approval of the lower dose level (see Table 1) in pediatric patients 5 -17 years of age (b) (4) .

Table 1. Proposed Pediatric Dosing in patients 5- 17 years of age

Body Weight Range (kg)	Total Daily Dose (g/day)	Total Daily Dose in mg/kg
17 – < 33	1.2	36 - 71
33 – < 54	2.0	37 - 61
54 – < 90	2.4	27 - 44

1.2 Post-Marketing Requirement and Post-Marketing Commitment

No post-marketing requirements or commitments are necessary for NDA 21-830/SE6 from a Clinical Pharmacology perspective.

1.3 Summary of Important Clinical Pharmacology Findings

Asacol® (NDA 19-651) and Asacol HD® (NDA 21-830) delayed release tablets of 400 and 800 mg mesalamine have been approved for use in adults for the treatment of mildly to moderately active UC and moderately active UC, respectively. With the approval of Asacol HD in 2005, the sponsor was required to fulfill a PREA requirement of conducting a study in pediatrics and developing an age appropriate formulation. With this submission, the sponsor is providing the results of this study to fulfill their PREA requirement and is seeking the indication (b) (4) in pediatric patients 5- 17 years of age with mildly to moderately active ulcerative colitis.

Mesalamine is considered to have anti-inflammatory effect and is administered orally in adults at either 2.4 (Asacol®) or 4.8 (Asacol HD®) g/day. No significant additional benefit has been shown at the 4.8 g/day dose over the 2.4 gram per day; however the 4.8 g dose was approved

based on a non-inferiority comparison to Asacol 2.4 g. The drug is thought to act locally in the colon and systemic exposures (BA ~ 20%) are relevant primarily from a safety perspective. High fat meals do not affect the bioavailability; however, the C_{max} is decreased 47% and delayed 14 hours. The C_{max} occurs between 10 – 16 hours post dose. Asacol is metabolized to N-acetyl-mesalamine in liver and gut prior to excretion in kidney. The apparent half-life is 12 h for mesalamine and 23 hr for its major metabolite (N-acetyl-mesalamine), however, these values are driven by the delayed release of the product and flip-flop pharmacokinetics.

The sponsor's clinical development program included a phase 2 dose-ranging and phase 3 trials in pediatric patients aged 5 – 17 years with mildly to moderately active UC. The phase 3 trial included low and high dose groups, which were based in part on body weight (1.2 or 2.0 g/day for 17 – <33 kg, 2.0 or 3.6 g/day for 33 – <54 kg, and 2.4 or 4.8 g/day for 54 – 90 kg). Efficacy was evaluated in the phase 3 trial by the rate of treatment success as defined by the PUCAI (pediatric UC activity index) score at the end of 6 weeks of treatment. The rate of treatment success at the end of 6 weeks was no different between the low and high dose groups (56% vs. 55% respectively, p-value =0.94). However, the rates of remission (~56%) were comparable to those observed in adults (59% in adults with moderate disease at the 2.4 g/day dose). Additionally, results from an incomplete trial to evaluate the maintenance of remission at 26 weeks were submitted. The trial was terminated early due to enrollment limitations. (b) (4)

As the site of action is located within the GI tract, traditional exposure-response analyses and systemic exposure matching to adults may not be appropriate or possible for pediatric dose selection. Exposure-response relationships were evaluated with logistic regression models for both systemic plasma concentrations and predicted gut concentrations against the probability of treatment success for inducing remission at the end of 6 weeks in the sponsor's phase 3 studies (both pediatric and adult data). No exposure-response relationships were identified for either exposure metric for both adults and children. The lack of gut concentration-response relationship was consistent with lack of dose-response observed in the phase 3 trial. Exposure-response was also evaluated for the N-acetyl-metabolite plasma AUC, however due to the high correlation with the parent, no correlation with response was observed. (b) (4)

Thus, the sponsor's proposal for the lower of the two studied dose levels is acceptable. (b) (4)

2 Question Based Review

2.0 Key Review Questions:

2.0.1

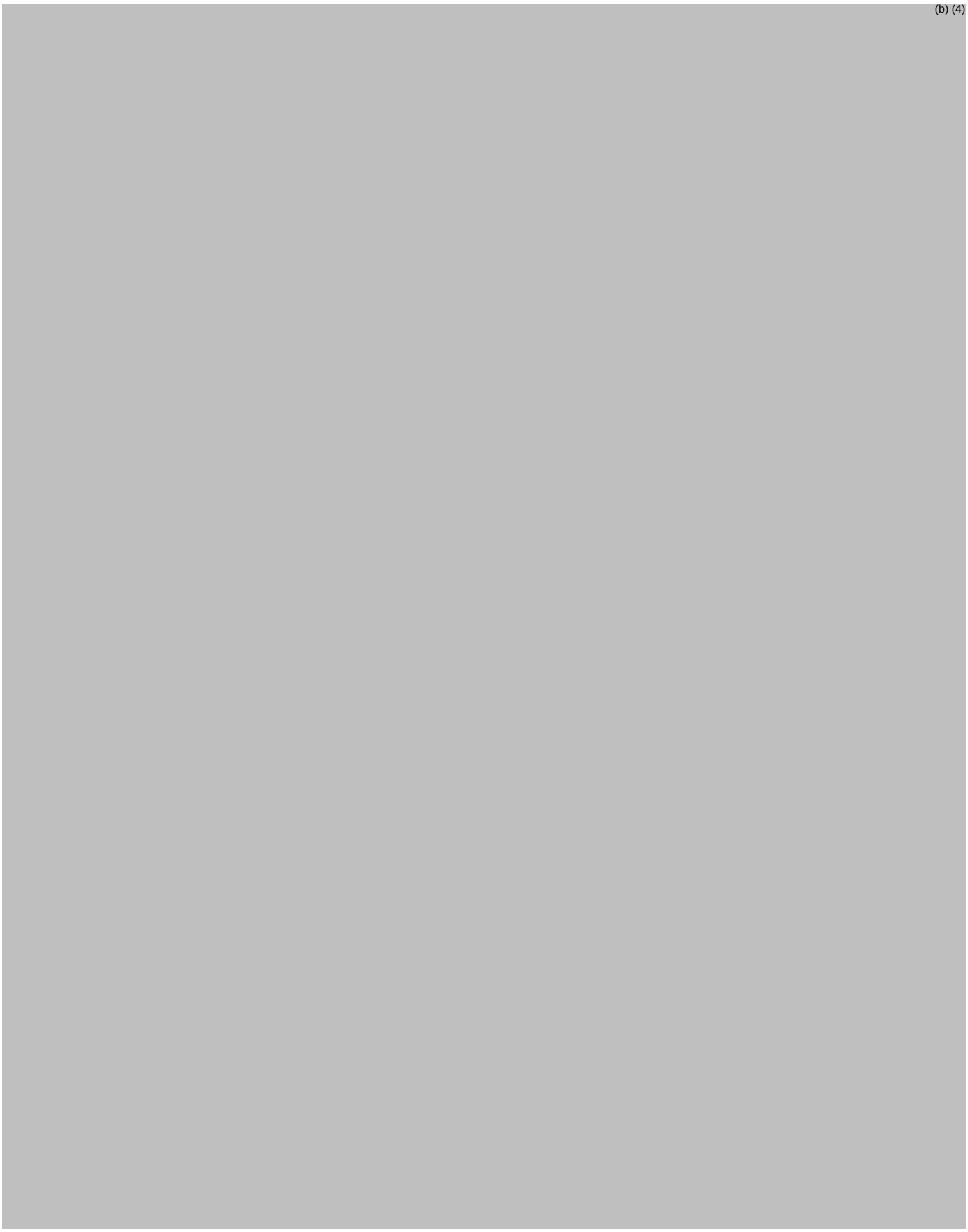
(b) (4)

(b) (4)

(b) (4)

The current guidelines for pediatric ulcerative colitis by ECCO and ESPGHAN societies recommend 60 – 80 mg/kg/day[1]. Of the two doses levels studied in the phase 3 trial 2007017, the low dose was comparable to 30 – 60 mg/kg/day while the high dose was comparable to 60 – 110 mg/kg/day.

[1] Turner D, et. al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr*. 2012 Sep;55(3):340-61.


(b) (4)

2.0.2 Are mesalamine PK in children at the proposed dose with UC similar to that in adults with the approved dose?

Yes, the population PK model suggests that systemic pediatric exposures after the proposed dose of 1.2, 2.0, or 2.4 g/day (depending on body weight) would produce exposures comparable to the low dose regimen in adults (2.4 g/day). Figure 3 shows the population predicted mean AUC by body weight and daily dose, without considering between subject variability. Figure 4 shows the estimated AUC values by body weight and daily dose for the studied population accounting for between subject variability. This latter plot suggest that when accounting for PK variability in the population that the range of exposures are quite comparable between pediatrics and adults at the proposed doses.

Figure 3. Predicted mesalamine exposures in pediatrics are comparable to those in adults after the sponsor's proposed dosing based on the individuals body weight (left panel) and their daily dose (right panel).

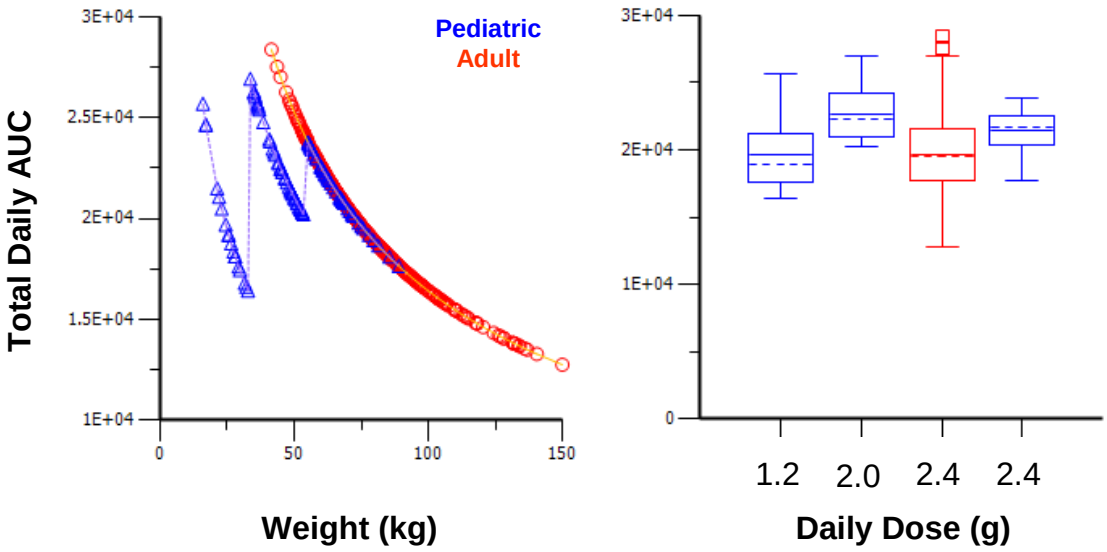
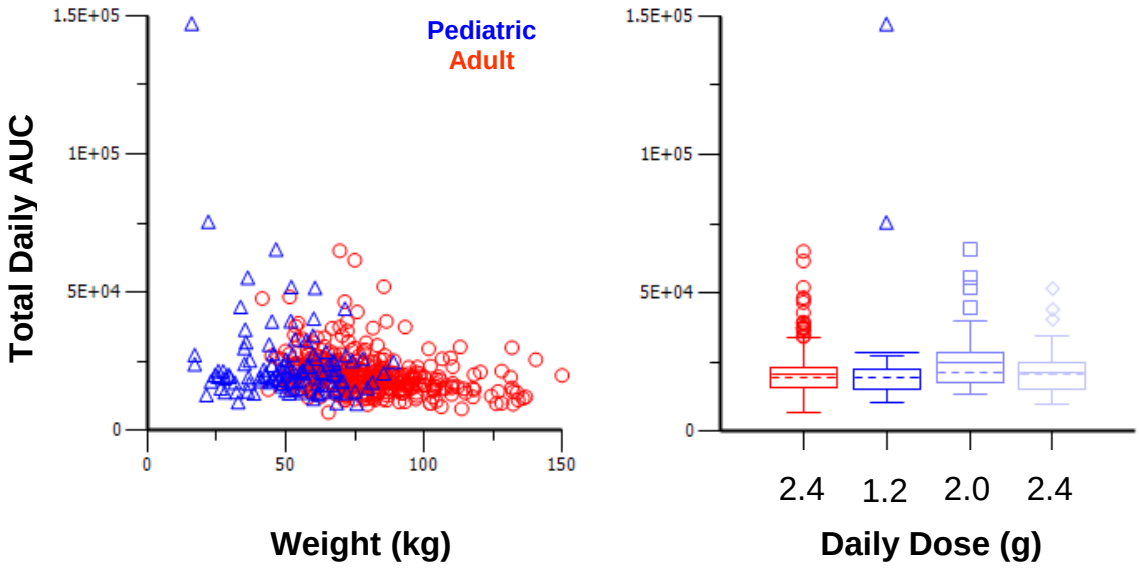


Figure 4. Individual estimated mesalamine exposures in pediatrics are comparable to those in adults based on the individuals body weight (left panel) and their daily dose (right panel).



Based on information from the Asacol HD NDA 21-830, the mean (arithmetic) steady state plasma levels of 5-ASA (Cavg) in adult patients were ~950 ng/mL following 2.4 g/day daily dose, and ~ 2000 ng/mL following 4.8 g/day daily dose of mesalamine.

In comparison, using mg/kg conversions of the approved adult doses, the Cavg values in the 30-40 mg/kg and the higher 60-80 mg/kg daily dose cohorts in the pediatric dose ranging study patients are 895 ng/ml and 2230 ng/mL, respectively. Data is from n = 8-9 patients per cohort.

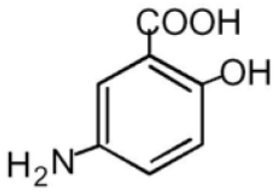
Thus Cavg values in pediatric following mg/kg/day dose equivalent to approved Asacol (30 – 40 mg/kg daily) and Asacol HD (60- 80 mg/kg daily) doses appear comparable to that noted in adults. The Cmin values appeared somewhat higher in pediatric patients.

(b) (4)

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Mesalamine (also referred to as 5-aminosalicylic acid or 5-ASA), an anti-inflammatory drug has the chemical name 5-amino-2-hydroxybenzoic acid; its structural formula is:



Molecular Weight: 153.1
Molecular Formula: $C_7H_7NO_3$

While the PREA requirement was issued under the NDA for Asacol HD® (800 mg; 21-830), the pediatric trials used Asacol® (400 mg delayed release tablets; NDA 19-651) as the age appropriate formulation.

Each Asacol delayed-release tablet for oral administration contains 400 mg of mesalamine. The Asacol delayed-release tablets (b) (4) acrylic based resin, Eudragit S (methacrylic acid copolymer B, NF), which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The mechanism of action of mesalamine 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. Mesalamine is currently approved in adults for the treatment of mildly to moderately active ulcerative colitis.

The sponsor is seeking to market Asacol for (b) (4) pediatric patients 5 years and older with mildly to moderately active ulcerative colitis.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dosing recommendation is for oral administration of 400 mg tablets for a total of 1.2 (children weighing 17 – <33 kg), 2.0 (children weighing 33 – <54 kg), or 2.4 (children weighing 54 – <90 kg) g/day broken into two administrations daily, taken with or without food for a duration of 6 weeks.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor's clinical development program included a phase 2 dose-ranging study and phase 3 trial in children aged 5 – 17 years with mild to moderately active ulcerative colitis.

Pediatric dose-ranging PK study # 2005018: This was a 28-day study designed to assess the multiple-dose pharmacokinetics of mesalamine and its metabolite N-acetyl-mesalamine. In this open label study, 5- 8 years (n = 6); 9-17 years (n = 27) pediatric and adolescent patients with mildly to moderately active UC (either newly diagnosed or previously diagnosed) were dosed with one of the three dose levels of mesalamine twice daily (q12 h) for 28 days. Asacol 400 mg tablets were used. The red-brown, capsule-shaped tablets were coated with acrylic-based resin coating, which is designed to release mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon. Patients were not enrolled if they had a history of cancer, intestinal surgery or malabsorption, or use proton-pump inhibitors or antacids, among other exclusions, or had renal insufficiency (Clcr <= 30 ml/min). Thirty-three patients were randomized across 3 dose groups: 30 mg/kg/day, 60 mg/kg/day, and 90 mg/kg/day in two divided doses. No efficacy assessments were collected during this trial. The patients took the study medication at approximately the same time each day without regard to meals. In cases where the total daily dose was an uneven number of tablets, patients took the greater number of tablets at the morning dose. Follow-up visits occurred on Day 7, Day 14, Day 21, and Day 27. Extensive sampling for PK occurred after the last dose and trough samples were obtained during interim visits.

Phase 3 pediatric trial # 2007017 (b) (4)**)**: This was a 6-week trial (b) (4) included a low and high dose group. This was a randomized, double-blind, parallel-group, 6-week study of 2 dose levels of Asacol in pediatric subjects. 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); Mild disease severity was defined as a baseline PUCAI score of 10 to 30, inclusive, whereas moderate disease severity was 35 to 55, inclusive; A total of 83 subjects were randomized (41 to the Low Dose group and 42 to the High Dose group). The low and high doses were based in part on body weight (1.2 or 2.0 g/day for 17 – <33 kg, 2.0 or 3.6 g/day for 33 – <54 kg, and 2.4 or 4.8 g/day for 54 – 90 kg). Subjects took study medication twice daily every 12 hours, at approximately the same time each day without regard to meals, for 6 weeks. Efficacy was evaluated in the phase 3 trial by the rate of treatment success as defined by the PUCAI (pediatric UC activity index) score at the end of 6 weeks of treatment. All subjects provided sparse PK samples for quantitation of 5-ASA and N-Ac-5-ASA at Weeks 3 and 6, and any time when an SAE occurred, anytime an AE suggestive of salicylate toxicity (including tinnitus) was recorded, or at the request of the Sponsor. .

Phase 3 pediatric trial # 2008085 (Maintenance of remission): Additionally, results from an incomplete trial to evaluate the maintenance of remission at 26 weeks were submitted (Study 85). The objectives of this study were to assess the safety and effiacacy

of a high and low dose of delayed release mesalamine (Asacol) given twice daily for 26 weeks in maintenance of remission of ulcerative colitis in children and adolescents. This was a randomized, double-blind, parallel-group, multi-center, 26 week study of two dose levels of Asacol 400 mg tablets in pediatric UC patients ages 5- 17 years. The doses evaluated in this maintenance study were same as those evaluated for induction of remission (Low: 1.2, 2.0, 2.4 g/day and High: 2.0, 3.6, and 4.8 g/day, stratified by BW cohorts). The trial was terminated early due to enrollment limitations. Of the 39 subjects randomized in the trial, only 19 completed (10 in the high dose group and 9 in the low-dose group).

2.2.2 What is the basis for selecting the response endpoints [i.e., clinical or surrogate endpoints or biomarkers] for dose selection and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy objective in the efficacy trials was to assess the proportion of subjects who achieved treatment success (TS) using the validated Pediatric Ulcerative Colitis Activity Index (PUCAI). PUCAI Diary Card rates the stomach/abdominal pain, rectal bleeding, diarrhea while sleeping, stool/bowel movement frequency, stool consistency, and activity level.

A treatment success (PUCAI-TS) was defined as a PUCAI score < 10 at Week 6 (indicating remission or a complete response, PUCAI-CR) or a reduction of the PUCAI score of ≥ 20 points from Baseline to Week 6 with an absolute PUCAI score ≥ 10 at Week 6 (indicating a partial response, PUCAI-PR).

Per the sponsor, PUCAI has been shown to be highly correlated with the Physician's Global Assessment, Mayo score, as well as the colonoscopic appearance and is a noninvasive, reliable, and responsive index with which to assess disease activity in pediatric UC.

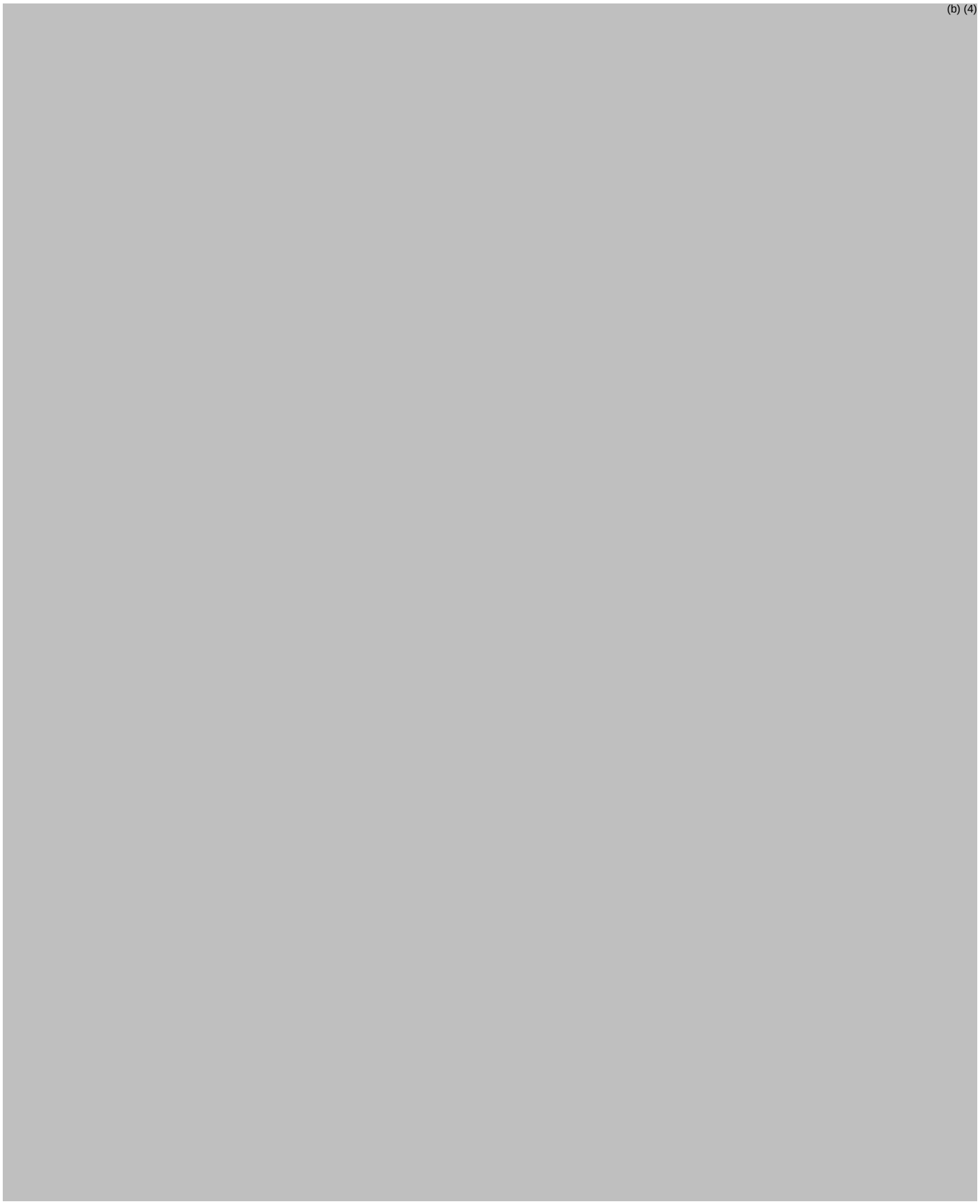
Additional efficacy objectives were to assess response based on Truncated Mayo Score (TM-Mayo; rectal bleeding and stool frequency).

An additional objective was to assess fecal biomarkers, lactoferrin and calprotectin. According to the sponsor's rationale, multiple clinical studies have reported that elevated levels of these 2 marker proteins correlate well with active UC (D'Inca et al. 2007, Kane et al. 2003, Konikoff et al. 2006). Calprotectin and lactoferrin are predominantly neutrophil proteins that are released into the intestinal lumen during inflammation. Thus, increases in intestinal inflammation result in elevated levels of calprotectin and lactoferrin in stool. Studies have shown that these fecal protein markers can be used in monitoring UC (Silberer et al. 2005). These markers decrease in subjects after treatment and increase before and during the flares.

2.2.3 Are the active moieties (parent drug and relevant metabolites) in the plasma (or other biological fluids) appropriately identified and measured to assess PK parameters and exposure-response relationships?

Mesalamine (5-ASA) and N-acetyl mesalamine (N-Ac-5-ASA) levels were adequately quantified in human plasma using validated HPLC-MS/MS methods. The nominal ranges for quantitation of the analytes are 10 to 1500 ng/mL for 5-ASA and 20 to 2500 ng/mL for N Ac-5-ASA. Methods demonstrated acceptable precision and accuracy values. Please refer to section 2.6 for additional details.

(b) (4)


(b) (4)

Biomarkers: Fecal calprotectin and lactoferrin were assessed at baseline and again at week 3 and week 6 during this pediatric efficacy trial. There was evidence of dose response with respect to the biomarkers assessed: Per sponsor,

- Reduction in fecal calprotectin levels were noted in 20 (60.6%) subjects in the Low Dose group and 22 (68.8%) subjects in the High Dose group at Week 3 and in 16 (53.3%) in the Low Dose group and 22 (75.9%) in the High Dose group at Week 6.

- Reduction in fecal lactoferrin levels were noted in 20 (60.6%) subjects in both low and high dose treatment groups at Week 3 and in 17 (56.7%) subjects in the Low Dose group and 21 (70.0%) in the High Dose group at Week 6.

- In subjects with fecal calprotectin levels above the upper limit of normal at Baseline, values had shifted into the normal range at the Final Assessment in 2 (7.1%) subjects in the Low Dose group and 4 (13.3%) in the High Dose group.

• In subjects with fecal lactoferrin levels above the upper limit of normal at Baseline, values had shifted into the normal range at the Final Assessment in 4 (14.3%) subjects in the Low Dose group and 4 (13.3%) in the High Dose group.

Table 4: Biomarker baseline information and treatment effects with low and high doses.

Fecal Biomarkers µg/g	Baseline		Week 3		Week 6	
	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose
Calprotectin	1150 (1829) N = 39	1522 (2133) N = 40	944 (1909) N = 36	1292 (3455) N = 37	696 (1071) N = 32	1218 (2454) N = 33
Mean change from baseline Calprotectin			***-238 N = 33***	***-314 (n = 36)***	***-189 (n = 30)***	***-392 (n = 33)***
Lactoferrin	471 (715) N = 39	522 (936) N = 41	505 (963) N = 36	343 (576) N = 37	438 (785) N = 32	391 (780) N = 34
Mean change from baseline in Lactoferrin			***18 N = 33***	***-222 (N = 36)***	***104 (n= 30)***	***-194 (n = 34)***

The variability in fecal biomarker data was very high. Overall, a decrease from baseline was consistently noted for calprotectin after low and high doses of mesalamine, while for lactoferrin a more consistent decrease was noted at the high dose. Dose-related (low vs. high) decreases from baseline were noted for both biomarkers at week 3 and week 6.

No definite correlations were noted between biomarkers and clinical endpoints, or biomarkers and plasma mesalamine concentrations.

2.2.4.2 What are the characteristics of the E-R relationships (dose-response, concentration-response) for *safety*?

(b) (4) [redacted]

Table 5 shows the number of safety events in the pediatric database (b) (4) [redacted]

Table 5. Treatment emergent adverse events (safety population) for study 2007017.

Preferred Term	Low Dose (N=41) n (%) nAE	High Dose (N=41) n (%) nAE	Overall (N=82) n (%) nAE
OVERALL	23 (56.1%) 50	21 (51.2%) 41	44 (53.7%) 91
Nasopharyngitis	4 (9.8%) 4	4 (9.8%) 4	8 (9.8%) 8
Colitis ulcerative	5 (12.2%) 5	2 (4.9%) 2	7 (8.5%) 7
Headache	4 (9.8%) 4	2 (4.9%) 2	6 (7.3%) 6
Dizziness	3 (7.3%) 3	1 (2.4%) 1	4 (4.9%) 4
Fatigue	1 (2.4%) 1	3 (7.3%) 3	4 (4.9%) 4
Abdominal pain upper	2 (4.9%) 5	1 (2.4%) 1	3 (3.7%) 6
Pyrexia	0 (0.0%) 0	3 (7.3%) 3	3 (3.7%) 3
Rash	2 (4.9%) 2	1 (2.4%) 1	3 (3.7%) 3
Sinusitis	3 (7.3%) 3	0 (0.0%) 0	3 (3.7%) 3
Abdominal pain	2 (4.9%) 2	0 (0.0%) 0	2 (2.4%) 2
Cough	2 (4.9%) 2	0 (0.0%) 0	2 (2.4%) 2
Diarrhoea	2 (4.9%) 2	0 (0.0%) 0	2 (2.4%) 2
Lipase increased	0 (0.0%) 0	2 (4.9%) 2	2 (2.4%) 2
Rhinorrhoea	1 (2.4%) 1	1 (2.4%) 2	2 (2.4%) 3
Upper respiratory tract infection	1 (2.4%) 1	1 (2.4%) 1	2 (2.4%) 2
Adenovirus infection	1 (2.4%) 1	0 (0.0%) 0	1 (1.2%) 1
Anaemia	0 (0.0%) 0	1 (2.4%) 1	1 (1.2%) 1
Asthenia	0 (0.0%) 0	1 (2.4%) 1	1 (1.2%) 1
Bacteriuria	1 (2.4%) 1	0 (0.0%) 0	1 (1.2%) 1
Bilirubinuria	0 (0.0%) 0	1 (2.4%) 1	1 (1.2%) 1

(Source: Sponsor's Study Report for Study 2007017, Table 26)

Urinary pthalates: Asacol formulation consists of dibutylphthalate, DBS (b) (4) excipient in its enteric coating. In the present study, sponsor assessed urinary phthalates to evaluate the systemic uptake of this moiety due to a potential safety concern. The presence of its metabolite mono-n-butyl phthalate was assessed in the urine samples of the phase 3 clinical trial in pediatric patients using a validated technique. Sponsor notes that low levels of mono butyl pthlate, were present in all human urine samples tested potentially due to environmental exposure. Note that reformulated Asacol (Delzicol, NDA 204412) does not contain this excipient.

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 (b) (4) excipient; data was highly variable and did not suggest a trend for higher uptake with higher Asacol dose:

Table 6: Summary of baseline and change from baseline in urinary phthalates

Mean ± SD	Screening	Week 6	Change from

ng/mL			Screening
Low dose	837 ± 2103	16541 ± 15579	16583 ± 16991
High dose	1290 ± 3487	11392 ± 9796	9520 ± 11214

2.2.4.3 Does this drug prolong the QT or QTc interval?

QT prolongation has not been studied for any of the mesalamine products.

2.2.4.4 Is the dose and/or dosing regimen selected by the sponsor [redacted] (b) (4)

[redacted] (b) (4)

, sponsor's proposal to label only the low dose level in pediatric UC patients appears reasonable. [redacted] (b) (4) As the mechanism of action appears to be local to the gastrointestinal tract and bioavailability is low: 1) individualized dosing is difficult and 2) effects due to body weight on exposure to the drug at the site of action are not predicted to be significant based on allometric scaling of the gut volume. See the pharmacometric review (Appendix 3) for further details.

2.2.5 What are the PK characteristics of the drug and its relevant metabolites?

2.2.5.1 What are the single dose and multiple dose PK parameters of the parent drug and its relevant metabolites in the target population?

Table 7 shows the multiple-dose results from the sponsor's dose-ranging study in children, stratified by age. Single-dose PK were not evaluated in pediatric patients. The pharmacokinetics of mesalamine and its metabolite are linear across dose-groups. However, between age groups the exposures in older patients are higher than those in the younger patients. These numbers need to be interpreted with caution as the there were only 2 in this age range in the 60 mg/kg/day group and 3 in this range in the 90 mg/kg/day group. Age was evaluated as a covariate in the population PK model and did not significantly influence the model (see the Pharmacometric Review for further details).

Table 7. Sponsor's non-compartmental analysis of the pharmacokinetic data from the dose-ranging study in pediatric (Study 2005018).

PK parameters	30 mg/kg/day		60 mg/kg/day		90 mg/kg/day	
	5-8 years (n = 0)	9-17 years (n = 7)	5-8 years (n = 2)	9-17 years (n = 8)	5-8 years (n = 3)	9-17 years (n = 7)
5-ASA						
C_{max} (ng/mL)	No data	1501.6 (441, 9050)	1419.4 (1380, 1460)	3633.5 (1980, 6840)	1801.878 (789, 3340)	4640.4 (1770, 9210)
AUC_{0-24} (ng.hr/mL)	No data	15812.67 (5383, 47752)	9585.48 (4452, 20637)	35000.54 (11477, 101508)	19479.65 (13515, 39019)	50325.13 (20167, 112036)
C_{avg} (ng/mL)	No data	658.861 (224.30, 1989.66)	399.395 (185.51, 859.88)	1458.356 (478.22, 4229.50)	811.653 (563.14, 1625.77)	2096.880 (840.31, 4668.18)
N-Ac-5-ASA						
C_{max} (ng/mL)	No data	2246.2 (953, 5360)	1116.6 (878, 1420)	3511.2 (2610, 6830)	2061.50 (1170, 3840)	4674.6 (2200, 9980)
AUC_{0-24} (ng.hr/mL)	No data	29606.98 (11937, 69384)	9896.86 (4201, 23316)	41061.72 (20358, 71617)	26977.16 (15965, 51757)	58746.20 (27584, 106728)
C_{avg} (ng/mL)	No data	1233.624 (497.39, 2891.00)	412.369 (175.04, 971.50)	1710.905 (848.23, 2984.06)	1124.048 (665.21, 2156.53)	2447.758 (1149.35, 4447.00)

Table 8: Urinary excretion data for parent mesalamine and metabolite in pediatric UC patients (Study 2005018)

% of dose excreted in urine as parent or metabolite; A'e (%)		
Age Cohort: 5- 8 years		
Dose	**5-ASA**	**N-Ac-5-ASA**
30 mg/kg (n = 1)	19.1	62.2
60 mg/kg (n = 1)	5.3	19.0
90 mg/kg (n = 3)	6.7	21.2
Age Cohort: 9- 17 years		
Dose	**5-ASA**	**N-Ac-5-ASA**
30 mg/kg (n = 7)	7.3	27.4
60 mg/kg (n = 8)	8.4	21.1
90 mg/kg (n = 7)	10.9	26.8

For PK parameters in adults, see the review by Suliman I. Al-Fayoumi, Ph.D. in DARRTS on 8/1/2005 for NDA 21830.

2.2.5.2 How does the PK of the drug and its relevant metabolites in patients with the target disease compared to that in healthy volunteers?

A comparison of the PK of mesalamine and its metabolite between healthy vs. patient populations is not available for the pediatric population. In general, the presence of

an inflamed/damaged colonic mucosa in UC may allow a greater systemic absorption of mesalamine from colonic sites in patients compared to healthy volunteers with an intact colonic mucosa. Theoretically such an increase may not persist with chronic dosing if the mucosal integrity is improved with ongoing anti-inflammatory treatment using mesalamine. The safety and efficacy implications of a potentially greater systemic exposure in UC patients are not understood.

2.2.5.3 What are the characteristics of drug absorption?

About 20% of the dose is absorbed into the systemic circulation with a Tmax occurring at about 24 hours post-dose.

2.2.5.4 What are the characteristics of drug distribution?

The apparent volume of distribution is estimated to be 4.8 L based on the reviewer's population PK model (see Appendix 3).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the primary route of elimination?

No mass balance study has been presented as part of NDA 21830.

Fecal excretion is the primary route of elimination of the drug as ~20% of the dose is absorbed into the systemic circulation.

2.2.5.6 What are the characteristics of drug metabolism?

Mesalamine is metabolized to N-acetyl-mesalamine in the gut mucosal wall and liver prior to excretion in the feces or the kidney. The systemic bioavailability of 20% was determined from a cumulative urinary excretion study.

2.2.5.7 What are the characteristics of drug excretion?

Approximately 80% of the mesalamine dose is eliminated in the fecal matter. Approximately 20% is absorbed into the systemic circulation. The systemic route of elimination is rapid acetylation to N-acetyl-mesalamine followed by excretion in the urine.

2.2.5.8 Based on PK parameters, what is the degree of linearity (dose proportionality) or nonlinearity in the dose-concentration relationship?

The pharmacokinetics of mesalamine are linear within the studied dose range of 30 – 90 mg/kg/day. See the PK results shown in section 2.2.5.1

Table 9: Dose linearity and proportionality assessment for mesalamine in pediatric UC patients of study 2005018

Dose Linearity and Proportionality for Mesalamine (5-ASA) as a Function of Total Daily Dose and Weight Adjusted Dose (PK Evaluable)						
Parameter	P-value[a]	Conclusion[b]	Slope	95% CI	P-value[c]	Conclusion[d]
Total Daily Dose (mg)						
AUC_t - $AUC_{0\text{-}24\ Hours}$ (ng*h/mL)	0.6784	Lin	1.365	(0.883,1.846)	0.1316	DP
C_{max} - Max Concentration (ng/mL)	0.8017	Lin	1.043	(0.467,1.619)	0.8785	DP
Cl_o - Oral Clearance (mL/min)	0.6784	Lin	-0.365	(-0.846,0.117)	0.1316	DI
Cl_r - Renal Clearance (mL/min)	0.3261	Lin	0.530	(0.078,0.982)	0.0234	NDI
Weight Adjusted Dose (mg/kg)						
AUC_t - $AUC_{0\text{-}24\ Hours}$ (ng*h/mL)	0.9513	Lin	0.887	(0.086,1.688)	0.7741	DP
C_{max} - Max Concentration (ng/mL)	0.7170	Lin	0.817	(0.031,1.603)	0.6357	DP
Cl_o - Oral Clearance (mL/min)	0.7107	Lin	-0.199	(-0.794,0.395)	0.4963	DI
Cl_r - Renal Clearance (mL/min)	0.0879	Lin	0.218	(-0.298,0.733)	0.3917	DI

[a] P-value is for the test of quadratic effect.
[b] Lin = linear over dose range. Nlin = nonlinear over dose range.
[c] P-value is for the test that slope parameter equals 1 for dose-dependent parameters and 0 for dose-independent parameters.
[d] DP=dose proportional over dose range. DI=dose independent over dose range.
NDP=not dose proportional over dose range. NDI=not dose independent over dose range.
(/var/opt/stat/areas/ASACOL/PK/2005018/final/analysis/dldp.sas SAS 8.2 27NOV07:15:42 f15aug07 ty1398)

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The clearance of mesalamine does not appear to change with chronic dosing. In the dose-ranging pediatric PK study 2005018, steady-state was achieved with respect to both 5-ASA and N-Ac-5-ASA by Day 7, i.e., 144 hours following the first study dose.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters of the drug and its relevant metabolites? What are the major causes of variability? What is the clinical relevance?

Mesalamine pharmacokinetics are known to be characterized by high inter- and intra-subject variability. Based on the population PK analysis described in Appendix 3, the inter-subject variability is 54% for clearance. A population model was not developed for the metabolite, as the metabolite has not shown evidence of activity. Only 2% of the inter-subject variability was explained by body weight. No other covariates were identified. Systemic uptake in patients may be influenced by location and extent of mucosal ulceration in UC, as well as the treatment of the disease with ongoing mesalamine therapy that may restrict further absorption. In healthy volunteers as well as in patients, the need for a high pH of ~7 for drug release to occur as well as the gastrointestinal transit time variability across individuals may influence the amount of drug absorbed from the intestine. (b) (4)

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

For children, body weight was the only intrinsic factor identified in the reviewer's population PK analysis. The sponsor did not evaluate intrinsic factors on pediatric PK.

Mesalamine clearance appeared to modestly increase with body weight based on the model fitting. The allometric coefficient was 0.62 and this covariate reduced the between subject variation by 2%, as determined from the population PK analysis including both pediatric and adult PK data. See the pharmacometric review (Appendix 3) for futher details.

Exploratory analyses:

UC disease severity and PUCAI: As anticipated, a higher baseline PUCAI score was evident for moderate UC vs. mild UC. Mild disease severity was defined in the protocol as a baseline PUCAI score of 10 to 30, inclusive, whereas moderate disease severity was 35 to 55, inclusive.

Within each disease category, again there was a lack of dose-response for response rates (PUCAI) [considering only the complete responders]:

Table 10. Responder analyses in pediatric patients by UC disease severity (mild vs. moderate)

Response (n)	**Mild UC**		**Moderate UC**	
Dose level	**Low**	**High**	**Low**	**High**
Responder	11	9	8	8
Partial Responder	1	1	3	4
Failure	9	9	4	5
% Complete responders	***52.3 %***	***47.3 %***	***53.3 %***	***47.05%***

Extent of UC and PUCAI: The extent of UC was available for several patients (~ n = 50); baseline PUCAI and the % change from baseline PUCAI are presented below by disease extent; Data suggests that significant changes from baseline PUCAI total are noted by week 6 of mesalamine treatment in all disease extent categories; the sample sizes in each UC extent cohorts are small and/or varied and disease extent status was unknown for several and therefore it is difficult to conclude any correlation between extent of disease and % change from baseline PUCAI:

Table 11. Baseline and % change from baseline in PUCAI by extent of disease.

Extent of Disease (N)	**Baseline Total PUCAI**	**Week 6 Total PUCAI**	**% Change from baseline PUCAI *Mean % (S.D.)***
Extensive Colitis (EXTC; 3)	41.7	5	-89 % (16)

Left-sided Colitis (LFTC; 11)	34.1	19	-34 % (62)
Pancolitis (PANC; 23)	36.5	14.3	-61 % (63)
Proctitis (PROC; 6)	33.3	4	-87 % (22)
Procto-sigmoiditis (PRSG; 6)	39.2	20	-46 % (40)
None noted? (N; 3)	33.3	2.5	-94 % (8)
Unknown (UNK; 3)	30.0	23.3	-22 % (134)

EXTC: Extensive Pancolitis (Proximal to Splenic Flexure)
LFTC: Left-Sided Colitis (Beyond Sigmoid Descending Junction up to Splenic Flexure)
PANC: Pancolitis [severe form of UC affecting entire large intestine]
PROC: Proctitis [inflammation of the anus and lining of the rectum]
PRSG: Proctosigmoiditis [inflammation of the rectum and the sigmoid colon]

Figure 8. Percentage reduction from baseline PUCAI presented by extent of disease.

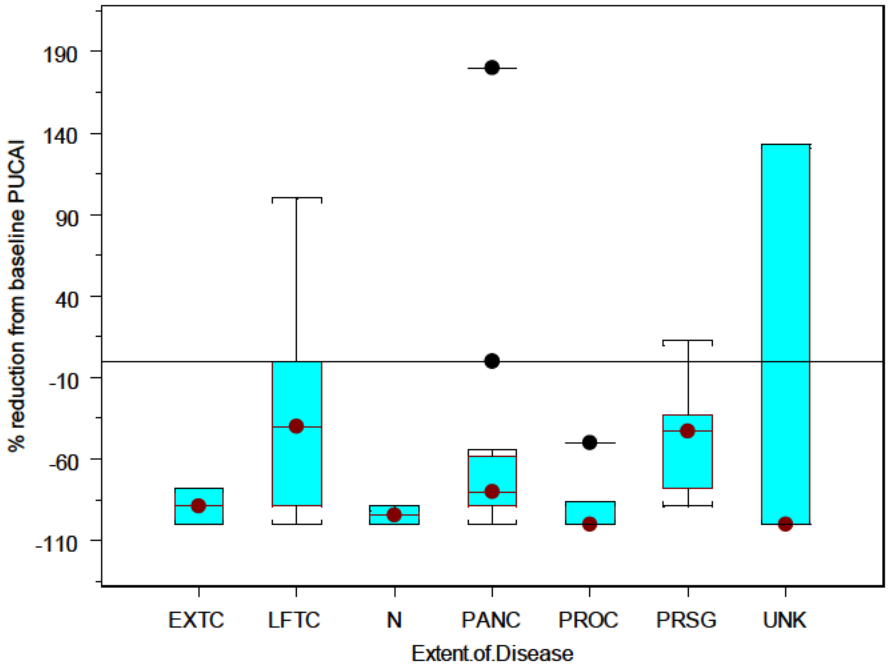
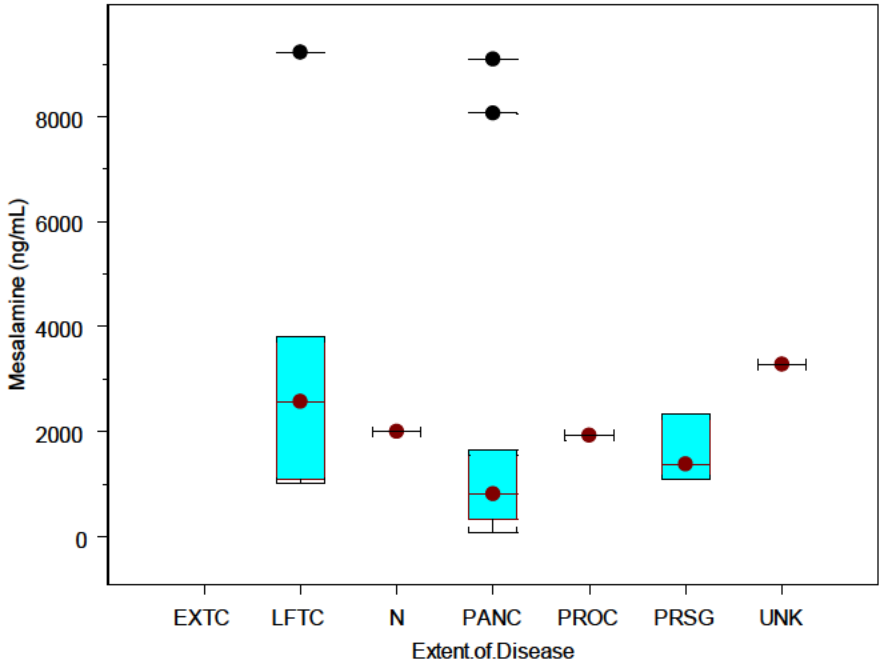


Figure 9. Average plasma mesalamine concentrations (ng/mL) by extent of disease.



Responder data (PUCAI) is summarized below by extent of disease; a clear impact of mesalamine therapy could be noted in the pancolitis group (n = 23), other disease groups are varied in the responder outcomes (sample sizes are small in these groups; in addition disease data is not available in all patients):

Table 12. Responder analyses by extent of disease (pediatric UC).

	n/N; [% All responders]	n/N; [% non-responders]	n/N; [% NA]
EXTC	2/3 [66.7 %]	0/3 [0 %]	1/3 [33.3 %]
LFTC	4/11 [36.4 %]	6/11 [54.5 %]	1/11 [9. 1 %]
PANC	16/23 [69.6 %]	4/23 [17.4 %]	3/23 [13 %]
PROC	4/6 [66.7 %]	1/6 [16.7 %]	1/6 [16.7 %]
PRSG	2/6 [33.3 %]	3/6 [50 %]	1/6 [16.6 %]

(b) (4)

, no conclusions regarding dose adjustments can be made based on systemic mesalamine exposure. This is consistent with the mechanism of action being topical and localized to the gastrointestinal tract.

Pediatric patients

This submission serves to fulfill the sponsor's PREA requirement. All studies submitted were either complete or terminated early. See Section 2.2.1 for further study details.

Renal impairment

This has not been evaluated for the Asacol products. In light of the low bioavailability and topical action of the drug, renal elimination is not the main elimination pathway nor a factor affecting response to therapy. However because of the occurrence of renal impairment in few individuals with mesalamine administration, the adult Asacol HD label states: (b) (4)

Hepatic impairment

This has not been evaluated for the Asacol products.

Approved label notes that "there have been reports of hepatic failure in patients with preexisting liver disease who have been administered mesalamine. Caution should be exercised when administering TRADENAME to patients with liver disease".

2.4 Extrinsic Factors

Drug-drug interactions: No formal drug-drug or drug-herbal interaction studies have been conducted with mesalamine products.

2.5 General Biopharmaceutics

Formulation details: Although the PREA requirement that resulted in the conduct of the present pediatric trials and submission of efficacy supplement was triggered by the approved of Asacol HD (mesalamine 800 mg delayed release tablets), the trials used Asacol 400 mg as the pediatric appropriate formulation. Hence the label for Asacol HD will include limited information in the pediatric use section but will not have an indication for pediatric UC.

The pediatric clinical trials submitted to NDA 21830/SE06 used an approved formulation, Asacol (400 mg mesalamine delayed release) tablets. Thus there were no changes to the formulation during the pediatric drug development nor there was a need for BE studies in this regard.

(b) (4)

Food-effect on PK: The pediatric supplement used the approved Asacol 400 mg delayed release tablet formulation in the clinical trials. The label for Asacol notes that drug can

be dosed without regard to food based on similar absorption of drug in fasted and fed subjects. In the pediatric UC trials, Asacol was dosed without regard to meals.

2.6 Analytical Section

Mesalamine (5 Aminosalicylic Acid (5 ASA)) and its metabolite N Acetyl 5 Aminosalicylic Acid (N Ac 5 ASA) in Human Plasma and urine were evaluated by validated Protein Precipitation and High-Performance Liquid Chromatography/Mass Spectrometry (HPLC/MS/MS) techniques. Validation was conducted at P & G pharmaceutical.

Method validation summaries:

Plasma method summary: 5-ASA and N-Ac-5-ASA and their respective stable isotope-labeled internal standards (13C6 5 ASA and D3 N Ac 5 ASA) are isolated from human plasma by a protein precipitation procedure using a 96-well format. 5 ASA and N Ac 5 ASA and their respective internal standards are then derivatized with propionic anhydride. The derivatized compounds are subjected to reverse-phase HPLC on a 3.5 micron C-18 column. Detection and quantitation are by negative ion Turbo Ion Spray ionization with multiple reaction monitoring (MRM) MS/MS conditions. Human plasma calibration standards (STD) are used to quantitate human plasma Quality Control (QC) samples and study specimens. The nominal ranges for quantitation of the analytes are 10 to 1500 ng/mL for 5 ASA and 20 to 2500 ng/mL for N Ac 5 ASA. This assay requires a 50 uL aliquot of human plasma. Sample concentrations are determined by back-calculation using a weighted (1/x2) linear regression of a calibration curve generated from spiked matrix standards.

Table 13. Summary of Validation Data for 5 ASA in Human Plasma

Type of Assay	HPLC/MS/MS
# Validation Runs	3
Specificity	No significant interferences from tested blank matrices
Goodness of Fit (Human Plasma)	Nominal Range of Std. Curve: 10 to 1500 ng/mL % Relative Error (Back Calculated Conc.) of Std Curve: -1.5% to 1.3%
Regression Algorithm	Weighted ($1/x^2$) linear regression
QC Sample Precision (LQC, MQC, HQC)	Intra-batch: 3.9% to 6.3% Inter-batch: 4.8% to 8.2%
QC Sample Accuracy (LQC, MQC, HQC)	Intra-batch: -2.7% to -0.4% Inter-batch: -2.5% to 0.3%
Stability	
Bench-top	24 hours at ambient (Reference 1)
Freeze thaw	6 cycles at -80 C nominal (Reference 1)
Process	12 days at 15°C nominal

Auto sampler	Approximately 15.7 hours (192 samples) at 15°C nominal
Long-term matrix	513 days (-80 C nominal) (Reference 2)
Aqueous stock solution	519 days (-80 C nominal) (Reference 2)
Aqueous spiking solution	Not Applicable. Prepare fresh.

Table 14. Summary of Validation Data for N Ac 5 ASA in Human Plasma:

Type of Assay	HPLC/MS/MS
# Validation Runs	3
Specificity	No significant interferences from tested blank matrices
Goodness of Fit (Human Plasma)	Nominal Range of Std. Curve: 20 to 2500 ng/mL % Relative Error (Back Calculated Conc.) of Std Curve: -1.6% to 2.7%
Regression Algorithm	Weighted ($1/x^2$) linear regression
QC Sample Precision (LQC, MQC, HQC)	Intra-batch: 4.3% to 6.4% Inter-batch: 4.9% to 8.0%
QC Sample Accuracy (LQC, MQC, HQC)	Intra-batch: -1.5% to 1.6% Inter-batch: -3.1% to 1.0%
Stability	
Bench-top	24 hours at ambient (Reference 1)
Freeze thaw	6 cycles at -80 C nominal (Reference 1)
Process	12 days at 15°C nominal
Auto sampler	Approximately 15.7 hours (192 samples) at 15°C nominal
Long-term matrix	473 days (-80 C nominal) (Reference 2)
Aqueous stock solution	519 days (-80 C nominal) (Reference 2)
Aqueous spiking solution	Not Applicable. Prepare fresh.

Urine Assay Procedure: 5-ASA and N-Ac-5-ASA in human urine along with the added isotopically labeled internal standards are derivatized with propionic anhydride. The derivatized analytes and internal standards are then subjected to reverse-phase HPLC on a 3.5 micron C-18 column. The analytes and internal standards are detected and quantitated by mass spectrometry operating under multiple reaction monitoring (MRM) MS/MS conditions. Quantitation is by ratio of peak area of each analyte to its isotopically labeled internal standard. The concentration of the analytes in samples is predicted from a weighted regression of a calibration curve of spiked matrix standards. The lower limit of quantitation is approximately 0.05 ug/mL for 5-ASA and 0.15 ug /mL for N-Ac-5-ASA using a 50 uL urine sample.

Table 15. Summary of Validation Data for 5 ASA in Human Urine.

Type of Assay	HPLC/MS/MS
# Validation Runs	3
Specificity	No significant interferences from tested blank matrices
Goodness of Fit (Human Urine)	Nominal Range of Std. Curve: 0.05 – 10 µg/mL % Relative Error (Back Calculated Conc.) of Std Curve: -6.3% to 2.6%
Regression Algorithm	Weighted ($1/x^2$) linear regression
QC Sample Precision (LQC, MQC, HQC)	Intra-batch: 3.4% to 17.8% Inter-batch: 3.9% to 12.3%
QC Sample Accuracy (LQC, MQC, HQC)	Intra-batch: -4.7% to 11.4% Inter-batch: -2.0% to 6.6%
Stability	
Bench-top	4 hours at ambient
Freeze thaw	3 cycles at -20°C nominal (Reference 2)
Process	8 days at 15°C nominal
Auto sampler	Approximately 14.6 hours at 2-8°C
Long-term matrix	252 days (-80°C nominal)
Aqueous stock	519 days (-80°C nominal) (Reference 3)
Aqueous spiking solution	Not Applicable. Prepare fresh.

Table 16. Summary of Validation Data for N Ac 5 ASA in Human Urine

Type of Assay	HPLC/MS/MS
# Validation Runs	3
Specificity	No significant interferences from tested blank matrices
Goodness of Fit (Human Urine)	Nominal Range of Std. Curve: 0.15 – 150 µg/mL % Relative Error (Back Calculated Conc.) of Std Curve: -4.5% to 2.8%
Regression Algorithm	Weighted ($1/x^2$) quadratic regression
QC Sample Precision (LQC, MQC, HQC)	Intra-batch: 3.3% to 21.4% Inter-batch: 4.7% to 14.0%
QC Sample Accuracy (LQC, MQC, HQC)	Intra-batch: 7.8% to 11.9% Inter-batch: 6.4% to 7.0%
Stability	
Bench-top (ambient)	4 hours at ambient
Freeze thaw	3 cycles at -20°C nominal (References 1 and 2)
Process	8 days at 15°C nominal
Auto sampler	Approximately 14.6 hours at 2-8°C
Long-term matrix	252 days (-80°C nominal)
Aqueous stock	519 days (-80°C nominal) (Reference 3)

Aqueous spiking solution	Not Applicable. Prepare fresh.

Analytical report review for study 2005018 (plasma and urine samples- quantitation of mesalamine and metabolite):

The primary objective of this clinical study was to characterize mesalamine (5-aminosalicylic acid; 5-ASA) pharmacokinetics following 28 days of oral administration of 30 mg/kg, 60 mg/kg, or 90 mg/kg of mesalamine, given in divided doses every 12 hours as Asacol 400 mg tablets, to patients with ulcerative colitis who are 5 to 17 years of age.

Plasma:

To support this clinical study, the Bioanalytical Section of Procter & Gamble Pharmaceuticals analyzed 482 human plasma specimens for 5-ASA and N-Ac-5-ASA using a validated high performance liquid chromatographic mass spectrometric (LC/MS/MS) method. The present report includes the plasma 5-ASA and N-Ac-5-ASA concentrations obtained for the study specimens as well as results from the standard and quality control samples that were analyzed with the specimens.

Specimen collection time to final specimen analysis (maximum duration):
5-ASA: 302 days
N-Ac-5-ASA: 218 days
Documented frozen (at or below-70°C) stability of analyte(s):
5-ASA: 513 days
N-Ac-5-ASA: 473 days

%RE statistics determined during sample analysis and method validation follows

	Specimen Analysis	Method Validation (ref. 4)
Analyte(s)	%RE (accuracy)	%RE (accuracy)
5-ASA	-6.7% to 5.5%	-2.0% to 1.5%
N-Ac-5-ASA	-7.0% to 5.7%	-2.4% to 4.9%

The coefficients of determination (r2) for 5-ASA and N-Ac-5-ASA were greater than 0.991.

Accuracy and precision for QC samples in the specimen analyses runs (as compared to validation results):

	Specimen Analysis	
Analyte(s)	%RE (accuracy)	%CV (precision)
5-ASA	-6.3% to -2.5%	3.1% to 11.7%
N-Ac-5-ASA	-5.5% to 4.4%	3.1% to 12.0%

	Method Validation (ref. 4)	
Analyte(s)	%RE (accuracy)	%CV (precision)
5-ASA	-5.6% to -4.1%	2.9% to 4.6%
N-Ac-5-ASA	-2.0% to -0.6%	2.4% to 3.6%

Urine:

To support this clinical study, the Bioanalytical Section of Procter & Gamble Pharmaceuticals analyzed 150 human urine samples for 5-ASA and N-Ac-5-ASA using a validated high performance liquid chromatographic mass spectrometric (LC/MS/MS) method. The present report includes the urine 5-ASA and N-Ac-5-ASA concentrations obtained for the study specimens as well as results from the standard and quality control samples that were analyzed with the specimens.

Storage temperature: At or below -70°C
Longest individual specimen collection time to final specimen analysis: 207 days
Documented frozen (at or below -70°C) stability of analyte(s):
5-ASA: 252 days
N-Ac-5-ASA: 252 days

%RE statistics determined during sample analysis and method validation follows.

	Specimen Analysis	Method Validation
Analyte(s)	%RE (accuracy)	%RE (accuracy)
5-ASA	-2.0% to 3.0%	-6.3% to 2.6%
N-Ac-5-ASA	-6.1% to 4.0%	-4.5% to 2.8%

The coefficients of determination (r2) for 5-ASA were greater than 0.993 and N-Ac-5-ASA were greater than or equal to 0.997.

QC samples in the runs:

	Specimen Analysis		Method Validation	
Analyte(s)	%RE (accuracy)	%CV (precision)	%RE (accuracy)	%CV (precision)
5-ASA	-3.8% to 6.4%	1.5% to 11.5%	-2.0% to 6.6%	3.9% to 12.3%
N-Ac-5-ASA	0.8% to 2.5%	3.8% to 5.0%	6.4% to 7.0%	4.7% to 14.0%

Analytical report for phase 3 clinical trial 2007017:

Plasma: The overall objective of this study is 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 mildly-to-moderately active ulcerative colitis.

A total of 147 specimens were collected in this study. Of these 147 specimens, 147 were analyzed.

Storage temperature: At or below -70°C

Maximum duration between specimen collection time and specimen analysis: 492 days
Documented frozen (at or below -70°C) stability of analyte(s):

5-ASA: 513 days
N-Ac-5-ASA: 513 days

%RE statistics determined during sample analysis and method validation follows.

	Specimen Analysis	Method Validation
Analyte(s)	%RE (accuracy)	%RE (accuracy)
5-ASA	-3.1% to 4.8%	-2.0% to 1.5%
N-Ac-5-ASA	-6.1% to 7.7%	-2.4% to 4.9%

The coeffients of determination (r2) for 5-ASA and N-Ac-5-ASA were greater than 0.984.

Quality control samples:

	Specimen Analysis		Method Validation	
Analyte(s)	%RE (accuracy)	%CV (precision)	%RE (accuracy)	%CV (precision)
5-ASA	2.5% to 4.2%	10.2% to 11.7%	-5.6% to -4.1%	2.9% to 4.6%
N-Ac-5-ASA	0.0% to 7.8%	7.6% to 9.7%	-2.0% to -0.6%	2.4% to 3.6%

Incurred Sample Re-Analysis: For 5-ASA 93.3% of the samples were within 30 % of the original assay and for N-Ac-5-ASA 86.7% were within 30 % of the original assay. This meets the SOP defined acceptance criteria for incurred sample analysis.

Method validation and sample assay reports for 5-ASA and its metabolite in plasma and urine samples of pediatric patients in studies 2005018 and 2007017 are acceptable.

VALIDATION OF A METHOD FOR THE DETERMINATION OF MONO-BUTYL PHTHALATE IN HUMAN URINE BY SOLID PHASE EXTRACTION AND HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY (HPLC/MS/MS)

Mono-n-butylphthalate and its stable-isotope-labeled internal standard $^{13}C_4$ mono-n-butylphthalate) are isolated from human urine by a solid phase extraction procedure using a 96-well format. The analyte(s) and internal standard(s) are subjected to reverse-phase high performance liquid chromatographic (HPLC) analysis; detection and quantitation are by mass spectrometry operating under multiple reaction monitoring (MRM) MS/MS conditions. Calibration standards (STD) are prepared in water and are used to quantitate human urine Quality Control (QC) samples and unknown human urine specimens. The nominal range of quantitation is 2 to 2000 ng/mL. QC samples were of 6, 150, 1500 ng/ml concentrations. The assay requires a 0.4 mL aliquot of human urine. Specimen concentrations are determined by back-calculation using a weighted ($1/x^2$) quadratic regression of a calibration curve generated from standards in water.

A significant amount of mono-n-butylphthalate is excreted as a glucuronide. Samples are treated with -glucuronidase to deconjugate the glucuronide metabolite. This assay reports the total amount of mono-n-butylphthalate. 4-methylumbelliferyl glucuronide is added to samples, standards, and QCs. The formation of 4-methylumbelliferone is monitored to ensure that the deconjugation reaction is sufficiently complete.

Table 17. Summary of validation data for mono-n-butylpthalate in human urine is presented:

	Results			Acceptance Criteria/Specifications
Goodness of Fit (Table 1.1)	Actual Range of Standard Curve: 2 to 2000 ng/mL Accuracy (%RE): -3.8 % to 5.5 %			• Curve contains at least 6 unique non-zero standards. • ≥67% of the standards analyzed must meet the accuracy (%RE) criteria. • LLOQ Std: -20% ≥ %RE ≤ +20%; All other Stds: -15% ≥ %RE ≤ +15%.
Intra-run QC Sample + (Table 2.1)		Accuracy (%RE)	Precision (%CV)	LLOQ QC samples: -20% ≥ %RE ≤ +20% -20% ≥ Mean %RE ≤ +20% and ≤20%CV LQC, MQC, HQC, ULOQ QC samples: -15% ≥ %RE ≤ +15% -15% ≥ % Mean RE ≤ +15% and ≤15%CV Each Concentration: ≥ 50% of QC samples must meet the above precision and accuracy criteria Same precision and accuracy criteria for mean data as above. Overall: ≥67% of total no. of QC samples must meet the above precision and accuracy criteria
	L, M, H *	-11..3 % to 8.5 %	0.7 % to 9.4 %	
	LLOQ	1.3 to 6.3%	2.3 % to 3.0 %	
	ULOQ	-3.5 % to -1.0 %	4.3 % to 11.0 %%	
Inter-run QC Sample (Table 2.1)		Accuracy (%RE)	Precision (%CV)	
	L, M, H *	-6.0 % to 5.9 %	1.7 % to 5.7 %	
	LLOQ	4.1 %	3.3 %	
	ULOQ	-2.5 %	6.9 %	
Dilution Integrity (DQC) (Table 2.1)	Intra-run Accuracy (%RE): -5.6% to 2.0 % Intra-run Precision (%CV): 1.6 to 2.9 % Inter-run Accuracy (%RE): -0.8 % Inter-run Precision (%CV): 4.2 %			• For ≥50% of the DQC samples, -20% ≥ %RE ≤ +20% • -20% ≥ Mean %RE ≤ + 20% and ≤ 20%CV

Stability		
Process	3 days 21 hours at ~15 °C	The reinjected batch must meet batch acceptance criteria (Goodness of Fit and Intra-run QC Sample).
Autosampler	~32 hrs (192 injections) at ~15 °C	Batch must meet acceptance criteria (Goodness of Fit and Intra-run QC Sample).
Benchtop (Table 3.1)	24 hours (ambient)	LQC and HQC stability samples: -15% ≥ %RE ≤ +15% -15% ≥ % Mean RE ≤ +15% and ≤15%CV Each Concentration: ≥ 50% of stability QC samples must meet the above precision and accuracy criteria Overall: ≥67% of total no. of stability QC samples must meet the above precision and accuracy criteria
Freeze-thaw (Table 4.1)	4 cycles at or below -70 °C/Ambient	LQC and HQC stability samples: -15% ≥ %RE ≤ +15% -15% ≥ % Mean RE ≤ +15% and ≤15%CV Each Conc.: ≥ 50% of stability QC samples must meet the above precision and accuracy criteria Overall: ≥67% of total no. of stability QC samples must meet the above precision and accuracy criteria
Standard stock (in acetonitrile)	36 days at ~4 °C and at or below -70 °C	• The mean area ratios of the freshly prepared solution and the stored solution should agree within ± 10%. • %CV of each set of values must be ≤ 15%
Aqueous standards	34 days at or below-70 °C.	• The mean area ratios of the freshly prepared solution and the stored solution should agree within ± 10%. %CV of each set of values must be ≤ 15%
Long-term matrix	24.8 days at or below -70 °C.	• For each QC level, the final analyte concentration is within ±15% of the original with 90% confidence as assessed by a two-sided 90% confidence interval evaluation. • The reported duration of stability is the minimum duration of stability for all QC levels tested. • The reported duration of stability ≤ duration of QC sample storage.

* - Accuracy and Precision based on LQC, MQC and HQC Samples (L, M, H)
+ - Based on ME run, 2-Feb-2009

Background levels of MBP: Sponsor notes that low levels of mono butyl pthlate, a metabolite of the widely used plasticizer dibutylphthalate were present in all human urine samples tested. Sponsor notes that this is to be expected due to environmental exposure. Final QC concentrations were corrected for the residual level of MBP in the pooled urine. Thus assay specificity requirement was not part of the validation plan. Special precautions were taken to minimize further MBP levels due to contamination.

Sample assay for mono-n-butyl phthalate: Dibutylphthalate (DBP) is (b) (4) in the enteric coating for Asacol tablets. The presence of its metabolite mono-n-butyl phthalate was assessed in the urine samples of the phase 3 clinical trial in pediatric patients using a validated technique described above.

3 DETAILED LABELING RECOMMENDATIONS

Asacol HD Label

APPENDICES (SUPPORTING MATERIALS)

APPENDIX 1. Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

(b) (4)

The current guidelines for pediatric ulcerative colitis by ECCO and ESPGHAN societies recommend 60 – 80 mg/kg/day[1]. Of the two doses levels studied in trial 2007017, the low dose was comparable to 30 – 60 mg/kg/day while the high dose was comparable to 60 – 110 mg/kg/day.

[1] Turner D, et. al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr*. 2012 Sep;55(3):340-61.

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(b) (4)

1.1.2 Are mesalamine PK in children at the proposed dose with UC similar to that in adults with the approved dose?

Yes, the population PK model suggests that systemic pediatric exposures after the proposed dose of 1.2, 2.0, or 2.4 g/day (depending on body weight) would produce exposures comparable to the low dose regimen in adults (2.4 g/day). Figure 3 shows the population predicted mean AUC by body weight and daily dose, without considering between subject variability. Figure 4 shows the estimated AUC values by body weight and daily dose for the studied population accounting for between subject variability. This latter plot suggest that when accounting for PK variability in the population that the range of exposures are quite comparable between pediatrics and adults at the proposed doses.

Figure 3. Predicted mesalamine exposures in pediatrics are comparable to those in adults after the sponsor's proposed dosing based on the individuals body weight (left panel) and their daily dose (right panel).

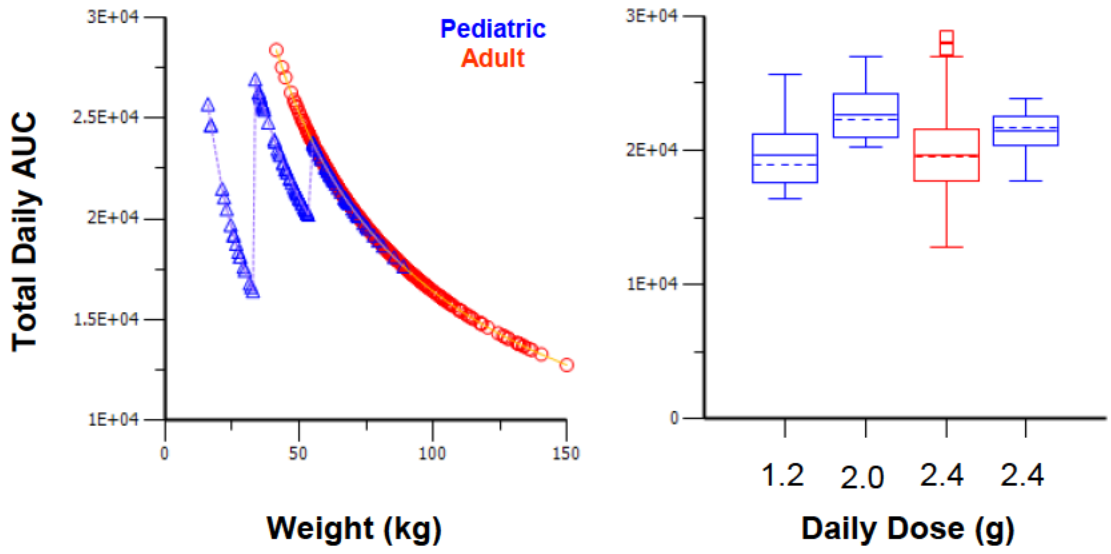
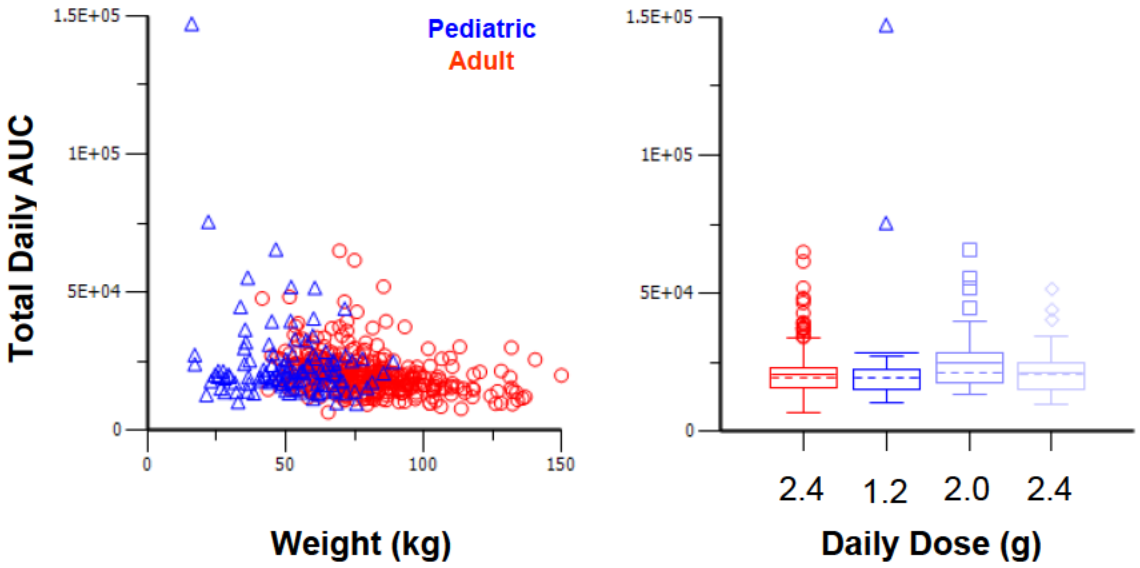


Figure 4. Individual estimated mesalamine exposures in pediatrics are comparable to those in adults based on the individuals body weight (left panel) and their daily dose (right panel).



(b) (4)

1.2 Recommendations

The Office of Clinical Pharmacology, Division of Pharmacometrics has review this application and found it to be approvable (b) (4). We recommend the approval of lower dose (see Table 1) in pediatrics (b) (4).

Table 1. Proposed Pediatric Dosing

Body Weight Range (kg)	Total Daily Dose (g/day)	Total Daily Dose in mg/kg
17 – < 33	1.2	36 - 71
33 – < 54	2.0	37 - 61
54 – < 90	2.4	27 - 44

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2 PERTINENT REGULATORY BACKGROUND

Asacol® and Asacol HD® delayed release tablets of 400 and 800 mg mesalamine have been approved for use in adults for the treatment of moderately active ulcerative colitis. With the approval of Asacol HD in 2005, the sponsor was required to fulfill a PREA requirement of conducting a study in pediatrics and developing an age appropriate formulation. With this submission, the sponsor is providing the results of this study to fulfill their PREA requirement and is seeking the indication (b) (4) in pediatric patients with moderately active ulcerative colitis.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Clinical Trials

3.1.1 Dose Ranging Phase 2 Study 2005018 – Pediatrics

This was 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 400 mg delayed-release tablets given every 12 hours for 28 days to children and adolescents with active ulcerative colitis. 33 patients completed the study with 9, 12, and 12 children in the 30, 60, and 90 mg/kg/day dose groups, respectively. Pharmacokinetic samples were collected on days 1, 15 and 27 – 28. No efficacy assessments were collected.

3.1.2 Phase 3 Induction of Remission Study 2007017: Pediatrics

This was a randomized, double-blind, parallel-group study to assess the safety and efficacy of Asacol (1.2 to 4.8 g/day) administered as 400 mg delayed-release tablets given every 12 hours for 6 weeks to children and adolescents with mildly-to-moderately active ulcerative colitis. 83 subjects were randomized to receive either low dose (1.2, 2.0, or 2.4 g/day depending on body weight, n=41) or high dose asacol (2.0, 3.6, or 4.8 g/day depending on body weight, n=42). Dose amounts were assigned by body weight so the youngest pediatrics would not be overdosed. These categores were 17 - <33 kg, 33 – <54 kg, and 54 - < 90 kg and correspond to the dose amounts listed above (e.g. low dose patient between 17 and 33kg received 1.2 g/day). The primary efficacy endpoint was to assess the proportion of subjects who achieved treatment success (PUCAI-TS) using the validated Pediatric Ulcerative Colitis Activity Index (PUCAI) at six weeks. A treatment success (PUCAI-TS) was defined as a PUCAI score < 10 at Week 6 (indicating remission or a complete response, PUCAI-CR) or a reduction of the PUCAI score of ≥ 20 points from Baseline to Week 6 with an absolute PUCAI score ≥ 10 at Week 6 (indicating a partial response, PUCAI-PR). There was no difference in the rate of treatment success between the low and high dose in children (Table 2). Pharmacokinetic samples were collected at week 3 and week 6.

Table 2. Sponsor's Primary Efficacy Analysis Results for Study 2007017.

Treatment Outcome	Low Dose (N = 41) n (%)	High Dose (N = 41) n (%)	Total (N = 82) n (%)	p-value [a]	High - Low Dose Difference in Success Rates [b]	95% Confidence Interval for High - Low Dose[c]
Success	23 (56.1%)	22 (55.0%)	45 (55.6%)			
Failure	18 (43.9%)	18 (45.0%)	36 (44.4%)			
Total	41	40	81	0.9240	-1.1	(-22.7, 20.5)

3.1.3 Phase 3 Maintenance of Remission Study 85: Pediatrics

This was a 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. Low and high doses were the same as for study 2007017. The study was terminated early due to lack of enrollment. There were 21 children who completed the trial with 90% of subjects in both treatment groups maintaining remission at week 26.

3.1.4 Phase 3 Study 2000082 – Asacol HD (Adults)

This was a double-blind, randomized, 6-week, parallel-group designed trial to assess the safety and efficacy of asacol 4.8 g/day (800 mg tablet) versus asacol 2.4 g/day (400 mg tablet) for the treatment of moderately active ulcerative colitis. 386 patients were randomly assigned to either the 2.4 g/day or 4.8 g/day treatment groups in a 1:1 parallel group design. The primary efficacy endpoint was the percentage of patients with moderate disease at baseline whose treatment outcome at Week 6 was classified as treatment success (as defined by a UCDAI and physicians global assessment score), which showed a statistically significant difference favoring 4.8 g/day over 2.4 g/day (72% versus 59%, respectively; p = 0.036).

Results of this trial supported approval of asacol HD (800 mg) tablets in 2005 and further details can found in the clinical pharmacology review by Suliman I. Al-Fayoumi, Ph.D. in DARRTS on 8/1/2005. For the purposes of this review, results of this trial were utilized to evaluate the exposure-response relationship in adults.

3.2 Sponsor's Justification for Dose

3.2.1 Selection of the Doses studied in the Pediatric Phase 3 Clinical Trials:

The sponsor based their dose selection on three criteria:

(b) (4)

[2] Turner D, et. al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr*. 2012 Sep;55(3):340-61.

(b) (4)

The following text is their dose selection rational for their phase 3 studies in pediatrics.

(b) (4)

3.2.2 Proposed Dose for Labeling:

The following is the sponsor's conclusions regarding their proposed dose for labeling:

(b) (4)

3.3 Reviewer's Comments:

Results of the trial in adults 2000082 suggest that the high dose was more effective than the low dose. This is different from the lack of dose-response observed in pediatrics. The efficacy endpoint between the two populations differed by the inclusion of an endoscopic assessment in the adult trial. The pediatric efficacy endpoint did not include an endscopic assessment. Therefore it is difficult to compare these results directly.

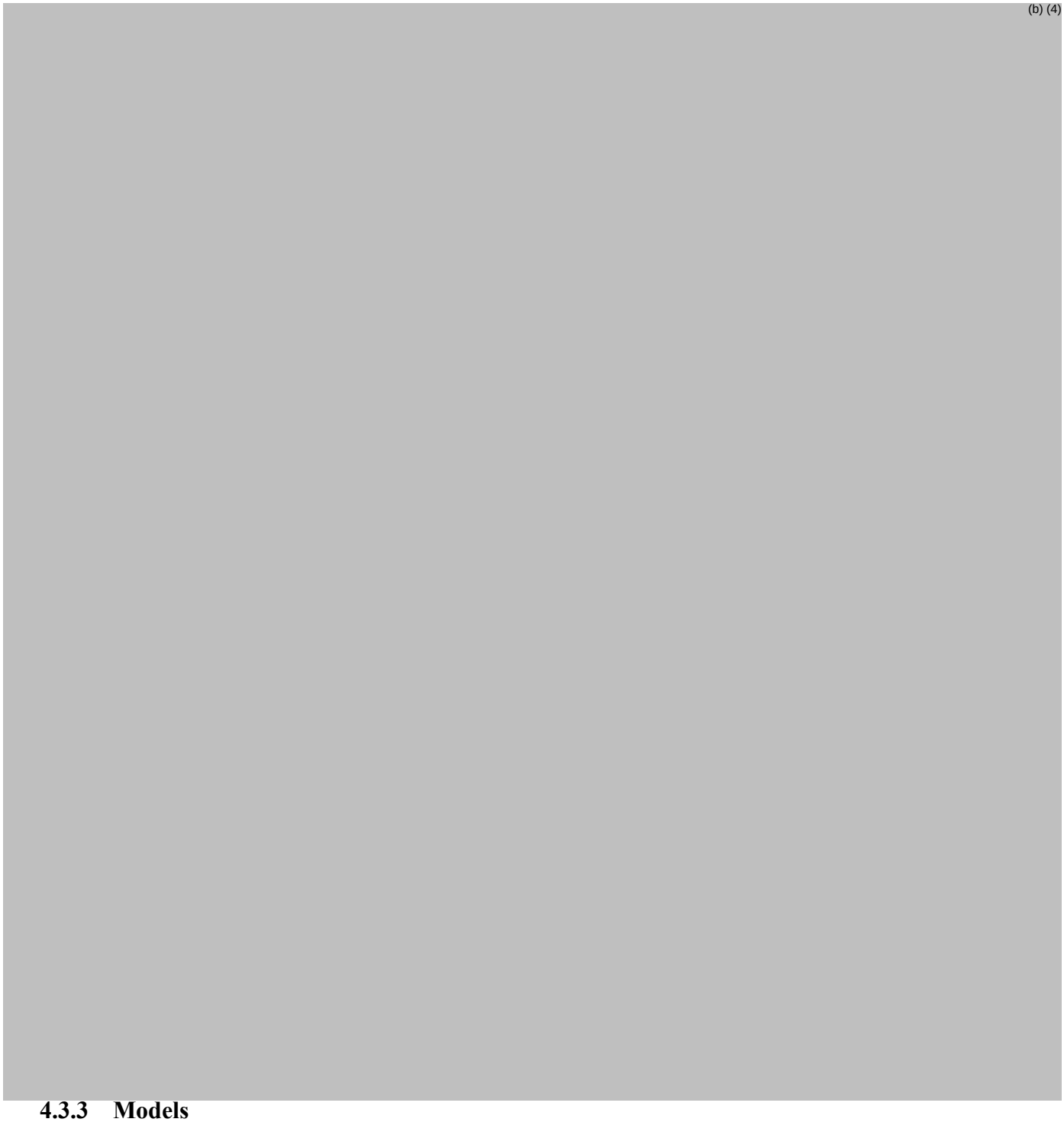
The sponsor did not conduct a population PK analysis and evaluate the effects of body weight on the PK. Additionally the sponsor did not evaluate exposure-response relationships for plasma mesalamine or metabolite concentrations or gut concentrations with the rate of remission. Neither of these analyses were conducted for both pediatrics and adults. Without these relationships taken into consideration, the sponsors proposed dose is acceptable.

See section 4 for details on these analyses by the reviewer.

4 REVIEWER'S ANALYSIS

4.1 Introduction

(b) (4)



4.3.3 Models

A population PK models was developed for both pediatric and adults mesalamine data. This model was utilized to estimate individual plasma AUC values for exposure-response analyses.

The NLME package of Phoenix was used to develop these models.

4.3.3.1 Data

Pharmacokinetic data from pediatric studies 2005018 and 2007017 and adult trials 2000082 were utilized to construct the population PK models. Data from study 2005018 included rich sampling from three dose levels (30, 60, and 90 mg/kg) while data from studies 2007017 and 2000082 were sparse sample collection with ~2-3 samples per subject (baseline, week 3, and week 6).

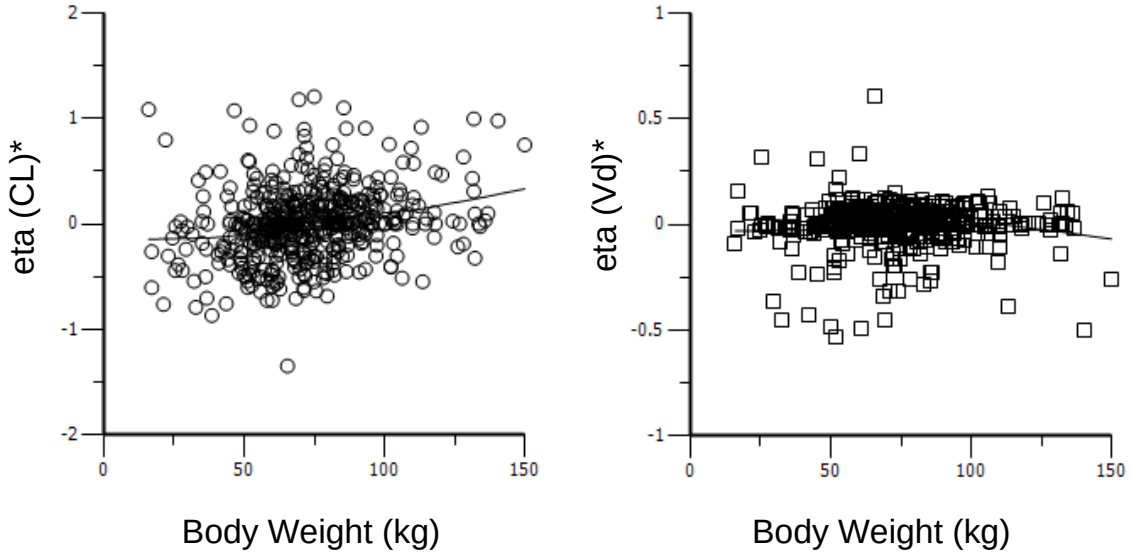
4.3.3.2 Structural Model

Both 1-compartment and 2-compartment linear models were applied with 1st order absorption. The data supported the use of the 1-compartment model as there was no visual evidence of a second compartment and the addition of the second compartment did not significantly influence the model. Further estimates of the peripheral volume of distribution tended towards zero for the 2-compartment scenario.

4.3.3.3 Covariate Evaluation

The covariate evaluation only explored the effect of body weight, as the aim of this analysis was to capture the PK of each individual and use the individual's post hoc estimates of CL to calculate steady-state AUC values for the exposure-response analysis. In this case, body weight had a significant effect mesalamine clearance. The reduction in the -2LL was 78 and the allometric coefficient on clearance using a power function centered about the median body weight was 0.62. The reduction in the between-subject variation of CL was only 2%.

Figure 5. Body weight is correlated with clearance (left panel) and not volume of distribution (right panel). *Results shown are from the base pharmacokinetic model with no covariates included.



4.3.3.4 Final Model

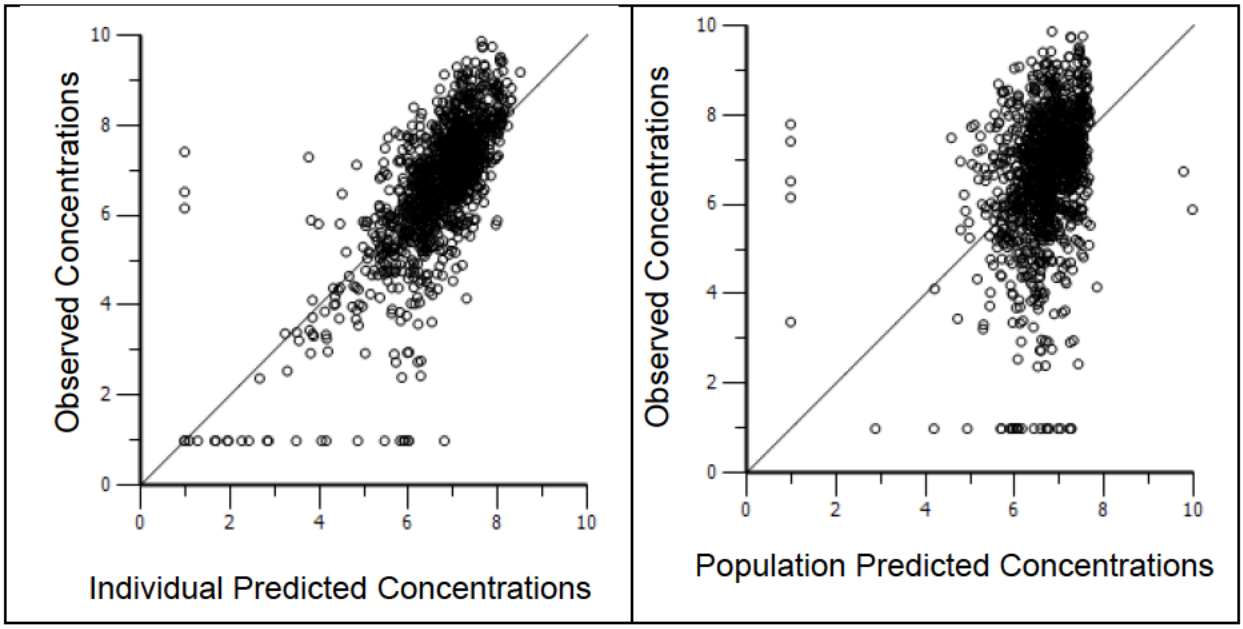
The final model used for the calculation of individual AUC values in studies 2007017 and 2000082 was a 1-compartment linear model with first order absorption and body weight as a covariate only on CL. Model parameters are shown in Table 4. Goodness of fit plots are shown in Figure 6. It is apparent that the highest concentrations are underpredicted by the model. This

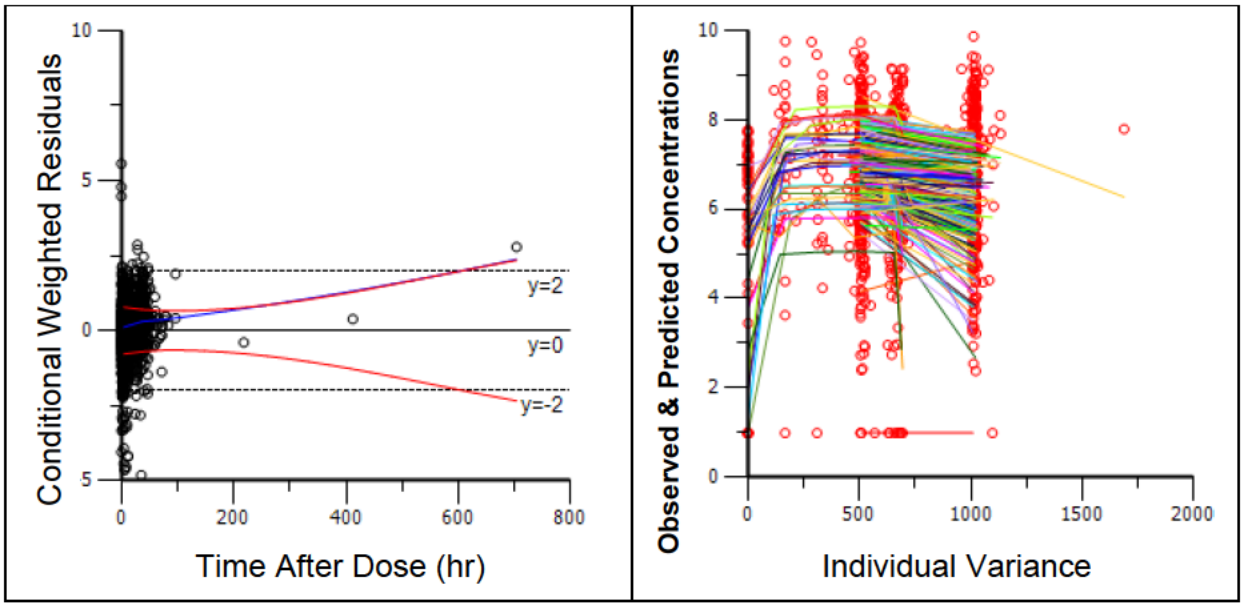
is particularly relevant when basing conclusions on C_{max} and is often common for population PK models. The utility of the population PK model was to generate AUC values for the exposure response analysis. As AUC is related to CL and the bias in the higher concentrations relates to Vd, this bias should not influence the results of the exposure-response analysis.

Table 4. Pharmacokinetic Parameters of the Final Mesalamine Population PK Model for both Pediatric and Adult UC Patients.

Parameter	Final Estimate	CV% for Between-Subject Variability
Ka (1/hr)	1.42	32
CL/F (L/hr)	0.118	5.7
Vd/F (L)	4.84	15
Wt Coefficient on CL	0.622	20

Figure 6. Goodness of fit plots for the final population PK model.





4.4 Results

(b) (4)

The response metrics used were the Probability of Remission at week 6. For pediatric subjects, this was assessed by the PUCAI score. In adults efficacy was assessed by the Ulcerative Colitis Disease Activity Index and the physicians global assessment. The major difference between these two scores is that the PUCAI score did not include an endoscopic assessment of the disease. A treatment success based on PUCAI was defined as a PUCAI score < 10 at Week 6 or a reduction of the PUCAI score of ≥ 20 points from Baseline to Week 6 with an absolute PUCAI score ≥ 10 at Week 6.

For both pediatrics and adults, the exposure-response relationship for the probability of treatment success was evaluated by logistic regression on either plasma mesalamine AUC values or predicted gut concentrations.

4.4.1.1 Pediatrics

Results are shown in Section 1.1.1

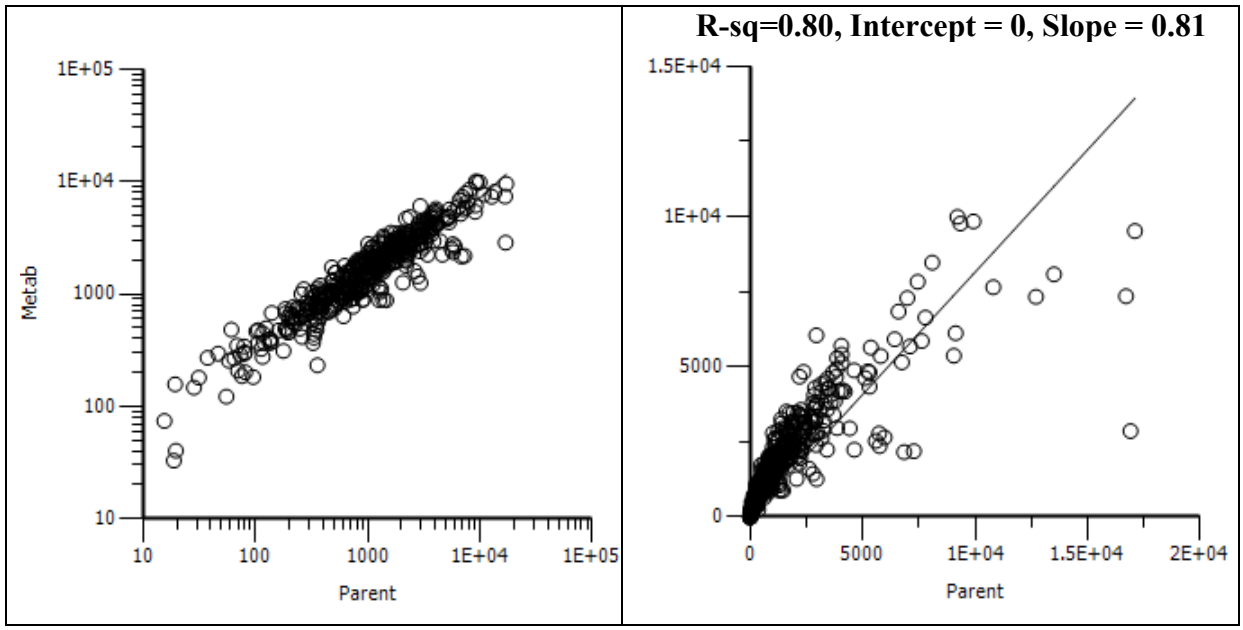
4.4.1.2 Adults

Results are shown in Section 1.1.1

4.4.1.3 Metabolite Exposure – Response

(b) (4) the question was raised whether the metabolite could be correlated with the rate of remission. However, Figure 7 shows that the metabolite concentrations are highly correlated with the parent concentrations. Therefore, no exposure response relationship is expected with the metabolite.

Figure 7. Metabolite concentrations are highly correlated with mesalamine concentrations. Left panel shows the correlation on logarithmic axes while the right panel shows the correlation on the linear axes.



(b) (4)

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
PedPopPKData.SSC	Population PK Dataset Construction	\Reviews\PM Review Archive\2013\AsacolHD_NDA21830_JCE\PPK Analyses
Asacol Pop PK (June13).phxproj	Exposure-Response Analysis Code	\Reviews\PM Review Archive\2013\AsacolHD_NDA21830_JCE\ER Analyses
PKDiagnost_ERPucai.S	Population PK Diagnostics	\Reviews\PM Review

		Archive\2013\AsacolHD_NDA21830_JCE\ER Analyses

APPENDIX 2. OCP 21st Century Review Filing Checklist

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21830/ Supplement 6**	**Brand Name**	**Asacol HD**
OCP Division (I, II, III, IV, V)	**DCPIII**	**Generic Name**	**Mesalamine Delayed Release Tablets**
Medical Division	**DGIEP**	**Drug Class**	**Non-Steroidal Anti-Inflammatory**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Pediatric Ulcerative Colitis**
OCP Team Leader	**Sue Chih Lee, Ph.D.**	**Dosage Form**	**Delayed Release Tablets**
Pharmacometrics Reviewer	**Justin Earp, Ph.D.**	**Dosing Regimen**	**TBD**
Date of Submission	**12/21/2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**08/21/2013**	**Sponsor**	**Warner Chilcott**
Medical Division Due Date	**09/16/2013**	**Priority Classification**	**Standard**
PDUFA Due Date	**10/21/2013**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**3**		
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				**Pediatric Trials: 2005018 (dose-ranging, 28 day dosing study in 5-17 years patients);** **Primary efficacy trial 2007017 (limited PK)**
single dose:				
multiple dose:	**X**			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	**X**			**Study 2005018**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**			**Pediatric efficacy supplement**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**			**Exploratory Biomarkers: fecal lactoferrin and fecal calprotectin**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				**Primary efficacy 2007017; descriptive presentation of data; Pharmacometrics Division has been consulted**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**3**		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			Depends on their plan	The pediatric trials were conducted using approved Asacol 400 mg tablets that have the potentially unsafe excipient DBP. If they plan to eventually market the DBP free 400 mg formulation for children as well, then we already have data to demonstrate bioequivalence of a 400 mg DBP-free capsule formulation to approved 400 mg Asacol in adult volunteers (NDA 204412). If they develop a different, perhaps age appropriate formulation for children (e.g. 4x100 mg tablets in capsule) then we will need another BE study in adults to demonstrate that the new pediatric

					formulation will be BE to the 400 mg Asacol tablets used in these pediatric trials. Plans for a new pediatric formulation are not proposed in this (b) (4) supplement (b) (4).
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Label will provide same DDI and metabolism information as the approved product in adults
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Study 2005018 has PK information in pediatric patients; data in ages 5-8 years seems to be limited; subject to review.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			Validation reports for analytical methodologies will be requested
5	Has a rationale for dose selection been submitted?	X			Pending review of NDA data
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			(b) (4) ; based on text in the NDA summaries, sponsor appears to propose dosing based on body weight categories (range 1.2 – 2.4 mg/day); pending review
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-	X			Dose/efficacy, dose/biomarkers and dose/safety trends are described (b) (4) Pharmacometrics discipline is involved as

	Response guidance?				well.
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			Age, and body weight were assessed with respect to their relationship to systemic exposure; Pending review
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			Study 2007017 appear to satisfy PMR issued under NDA 21830 approval; Pending review
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			PMR under PREA; Appears that studies were conducted as per PMR requirements for NDA 21830; pending final review; adequacy of the pediatric formulation may need to be reviewed if indication if granted.
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

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

Information Requests:

Clinical Pharmacology: For each of the three analytes measured in this trial (5-ASA, N-acetyl metabolite and mono-n-butyl phthalate) submit the following: 1) Method validation reports of each analyte in the biological matrices of interest, 2) Study sample assay reports.
If already submitted, provide us with the exact location of these reports in the electronic submission.

Sandhya Apparaju, Ph.D.

Reviewing Clinical Pharmacologist Date

Sue Chih Lee, Ph.D.

Team Leader/Supervisor Date

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

/s/

JUSTIN C EARP
09/13/2013

SANDHYA K APPARAJU
09/13/2013

SUE CHIH H LEE
09/13/2013

NITIN MEHROTRA
09/13/2013