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APPLICATION NUMBER:

204412Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW - ADDENDUM

NDA#:	**204-412 (eCTD 0017)**
Submission Date:	1/4/2013
Generic Name:	Mesalamine Delayed-Release Capsules
Formulation:	Capsules
Strength:	400 mg
Applicant:	Warner Chilcott
Reviewer:	John Duan, Ph.D.
Submission Type:	Applicant's Response to FDA's IR

REVIEW'S ADDENDUM

Background: NDA 204-412 submitted on 7/31/2012, provides a new dosage form, mesalamine delayed-release capsules 400 mg (using dibutyl sebacate as plasticizer) to replace the currently marketed Asacol 400 mg tablets, which has dibutyl phthalate as excipient. To support the approval of the formulation change, the NDA included a bioequivalence study (reviewed by Office of Clinical Pharmacology) and in vitro dissolution studies.

Review: This review is an addendum to the Original Biopharmaceutics Review # 1 dated 12/28/12 in DARRTS.

In Biopharmaceutics Review #1, approval for the NDA was recommended with a pending post marketing commitment (PMC) issue (i.e., submission of additional dissolution data to set the final dissolution acceptance criteria). This issue was conveyed to the Applicant in an Information Request (IR) dated 12/12/12. There were additional communications between the Applicant and FDA on 12/14/12, 12/20/12, and 1/4/13.

This addendum to the original Biopharmaceutics review includes the specific details for the Biopharmaceutics PMC (i.e., collection of the dissolution data needed for setting the final acceptance criteria of the dissolution testing).

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 204-412 for Mesalamine Delayed release Capsules is recommended for approval with the following post-marketing commitment.

Post Marketing Commitment

Warner Chilcott agrees to the following post marketing commitment to further evaluate the dissolution specification and submit a supplement to the NDA.

- Collect additional dissolution profile data (including the additional 75 min timepoint, n=12) from the stability batches at the scheduled time points and from at least (b) (4) batches

manufactured during the first year after action date. These data will be used for the setting of the final dissolution acceptance criteria.

- Provide a report with the complete dissolution information/data under a supplement to the NDA within (b) (4) from action date.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
Team Leader
ONDQA Biopharmaceutics

cc: NDA 204-412/*Darrts, R. Lostritto*

APPENDIX I. Biopharmaceutics Evaluation

1. Introduction

NDA 204-412 provides mesalamine delayed-release capsules, 400mg as a new dosage form. The proposed indication and dosing regimen are the same as the approved Asacol (mesalamine) delayed-release tablets, 400 mg under NDA 19-651. The new dosage form is to address the Agency's concern related to the potential safety issue of dibutyl phthalate (DBP) as an excipient in Asacol products. In the new formulation (WC3045 capsules) dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the plasticizer dibutyl sebacate (DBS) and the tablet is then encapsulated.

In the original Biopharmaceutics Review #1 signed in DARRTS on 12/28/2012, the following information/data were reviewed.

- A multipoint dissolution profile comparison performed between WC3045 capsules and Asacol (mesalamine) delayed-release tablets, 400 mg, over a range of pH values (pH 4.5, 6.0, 6.5, 6.8, 7.2 and 7.5) along with the similarity factors (f2) values.

- An in vitro alcohol induced dose dumping study.

- A comparison between the clinical formulation and the to-be-marketed formulation.

- The dissolution methodology and acceptance criteria.

An approval was recommended in Biopharmaceutics Review #1, with a pending issue regarding the agreement of the post marketing commitment. The Applicant's proposed a post marketing commitment for the acceptance criterion of dissolution testing at pH 7.2. The Agency accepted the proposal and recommended a new timeline.

The current submission (eCDT 0017) dated 1/4/13 provides the final response from the Applicant.

2. Communication History

The following is a list of communications between the Agency and the Applicant.

1) Agency Request (e-mail sent on December 12, 2012)

1. The dissolution data provided in your NDA appear to support the acceptance criterion of Q=80% at 75 minutes in the medium of pH 7.2 using the proposed dissolution conditions (USP II, 50 rpm). We recommend that you implement this criterion and provide the revised specification table for your drug product

2) Warner Chilcott Response (e-mail sent on December 14, 2012):

Our team discussed the Agency's request to revise the specification for dissolution testing at pH7.2 from 90 minutes to 75 minutes. The proposed dissolution specification (90 minutes) in

NDA 204412 is based on USP <711> mesalamine delayed-release tablets and the specifications of the current approved Asacol and Asacol HD tablets. The dissolution testing is also a part of the stability testing, and 90 minute time point is reported in the stability study based on the proposed specification. There are no stability dissolution testing data at 75 minutes to support changing dissolution testing at pH7.2 from 90 minutes to 75 minutes.

Warner Chilcott acknowledges the Agency's suggestion to change dissolution testing at pH7.2 from 90 minutes to 75 minutes. We propose to collect stability dissolution data at the 75 minute time point at pH7.2, make an evaluation and report these data to the Agency (b) (4) If the stability data supports changing the dissolution testing at pH7.2 from 90 minutes to 75 minutes, the specification of the dissolution will be revised accordingly.

3) Agency Feedback (December 20, 2012 E-mail):

We acknowledge that limited dissolution data are available for your new product. Therefore, we agree to accept your proposal with the following conditions.

a. The proposed acceptance criteria for dissolution of mesalamine delayed release capsules listed below are accepted on an interim basis.

- *0.1N HCl (Type II Paddle 100 RPM, 2 hrs): No individual value exceeds 1% dissolved*
- *pH 6.0 (Type II Paddle 100 RPM, 1 hr): No individual value exceeds 1% dissolved*
- *pH 7.2 (Type II Paddle 50 RPM): Q=80% at 1.5 hrs*

b. You commit to collect additional dissolution profile data (including the additional 75 min timepoint, n=12) from the stability batches at the scheduled timepoints and from (b) (4) batches manufactured during the first year after action date. These data should be used for the setting of the final dissolution acceptance criteria.

c. You commit to provide a report with the complete dissolution information/data under a supplement to the NDA within (b) (4) from action date.

Based on the above, please propose a Phase IV commitment in your planned 12/19/12 submission.

4) Warner Chilcott Response (current submission January 4, 2013):

Warner Chilcott appreciates the Agency's feedback on the specification for dissolution testing and we understand that the following proposed specification, presented in the original NDA section 3.2.9.5, is unchanged.

- 0.1N HCl (Type II Paddle 100 RPM, 2 hrs): No individual value exceeds 1% dissolved
- pH 6.0 (Type II Paddle 100 RPM, 1 hr): No individual value exceeds 1% dissolved
- pH 7.2 (Type II Paddle 50 RPM): Q=80% at 1.5 hrs

Warner Chilcott agrees to the following post marketing commitment to further evaluate the dissolution specification and submit a supplement to the NDA.

Post Marketing Commitment

- Collect additional dissolution profile data (including the additional 75 min timepoint, n=12) from the stability batches at the scheduled time points and from at least (b) (4) batches manufactured during the first year after action date. These data will be used for the setting of the final dissolution acceptance criteria.

- Provide a report with the complete dissolution information/data under a supplement to the NDA within (b) (4) from action date.

The Reviewer's Comment:
In the 1/4/13 submission the Applicant accepted the FDA's post marketing commitment timelines. Therefore, an agreement between the FDA and the Applicant has been reached.

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

/s/

JOHN Z DUAN
01/11/2013

ANGELICA DORANTES
01/12/2013

ADDENDUM TO OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204412	Submission Date(s): 08/01/2012, 09/06/2012, 09/18/2012, 09/14/2012, 10/31/2012, 11/27/2012
Brand Name	To be determined
Generic Name	Mesalamine Delayed Release Capsules
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Warner Chilcott
Relevant IND(s)	26,093
Submission/Review Type	Original NDA; Priority Review
Formulation; Strength(s)	Delayed Release Capsules; 400 mg
Indication	Ulcerative Colitis

An optional intra-divisional level OCP briefing was held for NDA 204412 on December 19, 2012 from 1-2 PM in Room 3300 of Building 51 (White Oak). Attendees at this briefing included Drs.' Hae Young Ahn, Sue Chih Lee, Dilara Jappar, Kristina Estes and Sandhya Apparaju.

Overall Recommendation: NDA 204412 is acceptable from a Clinical Pharmacology perspective.

Background for the Review Addendum: NDA 204412 submitted on 08/01/2012 proposed a new mesalamine delayed release capsule formulation to eventually replace the currently marketed Asacol (mesalamine delayed release) 400 mg tablet formulation that has dibutyl phthalate as plasticizer. The new 400 mg formulation instead uses dibutyl sebacate as the plasticizer in the enteric coating. NDA included in vitro dissolution studies (reviewed by ONDQA biopharmaceutical group) and pivotal bioequivalence study (reviewed by Office of Clinical Pharmacology) to support the formulation change. The Clinical Pharmacology review of the original NDA has found the data presented to be acceptable pending outcomes of the Office of Scientific Investigations (OSI) inspections of the clinical and bioanalytical sites for the pivotal BE study PR08210. A Clinical Pharmacology review was thus entered into DARRTS on 12/20/2012 signed off by Drs' Apparaju and Lee.

Introduction to the Review Addendum: This addendum to our original Clinical Pharmacology addresses the OSI inspection related findings and makes final recommendations regarding NDA acceptability from a Clinical Pharmacology perspective. The final review and recommendations by OSI were entered into DARRTS on 01/08/2012 and are attached to this review as an appendix. One clinical site related issue [for Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX (WCTEPS)] and five issues related to the bioanalytical site (b) (4)

[(b) (4)] were identified during the inspections and FDA-Form 483s (Voluntary Action Indicated, VAI) were accordingly issued by OSI during their investigations. Subsequent to their review of sponsor's responses to these deficiencies, OSI has concluded that four of these issues to be adequately resolved. For these issues and information pertaining to their satisfactory resolution, please see OSI review in appendix to this review addendum. For two other issues (discussed further below), OSI recommended that the Office of Clinical Pharmacology review team review the issues and the sponsor's responses in this regard so as to make our own conclusions regarding data acceptability.

OCP Review and Recommendations Pertaining to OSI Findings and Sponsor-Responses:

Item 1: Deficiency noted by OSI in the FDA-Form 483 issued to Clinical site WCTEPS:

1. Failure to ensure that an investigation was conducted in accordance with the protocol for study #PR-08210. Specifically, protocol section 12.1, "PK blood sampling and processing," said that "the time between sample collection and placement in the freezer is not to exceed 60 min." However, the following deviations were observed in the clinical investigator files:
   - Subject 507319, (b) (6) Period 3, Sample at 30 hr was withdrawn at 12:18 but plasma was not frozen until 15:13, a period of 175 min after withdrawal.
   - Subject 507344, (b) (6) Period 1, Sample 12 hr was withdrawn at 18:43 but plasma was not harvested or shipped to the analytical lab for analysis.
   - Subject 507345, (b) (6) Period 1, Sample 24 hr was withdrawn at 06:44 but without documentation of when plasma was frozen.
   - Subject 507355, (b) (6) Period 4, Sample 4 hr was withdrawn at 10:54 but without documentation of when plasma was frozen.
   - Subject 507355, (b) (6) Period 4, Sample 6 hr was withdrawn at 12:54 but without documentation of when plasma was frozen.
   - Subject 507376, (b) (6) Period 2, Sample 36 hr was withdrawn at 19:15 but without documentation of when plasma was frozen.
- Subject 507393, (b) (6) Period 1, Sample 2 hr was withdrawn at 09:32 but without documentation of when plasma was frozen.
- Subject 507396, (b) (6) Period 3, Sample 10 hr was withdrawn at 17:35 but without documentation of when plasma was frozen.

Sponsor's response (in brief) regarding the clinical site issue: WCTEPS strives to maintain complete adherence to the protocol without deviation unless required for the safety and/or welfare of the subject. When deviations occur, WCTEPS takes steps to address and correct these deviations. Prior to the inspection, all of the deviations for the 7728 PK samples, including the findings noted above, were documented on the source document (Blood Harvest Logs) and were already recognized as deviations and documented on the protocol deviation log.
Concentration-time profiles reported in the final report for these subjects did not illustrate any obvious anomalies at the time in question for these samples omitted from the blood harvest logs.

OSI recommendation: The data generated from the following samples cannot be assured:

(b) (6)

- o Subject 507345 Period 1, Sample 24 hr
- o Subject 507355 Period 4, Sample 4 hr
- o Subject 507355 Period 4, Sample 6 hr
- o Subject 507376 Period 2, Sample 36 hr
- o Subject 507393 , Period 1, Sample 2 hr
- o Subject 507396 Period 3, Sample 10 hr

OCP reviewer's findings regarding the sample storage issue at WCTEPS: As highlighted in the data tables below, out of 6 samples indicated by OSI for which time of placement of samples in frozen storage after collection has not been documented, 5 had values below the limit of quantitation, BLQ and were supported by similar BLQ findings in samples before or after this time point. In one sample, where detectable drug levels were noted, the concentration-time profile in that individual did not signal anything out of ordinary with the inclusion of data from the indicated sample.

OCP review conclusion: Reviewer believes that the lack of documentation of sample storage time after collection for these 6 samples at WCTEPS has not affected the sample and data integrity. No further action is needed and data can be accepted without revisions.

Supportive data for clinical site issue (item 1 of this review): Yellow highlighted data in the tables below indicates the samples in question:

Table 14.2.1.2: Individual subject plasma mesalamine concentration data following replicate single-dose oral administration of a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

			Plasma mesalamine concentrations (ng/mL) by time (h) postdose														
Subject	Seq.	Period	0	2	3	4	5	6	7	8	10	12	14	16	24	30	36	48
507334	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	12.5	<10.0	21.6	36.8	60.1	56.8	75.8	95.8	153	93.8
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	25.0	95.5	92.0
507335	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	62.6	1889	246	122	356	152	94.3	26.3	16.6	15.6	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	491	453	341	182	32.4	67.1	27.1	<10.0
507336	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	82.2	180	450	389	238	112	71.1	19.2	17.3	13.7	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	70.8	522	220	107	317	371	194	49.7	31.1	16.9	11.6
507337	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	11.4	107	906	591	138	60.5	15.9	<10.0	<10.0	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	33.2	21.5	31.1	11.5	24.0	<10.0	10.7
507338	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	11.9	<10.0	<10.0
507339	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	47.2	104	20.6	22.9	12.1	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	143	149	88.8	32.9	45.1	38.2	<10.0
507340	B	2	<10.0	<10.0	<10.0	<10.0	18.2	203	385	325	152	77.6	50.4	27.4	<10.0	<10.0	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	27.5	54.4	43.8	243	105	49.6	15.8	33.6	<10.0	<10.0
507341	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	24.5	44.1	87.8	131	168	180	76.4	42.1	46.8	32.3
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	46.3	21.5	<10.0
507342	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	940	2436	377	318	133	49.0	<10.0	<10.0	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	678	518	280	197	81.5	<10.0	<10.0	<10.0	<10.0
507343	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	16.9	37.9	36.7	32.8	36.6	44.7	78.4	32.9
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	27.7	99.1	146	120	59.6	24.6
507344	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	67.8	318	64.6	<10.0		25.9	17.9	<10.0	<10.0	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	21.6	29.9	14.2	12.6	<10.0	<10.0
507345	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	28.8	114	146	109	94.2	67.3	13.8	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	93.5	2587	1798	227	101	62.9	38.2	<10.0	<10.0	10.2	<10.0

Table 14.2.1.2: Individual subject plasma mesalamine concentration data following replicate single-dose oral administration of a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

			Plasma mesalamine concentrations (ng/mL) by time (h) postdose															
Subject	Seq.	Period	0	2	3	4	5	6	7	8	10	12	14	16	24	30	36	48
507346	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
507347	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	31.4	138	95.7	69.2	43.8	<10.0	<10.0	<10.0	<10.0
507348	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	130	104	77.9	29.8	31.6	16.7	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	21.8	94.8	89.7	61.3	84.2	61.8	34.4
507349	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	81.3	111	68.9	52.8	40.9	21.8	15.9	22.5	12.4
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	35.0	188	194	133	148	48.0	18.7	13.9	<10.0	<10.0
507350	B	2	<10.0	<10.0	<10.0	<10.0	10.5	30.3	30.7	52.7	97.3	232	228	136	32.9	26.3	15.3	<10.0
	B	4	<10.0	<10.0	<10.0	34.7	3175	4263	2125	771	94.4	25.3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
507351	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	79.2	92.8	126	127	104	50.4	29.1	21.8	15.5	14.0	<10.0	<10.0	<10.0
507352	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	14.7	16.6	12.7	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
507353	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	24.0	70.6	56.9	53.5	14.6	11.5	<10.0	<10.0
	A	3	33.6	42.4	34.8	33.5	34.9	43.5	41.2	38.4	35.0	34.9	34.3	32.9	14.6	62.1	52.8	34.8
507354	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	31.4	96.9	132	95.5	53.3	65.3	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
507355	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	26.3	28.3	<10.0	134	132	74.5	30.0	<10.0	17.3	13.1	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	16.7	13.9	18.5	21.5	19.0
507356	B	2	<10.0	<10.0	<10.0	<10.0	19.8	26.5	558	778	564	337	163	57.0	18.1	<10.0	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	25.8	307	249	196	82.7	<10.0	<10.0	<10.0
507357	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	51.8	49.9	20.9	65.4	25.7	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	31.9	<10.0	63.8	57.8	18.1	22.9	18.2	<10.0
507358	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0

Table 14.2.1.2: Individual subject plasma mesalamine concentration data following replicate single-dose oral administration of a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

			Plasma mesalamine concentrations (ng/mL) by time (h) postdose															
Subject	Seq.	Period	0	2	3	4	5	6	7	8	10	12	14	16	24	30	36	48
507384	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	25.5	15.4	<10.0	13.9	12.5	15.6
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	40.7	39.0	21.3
507385	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	87.9	260	142	90.9	48.4	19.3	14.2	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	10.0	70.8	141	161	194	64.3	10.2	<10.0	<10.0	<10.0
507386	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	44.3	165	204	145	92.4	40.9	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	288	151	353	224	141	74.9	<10.0	<10.0	<10.0	<10.0
507387	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	61.3	140	85.6	31.4	16.3	<10.0	<10.0	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
507388	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	40.3	240	384	91.0	29.8	15.4	14.3	10.4	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	148	154	425	550	405	174	68.7	20.7	19.6	<10.0	<10.0
507389	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	15.6	<10.0	36.8	133	106	88.8	49.5	14.1	<10.0	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	12.2	<10.0	<10.0	<10.0	<10.0	23.6	13.5	15.2	<10.0
507390	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
	B	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	42.7	41.2	14.8
507391	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	38.3	1019	445	138	183	46.2	21.6	<10.0	<10.0	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	20.7	12.4	<10.0	24.5	19.6	11.9
507392	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	161	187	200	83.2	58.7	30.7	38.5	31.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	14.7	28.7	312	464	468	299	118	64.1	31.0	33.8	<10.0	<10.0
507393	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	33.7	88.7	73.2	108	76.4	51.5	25.6	17.0	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	29.5	29.0	181	179	85.7	21.9	11.9	<10.0	<10.0
507394	B	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	51.7	138	132	52.0	29.7	18.5	<10.0
	B	4	<10.0	<10.0	11.8	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	187	188	176	86.3	70.9	<10.0	<10.0
507395	A	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	77.5	124	95.6	62.4	29.3	17.3	17.7	<10.0	<10.0
	A	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	48.7	163	118	62.7	74.0	40.4	12.6	21.9	15.5	<10.0

Table 14.2.1.1: Individual subject plasma mesalamine concentration data following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) to fasted healthy volunteers, Study PR-08210

			Plasma mesalamine concentrations (ng/mL) by time (h) postdose														
Subject	Seq.	Period	0	2	3	4	5	6	7	8	10	12	14	16	24	30	36	48
507370	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	76.6	75.1	80.3	100	44.3	36.1	27.6
507371	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	576	289	23.4	39.2	42.3	96.2	14.8	15.2	10.7	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	48.0	24.8	<10.0	<10.0	43.4	46.3	55.6	23.4	21.4	12.9	<10.0
507372	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	20.4	41.0	51.4	16.3	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	67.5	124	13.3	<10.0
507373	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	54.9	86.6	77.2	58.9	42.2	21.6	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	18.3	99.1	122	104	103	67.2	33.8	39.7	27.1	<10.0
507374	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	110	79.5	136	45.8	20.3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	12.8	26.0	41.7	54.3	71.0	59.8	40.4	16.2	11.1	<10.0	<10.0	<10.0	<10.0
507375	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	15.9	79.6	78.3	22.2	<10.0	<10.0	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	13.3	42.2	33.5	19.9	13.3	12.8	10.1
507376	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	131	129	78.8	36.8	<10.0	<10.0	<10.0	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	69.7	57.6	49.6	49.2
507377	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	17.6	196	274	242	107	145	109	31.4
507378	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	58.3	168	88.5	65.1	25.0	12.7	12.4	10.6	13.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	47.7	116	213	96.6	48.6	41.1	52.1	12.9	10.4	<10.0
507379	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	42.7	45.2	52.9	45.8	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	27.2	750	354	201	97.0	54.9	34.0	<10.0	10.4	<10.0	<10.0
507380	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	21.2	14.4	151	77.1	75.1	61.5	21.0	<10.0	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	25.4	20.0	137	440	478	298	207	91.6	11.5	12.4	<10.0	<10.0
507381	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	32.5	83.1	62.7	37.1	<10.0	<10.0	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	116	113	78.5	34.4
507382	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	98.6	99.0	28.0	<10.0	<10.0	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	23.8	113	119	79.0	36.9	41.0	39.1	12.0

Table 14.2.1.1: Individual subject plasma mesalamine concentration data following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) to fasted healthy volunteers, Study PR-08210

			Plasma mesalamine concentrations (ng/mL) by time (h) postdose														
Subject	Seq.	Period	0	2	3	4	5	6	7	8	10	12	14	16	24	30	36	48
507395	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	88.8	143	212	156	49.5	16.4	14.7	15.9	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	18.6	<10.0	<10.0	11.0	55.8	57.7	29.3	13.7	10.9	<10.0	<10.0
507396	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	188	246	211	144	175	91.7	57.1	10.6	<10.0	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	36.1	34.2	57.8	<10.0	<10.0	<10.0
507397	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	17.5	104	91.1	85.0	78.3	116	71.9	20.4
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	20.5	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
507398	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	25.6	104	128	114	63.6	35.5	23.0	<10.0	<10.0	<10.0	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	18.3	<10.0	32.4	26.4	13.2
507399	B	1	<10.0	<10.0	<10.0	25.3	<10.0	128	463	380	160	80.3	56.0	36.2	10.2	15.3	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	19.0	51.1	81.4	57.2	62.6	48.4	34.9	19.7	<10.0
507400	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	141	96.5	167	147	37.1	18.9	27.6
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	30.0	19.9	28.1	64.2	109	54.0	22.6
507401	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	12.3	110	55.7	22.4	24.4
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
507402	B	1	<10.0	<10.0	<10.0	13.1	<10.0	10.9	406	520	375	214	90.7	38.1	11.3	<10.0	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	34.0	33.7	26.1	27.1	20.5	<10.0	<10.0	<10.0	<10.0
507403	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	11.5	39.8	162	90.9	40.3	38.1	10.9	<10.0	<10.0	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	56.8	245	219	125	58.8	44.6	15.2	11.4	<10.0	<10.0
507404	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	20.9	29.6	55.4	14.5	<10.0	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	14.7	24.7	19.1	65.6	329	133	139	59.9	<10.0	<10.0	<10.0
507405	A	2	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	345	868	360	290	194	42.6	<10.0	<10.0	<10.0	<10.0
	A	4	<10.0	<10.0	<10.0	<10.0	13.0	523	177	192	204	49.1	17.3	12.1	<10.0	<10.0	<10.0	<10.0
507406	B	1	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	158	38.5	69.3	146	142	85.7	11.4	<10.0	<10.0	<10.0
	B	3	<10.0	<10.0	<10.0	<10.0	<10.0	640	1027	189	84.0	82.0	51.9	25.1	14.2	13.8	12.2	20.2

Item 2: Issue #3 noted in the FDA-Form 483 for the bioanalytical site (b) (4)):

#3. Failure to apply the changed chromatographic integration parameters in 2 samples in runs #54 and 74 to all samples in the respective runs

Sponsor's response to OSI: This finding is acknowledged and agreed. Re-integrations were performed on two individual study samples using unique integration parameters that were not applied to the rest of the samples in these runs. In run 54 (b) (4) #6335 was reintegrated to correct the baseline, but remained BLQ regardless of the reintegration, so there is no impact to the reported results. It is noted however, that even

if the new parameters applied to #6335 had been applied to the entire run, reported sample results would have changed by less than 4%. In run 74 (b) (4) #8498 was reintegrated to correct the baseline, and if these parameters are applied to the entire run sample results would have changed by less than 2%. Refer to Exhibit 6. Upon discussing this with the Sponsor, these changes would be considered negligible, and would have no impact on the overall PK profiles in this study. It was therefore decided by the Sponsor to keep the reported data as is. Along with correspondence, further explanation and printouts of these comparisons have been added to the Study Binder for traceability.

OSI recommendation regarding issues # 3: In the opinion of the DBGLPC reviewer, the OCP reviewer should confirm the BE outcomes after considering the changed reintegration parameters in run #54 and #74.

OCP review findings regarding issue # 3 noted by OSI: Each of the two analytical runs (#54 and #74) noted in this issue had approximately 130 samples, along with duplicates of QCs and standards within each run. The identity of the subjects and treatments they received (test or reference) that were analyzed in these runs are not known to the reviewer. Observation of the data in Exhibit 6 (see data following the comments below) of the sponsor's response (data before or after applying the re-integration parameters) suggested the following:

Run 54:

- 67 % (86 out of 129) of study samples in run # 54 were unaffected as they remained below limit of quantitation, BLQ before or after reintegration.
- Of the remaining 43 study samples, 6 samples were unaffected by the reintegration (i.e. % difference of 0.0).
- Of the remaining 37 samples whose final concentrations will be affected to some degree if the reintegration were to be applied, n = 26 (70%) had changes < 2 % and the remaining (n = 11) samples had concentration changes in the range of 2 – 4 %.
- Among the 16 duplicate standards included in the run, n = 12 (75 %) had concentration changes ranging from 0 -1.5 %, while the remaining had concentration changes between 2 – 3 %.
- Concentrations of all QCs (n = 9) in the run were altered by 0 – 2 % with reintegration.
- Thus majority of the samples, standards and QCs in run # 54 were either unaffected (BLQ or 0 % change with reintegration; ~71 %) or minimally affected (ranging 0- 4%) with application of reintegration parameters. Therefore, it will not be necessary to reevaluate statistical outcomes with the new concentrations for run # 54.

Run 74:

- 67 out of 128 (52 %) study samples in the run 74 were unaffected by the reintegration as they remained at BLQ before and after the reintegration was applied.
- 11 study samples were unaffected by the reintegration (i.e. % difference of 0.0).
- Of the remaining 50 samples, majority (n = 37; 74 %) were affected by < 1 %, with few samples (n = 13) different by 1- 2 % with change in the integration parameters.
- Of the 16 duplicate standards that were included in run # 74, 15 were affected by < 1 %, with the exception of one standard (20 ng/mL) which was different by -4 .57 % with the use of a different integration method.
- Out of 8 duplicate QCs included in the run, 3 QCs were unaffected, and 3 had % change of < 1 %. Two QC duplicates were altered by < 2 %.
- Thus majority of the samples in run # 74 were either unaffected (BLQ or 0 % change in concentration; ~ 61 %), or were minimally affected (ranging 0 – 2 %) with the application of reintegration. Therefore, it will not be necessary to reevaluate statistical outcomes with the new concentrations for run # 74.

OCP conclusions related to issue # 3 ((b) (4) Reviewer finds the impact of reintegration on the final mesalamine concentrations in runs 54 and 74 to be minimal, with the majority of samples either remaining unaffected (61 -71 % in the two runs) or minimally affected (<2 - 4 % change) upon application of reintegration. Therefore, no further action is needed in this regard and NDA data can be accepted without further analyses of the BE data.

Supporting data tables continue below:

Run 54: Comparison of Reported Results Vs. Results if New Integration Applied Across Entire Run

Sample Name	Original (Reported) Calculated Concentration (ng/mL)	If New Reintegration Applied Calculated Concentration (ng/mL)	% difference
54b1a	N/A	N/A	-
54b1b	N/A	N/A	-
54c6226	< 10.0	< 10.0	-
54c6227	< 10.0	< 10.0	-
54c6228	< 10.0	< 10.0	-
54c6229	< 10.0	< 10.0	-
54c6230	< 10.0	< 10.0	-
54c6231	13.0	13.2	-1.52
54c6232	40.7	42.0	-3.10
54c6233	106	108	-1.85
54c6234	101	101	0.00
54c6235	77.8	78.3	-0.639
54c6236	39.7	40.5	-1.98
54c6237	30.2	30.5	-0.984
54c6238	10.8	11.2	-3.57
54c6239	< 10.0	< 10.0	-
54c6240	< 10.0	< 10.0	-
54c6241	< 10.0	< 10.0	-
54c6242	< 10.0	< 10.0	-
54c6243	< 10.0	< 10.0	-
54c6244	< 10.0	< 10.0	-
54c6245	< 10.0	< 10.0	-
54c6246	< 10.0	< 10.0	-
54c6247	< 10.0	< 10.0	-
54c6248	< 10.0	< 10.0	-
54c6249	< 10.0	< 10.0	-
54c6250	71.3	71.3	0.00
54c6251	373	373	0.00
54c6252	353	362	-2.49
54c6253	351	347	1.15
54c6254	122	122	0.00
54c6255	39.0	39.2	-0.510
54c6256	12.9	12.5	3.20
54c6257	< 10.0	< 10.0	-
54c6258	< 10.0	< 10.0	-
54c6259	< 10.0	< 10.0	-
54c6260	< 10.0	< 10.0	-
54c6261	< 10.0	< 10.0	-
54c6262	< 10.0	< 10.0	-
54c6263	< 10.0	< 10.0	-
54c6264	< 10.0	< 10.0	-
54c6265	24.7	25.2	-1.98
54c6266	53.2	53.8	-1.12
54c6267	52.0	52.5	-0.952
54c6268	30.4	30.0	1.33
54c6269	20.2	20.2	0.00
54c6270	36.6	37.3	-1.88
54c6271	20.9	21.1	-0.948
54c6272	12.6	12.3	2.44
54c6273	< 10.0	< 10.0	-
54c6274	< 10.0	< 10.0	-
54c6274r	< 10.0	< 10.0	-
54c6275	< 10.0	< 10.0	-
54c6276	< 10.0	< 10.0	-

Sample Name	Original (Reported) Calculated Concentration (ng/mL)	If New Reintegration Applied Calculated Concentration (ng/mL)	% difference
54c6277	< 10.0	< 10.0	-
54c6278	< 10.0	< 10.0	-
54c6279	18.0	17.7	1.69
54c6280	12.6	12.4	1.61
54c6281	< 10.0	< 10.0	-
54c6282	29.5	29.7	-0.673
54c6283	44.7	44.9	-0.445
54c6284	37.4	37.0	1.08
54c6285	41.1	41.3	-0.484
54c6286	28.4	28.7	-1.05
54c6287	26.9	27.4	-1.82
54c6288	23.6	24.4	-3.28
54c6289	< 10.0	< 10.0	-
54c6290	< 10.0	< 10.0	-
54c6291	< 10.0	< 10.0	-
54c6292	< 10.0	< 10.0	-
54c6293	< 10.0	< 10.0	-
54c6294	< 10.0	< 10.0	-
54c6295	< 10.0	< 10.0	-
54c6296	< 10.0	< 10.0	-
54c6297	< 10.0	< 10.0	-
54c6298	< 10.0	< 10.0	-
54c6299	< 10.0	< 10.0	-
54c6300	< 10.0	< 10.0	-
54c6301	< 10.0	< 10.0	-
54c6302	11.4	11.1	2.70
54c6303	11.0	11.1	-0.901
54c6304	< 10.0	< 10.0	-
54c6305	< 10.0	< 10.0	-
54c6306	< 10.0	< 10.0	-
54c6307	< 10.0	< 10.0	-
54c6308	< 10.0	< 10.0	-
54c6309	< 10.0	< 10.0	-
54c6310	< 10.0	< 10.0	-
54c6311	< 10.0	< 10.0	-
54c6312	< 10.0	< 10.0	-
54c6313	< 10.0	< 10.0	-
54c6314	36.3	37.4	-2.94
54c6315	27.3	27.2	0.368
54c6316	19.7	20.3	-2.96
54c6317	23.8	24.1	-1.24
54c6318	43.8	44.7	-2.01
54c6319	11.8	11.8	0.00
54c6320	< 10.0	< 10.0	-
54c6321	< 10.0	< 10.0	-
54c6322	< 10.0	< 10.0	-
54c6323	< 10.0	< 10.0	-
54c6324	< 10.0	< 10.0	-
54c6325	< 10.0	< 10.0	-
54c6326	< 10.0	< 10.0	-
54c6327	< 10.0	< 10.0	-
54c6328	< 10.0	< 10.0	-
54c6329	< 10.0	< 10.0	-
54c6330	< 10.0	< 10.0	-
54c6331	< 10.0	< 10.0	-
54c6332	24.4	24.7	-1.21

Sample Name	Original (Reported) Calculated Concentration (ng/mL)	If New Reintegration Applied Calculated Concentration (ng/mL)	% difference
54c6333	18.0	18.4	-2.17
54c6334	< 10.0	< 10.0	-
54c6335	< 10.0	< 10.0	-
54c6336	< 10.0	< 10.0	-
54c6337	< 10.0	< 10.0	-
54c6338	< 10.0	< 10.0	-
54c6339	< 10.0	< 10.0	-
54c6340	< 10.0	< 10.0	-
54c6341	< 10.0	< 10.0	-
54c6342	< 10.0	< 10.0	-
54c6343	< 10.0	< 10.0	-
54c6344	< 10.0	< 10.0	-
54c6345	< 10.0	< 10.0	-
54c6346	< 10.0	< 10.0	-
54c6347	< 10.0	< 10.0	-
54c6348	< 10.0	< 10.0	-
54c6349	< 10.0	< 10.0	-
54c6350	25.0	24.9	0.402
54c6351	< 10.0	< 10.0	-
54c6352	< 10.0	< 10.0	-
54c6353	< 10.0	< 10.0	-
54q1a	24.6	24.2	1.65
54q1b	26.2	26.1	0.383
54q2a	621	620	0.161
54q2ar	610	604	0.993
54q2b	611	610	0.164
54q3a	1221	1208	1.08
54q3b	1208	1196	1.00
54q4a	101	103	-1.94
54q4b	103	104	-0.962
54s0a	N/A	N/A	-
54s0b	N/A	N/A	-
54s1a	9.88	10.1	-2.18
54s1b	10.3	10.0	3.00
54s2a	19.4	19.5	-0.513
54s2b	20.0	20.0	0.00
54s3a	74.5	75.6	-1.46
54s3b	74.5	75.2	-0.931
54s4a	216	222	-2.70
54s4b	224	229	-2.18
54s5a	740	738	0.271
54s5b	775	767	1.04
54s6a	1142	1130	1.06
54s6b	1143	1131	1.06
54s7a	1288	1284	0.312
54s7b	1275	1262	1.03
54s8a	1493	1478	1.01
54s8b	1516	1501	1.00

Run 74: Comparison of Reported Results Vs. Results if New Integration Applied Across Entire Run

Sample Name	Original (Reported) Calculated Concentration (ng/mL)	If New Reintegration Applied Calculated Concentration (ng/mL)	% difference
74b1a	N/A	N/A	-
74b1b	N/A	N/A	-
74c8466	< 10.0	< 10.0	-
74c8467	< 10.0	< 10.0	-
74c8468	< 10.0	< 10.0	-
74c8469	< 10.0	< 10.0	-
74c8470	< 10.0	< 10.0	-
74c8471	< 10.0	< 10.0	-
74c8472	926	924	0.216
74c8473	1694	1683	0.654
74c8474	231	232	-0.431
74c8475	163	163	0.00
74c8476	56.5	56.1	0.713
74c8477	21.4	21.2	0.943
74c8478	11.2	11.0	1.82
74c8479	< 10.0	< 10.0	-
74c8480	< 10.0	< 10.0	-
74c8481	< 10.0	< 10.0	-
74c8482	< 10.0	< 10.0	-
74c8483	< 10.0	< 10.0	-
74c8484	< 10.0	< 10.0	-
74c8485	< 10.0	< 10.0	-
74c8486	20.0	19.8	1.01
74c8487	11.1	10.9	1.83
74c8488	< 10.0	< 10.0	-
74c8489	< 10.0	< 10.0	-
74c8490	< 10.0	< 10.0	-
74c8491	12.8	12.9	-0.775
74c8492	< 10.0	< 10.0	-
74c8493	< 10.0	< 10.0	-
74c8494	< 10.0	< 10.0	-
74c8495	229	229	0.00
74c8496	163	164	-0.610
74c8497	110	110	0.00
74c8498	13.8	13.7	0.730
74c8499	< 10.0	< 10.0	-
74c8500	< 10.0	< 10.0	-
74c8501	< 10.0	< 10.0	-
74c8502	< 10.0	< 10.0	-
74c8503	12.8	12.7	0.787
74c8504	< 10.0	< 10.0	-
74c8505	< 10.0	< 10.0	-
74c8506	< 10.0	< 10.0	-
74c8507	228	229	-0.437
74c8508	166	165	0.606
74c8509	110	110	0.00
74c8510	14.1	14.3	-1.40
74c8511	< 10.0	< 10.0	-
74c8512	< 10.0	< 10.0	-
74c8513	< 10.0	< 10.0	-
74c8514	< 10.0	< 10.0	-
74c8515	< 10.0	< 10.0	-
74c8516	< 10.0	< 10.0	-
74c8517	< 10.0	< 10.0	-

Sample Name	Original (Reported) Calculated Concentration (ng/mL)	If New Reintegration Applied Calculated Concentration (ng/mL)	% difference
74c8518	< 10.0	< 10.0	-
74c8519	< 10.0	< 10.0	-
74c8520	11.5	11.6	-0.862
74c8521	26.5	26.9	-1.49
74c8522	155	156	-0.641
74c8523	186	187	-0.535
74c8524	126	126	0.00
74c8525	105	104	0.962
74c8526	55.6	55.9	-0.537
74c8527	22.5	22.3	0.897
74c8528	< 10.0	< 10.0	-
74c8529	< 10.0	< 10.0	-
74c8530	< 10.0	< 10.0	-
74c8531	< 10.0	< 10.0	-
74c8532	< 10.0	< 10.0	-
74c8533	< 10.0	< 10.0	-
74c8534	< 10.0	< 10.0	-
74c8535	< 10.0	< 10.0	-
74c8536	< 10.0	< 10.0	-
74c8537	15.0	14.8	1.35
74c8538	21.5	21.7	-0.922
74c8539	13.1	13.2	-0.758
74c8540	12.1	12.3	-1.63
74c8541	11.5	11.4	0.877
74c8542	< 10.0	< 10.0	-
74c8543	12.6	12.5	0.800
74c8544	18.7	19.0	-1.58
74c8545	20.0	19.8	1.01
74c8546	< 10.0	< 10.0	-
74c8547	< 10.0	< 10.0	-
74c8548	< 10.0	< 10.0	-
74c8549	20.8	20.6	0.971
74c8550	12.5	12.5	0.00
74c8551	31.9	32.1	-0.623
74c8552	282	283	-0.353
74c8553	486	488	-0.410
74c8554	381	381	0.00
74c8555	193	193	0.00
74c8556	59.2	59.0	0.339
74c8557	18.1	17.9	1.12
74c8558	< 10.0	< 10.0	-
74c8559	< 10.0	< 10.0	-
74c8560	< 10.0	< 10.0	-
74c8561	< 10.0	< 10.0	-
74c8562	< 10.0	< 10.0	-
74c8563	< 10.0	< 10.0	-
74c8564	< 10.0	< 10.0	-
74c8565	12.9	12.8	0.781
74c8566	20.0	19.8	1.01
74c8567	12.8	12.7	0.787
74c8568	29.1	29.4	-1.02
74c8569	65.7	65.6	0.152
74c8570	76.7	76.4	0.393
74c8571	125	124	0.806
74c8572	57.8	58.0	-0.345
74c8573	19.8	20.1	-1.49

Sample Name	Original (Reported) Calculated Concentration (ng/mL)	If New Reintegration Applied Calculated Concentration (ng/mL)	% difference
74c8574	14.1	14.2	-0.704
74c8575	< 10.0	< 10.0	-
74c8576	< 10.0	< 10.0	-
74c8577	< 10.0	< 10.0	-
74c8578	< 10.0	< 10.0	-
74c8579	< 10.0	< 10.0	-
74c8580	< 10.0	< 10.0	-
74c8581	< 10.0	< 10.0	-
74c8582	< 10.0	< 10.0	-
74c8583	42.2	42.3	-0.236
74c8584	87.9	88.3	-0.453
74c8585	239	240	-0.417
74c8586	276	276	0.00
74c8587	126	126	0.00
74c8588	121	121	0.00
74c8589	36.4	36.5	-0.274
74c8590	< 10.0	< 10.0	-
74c8591	< 10.0	< 10.0	-
74c8592	< 10.0	< 10.0	-
74c8593	< 10.0	< 10.0	-
74q1a	23.3	23.7	-1.69
74q1b	24.3	24.8	-2.02
74q2a	590	587	0.511
74q2b	616	616	0.00
74q3a	1166	1159	0.604
74q3b	1201	1198	0.250
74q4a	103	103	0.00
74q4b	104	104	0.00
74s0a	N/A	N/A	-
74s0b	N/A	N/A	-
74s1a	10.1	10.0	1.00
74s1b	10.3	10.2	0.980
74s2a	18.8	19.7	-4.57
74s2b	19.4	19.5	-0.513
74s3a	76.3	77.0	-0.909
74s3b	72.5	73.0	-0.685
74s4a	228	227	0.441
74s4b	220	219	0.457
74s5a	758	754	0.531
74s5b	782	781	0.128
74s6a	1116	1109	0.631
74s6b	1111	1110	0.0901
74s7a	1284	1276	0.627
74s7b	1258	1254	0.319
74s8a	1570	1560	0.641
74s8b	1487	1486	0.0673

Appendix: OSI final review

M E M O R A N D U M

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

DATE: January 8, 2013

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

Edward D. Bashaw, Ph.D.
Director
Division of Clinical Pharmacology III
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204-412 Mesalamine Delayed Release Capsules, 400 mg from Warnex Chilcott Company, LLC, USA

At the request of the Division of Gastroenterology and Inborn Errors Products (DGIEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected the following study:

PR-08210: "A Study to Assess the Relative Bioavailability of Two WC3045 Formulations in Healthy Subjects, Study PR-08210"

Clinical:

The inspections of two clinical portions were conducted by Ethan P. Stegman (ORA) at **Comprehensive Clinical Development, Fort Myers, FL** and **Comprehensive Clinical Development, Miramar, FL.** Following the inspections (October 6-9, 2012 and October 22-26, 2012, respectively), no Form FDA-483 was issued.

The inspection of a third clinical portion was conducted by Todd R. Lorenz (ORA) at **Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX (WCTEPS).** Following the inspection (October 22-29, 2012), Form FDA-483 was issued (**Attachment 1**). The firm's response was received on November 13, 2012 (**Attachment 2**).

The Form FDA-483 observation, WCTEPS response to Form FDA-483 and our evaluation follow:

1. **Failure to ensure that an investigation was conducted in accordance with the protocol for study #PR-08210. Specifically, protocol section 12.1, "PK blood sampling and processing," said that "the time between sample collection and placement in the freezer is not to exceed 60 min." However, the following deviations were observed in the clinical investigator files:**
   - **Subject 507319 (b) (6), Period 3, Sample at 30 hr was withdrawn at 12:18 but plasma was not frozen until 15:13, a period of 175 min after withdrawal.**
   - **Subject 507344 (b) (6), Period 1, Sample 12 hr was withdrawn at 18:43 but plasma was not harvested or shipped to the analytical lab for analysis.**
   - **Subject 507345/ (b) (6), Period 1, Sample 24 hr was withdrawn at 06:44 but without documentation of when plasma was frozen.**
   - **Subject 507355 (b) (6), Period 4, Sample 4 hr was withdrawn at 10:54 but without documentation of when plasma was frozen.**
   - **Subject 507355 (b) (6), Period 4, Sample 6 hr was withdrawn at 12:54 but without documentation of when plasma was frozen.**
   - **Subject 507376/ (b) (6), Period 2, Sample 36 hr was withdrawn at 19:15 but without documentation of when plasma was frozen.**

- **Subject 507393/ (b) (6), Period 1, Sample 2 hr was withdrawn at 09:32 but without documentation of when plasma was frozen.**
- **Subject 507396/ (b) (6), Period 3, Sample 10 hr was withdrawn at 17:35 but without documentation of when plasma was frozen.**

WCTEPS responded that these deviations in PK sampling were documented in source records as a protocol deviation log. In addition, WCTEPS remarked that the concentration-time profiles displayed in the final report for these subjects did not show anomalies at the times in question for these samples.

In the opinion of the reviewer, the data from subject 507319/TTC/Period 3, sample 30 hr can be accepted because (b) (6) (analytical site) confirmed 5-ASA bench-top stability for about 6.5 hours (390 min).

The data from the following samples are not assured and their accuracy cannot be confirmed, as WCTEPS did not record when the plasma samples were frozen.

- Subject 507345 (b) (6) Period 1, Sample 24 hr
- Subject 507355 Period 4, Sample 4 hr
- Subject 507355 Period 4, Sample 6 hr
- Subject 507376 Period 2, Sample 36 hr
- Subject 507393 Period 1, Sample 2 hr
- Subject 507396 Period 3, Sample 10 hr

Analytical:

The inspection of the analytical portion was conducted by (b) (4)

Following the inspection (December 3-7, 2012), Form FDA-483 was issued (**Attachment 3**). The firm's response was received on December 21, 2012 (**Attachment 4**).

The Form FDA-483 observation, (b) (4) response to Form FDA-483 and our evaluation follow:

1. **Failure to conduct an experiment to evaluate the effects of hemolysis on 5-Amino Salicylic acid (5-ASA) quantification. In addition, failure to document the number of hemolysed samples after**

receiving plasma samples from the three clinical sites.

In their response to Form FDA-483, (b) (4) acknowledged this observation and performed additional hemolysis testing for 5-ASA by evaluating low and high QC samples with 1%, 2% and 5% hemolysis. The hemolysed QC samples were analyzed against calibrators and QCs prepared in non-hemolysed human plasma. (b) (4) demonstrated hemolysis had no impact on 5-ASA quantification.

In the opinion of the reviewer, (b) (4) response is adequate.

2. **Specificity of N-acetyl-5-ASA in plasma failed to meet acceptance criteria in runs (run #1 and 4), and could not confirm specificity during the validation. In addition, the firm failed to provide justification for its failure.**

In their response to Form FDA-483, (b) (4) acknowledged this observation and suggested that the reason for failure of the specificity experiments was due to 5-ASA in the N-acetyl-5-ASA reference standard. To confirm this hypothesis, (b) (4) repeated the experiment with freshly weighed N-acetyl-5-ASA and analyzed for both N-acetyl-5-ASA and 5-ASA. (b) (4) demonstrated that no inter-conversion of parent and metabolite occurred under the analytical and storage conditions. They suggest that the small amounts of 5-ASA found in run #1 and #4 chromatograms was due to an impurity in the N-acetyl-5-ASA reference standard instead of decomposition or non-specificity.

In the opinion of the reviewer, (b) (4) response is adequate.

3. **Failure to apply the changed chromatographic integration parameters in 2 samples in runs #54 and 74 to all samples in the respective runs**

In their response to Form FDA-483, (b) (4) acknowledged this observation and noted that the change in the estimated concentrations was about 4% for run #54 and about 2% for run #74. (b) (4) is of the opinion that this change will have no effect on the BE outcomes.

In the opinion of the DBGLPC reviewer, the OCP reviewer should confirm the BE outcomes after considering the changed re-integration parameters in run #54 and #74.

4. **The bioanalytical report contained the text "frozen stability has been proven for 287 days in human**

plasma at -80 degrees," however firm failed to provide the report containing long-term freezer stability data to the agency.

In their response to Form FDA-483, (b) (4) explained that an additional report on stability for 377 days at -80^{0}C and 38 days at -20^{0}C was in the possession of the sponsor at the time of inspection. The report was finalized on December 14, 2012 and attached to (b) (4) response.

In the opinion of the reviewer, (b) (4) response is adequate and this observation will have no impact on study outcomes.

5. **Calibration and maintenance procedures for LC-MS/MS instruments to include the auto-sampler and LC pumps are inadequate in that they do not assure maintenance and/or calibration within certain dates. For example, (b) (4) #16 was due for (b) (4) month maintenance on 11/7/12 and has not been conducted. In addition, the required maintenance was not performed for (b) (4) #14 between 10/1/12 and 12/3/12.**

In the opinion of the reviewer, this observation will have no impact on study outcomes as lapses in maintenance occurred several months after complete analysis of the study samples.

Conclusions:

Following evaluation of the inspectional findings and (b) (4) response, the DBGLPC reviewer recommends the following:

- The data generated from the following samples cannot be assured:

  - Subject 507345 (b) (6) Period 1, Sample 24 hr
  - Subject 507355 Period 4, Sample 4 hr
  - Subject 507355 Period 4, Sample 6 hr
  - Subject 507376 Period 2, Sample 36 hr
  - Subject 507393 Period 1, Sample 2 hr
  - Subject 507396 Period 3, Sample 10 hr

- The OCP reviewer should confirm the BE outcomes of study PR-08210 with concentrations using consistently integrated chromatograms in runs #54 and 74.

- The other clinical and analytical data from this study are acceptable for your review.

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

VAI – Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX
FEI: 3006724658

NAI – Comprehensive Clinical Development, Fort Myers, FL
FEI: 3007613146

NAI – Comprehensive Clinical Development, Miramar, FL
FEI: 3006116374

VAI – (b) (4)

cc:
OSI/Moreno
OSI/DBGLPC/Taylor/Dejernett
OSI/DBGLPC/BB/Haidar/Skelly/Mada
OND/ODE3/DGIEP/Davis/Barley/Griebel
OCP/DCP3/Bashaw/Apparaju
ORA/NYK-DO/Mendiola
ORA/DAL-DO/Lorenz
ORA/FLA-DO/Stegman
Draft: SRM 01/07/2013
Edit: MFS 01/07/2013; WHT 01/08/2013
OSI: BE6381; O:\Bioequiv\EIRCover\204412.war.mes
FACTS: 1453828

ATTACHMENT: 1

77 pages have been withheld as b4 (CCI/TS) immediately following this page

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/s/

SRIPAL R MADA
01/08/2013

WILLIAM H TAYLOR
01/08/2013

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/s/

SANDHYA K APPARAJU
01/10/2013
Review Addendum

SUE CHIH H LEE
01/11/2013

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**204-412/S-000**
Submission Date:	7/31/2012//11/16/2012
Brand Name:	(b) (4)
Generic Name:	Mesalamine Delayed-Release Capsules
Formulation:	Capsules
Strength:	400 mg
Applicant:	Warner Chilcott
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

SYNOPSIS

The submission: NDA 204-412 provides a new dosage form, mesalamine delayed-release capsules, 400 mg. The proposed indication and dosing regimen are the same as the approved Asacol (mesalamine) delayed-release tablets, 400 mg under NDA 19-651. The new dosage form is to address the Agency's concern related to the potential safety issue of dibutyl phthalate (DBP) as an excipient in Asacol products. In the new formulation (WC3045 capsules) dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the plasticizer dibutyl sebacate (DBS) and the tablet is then encapsulated. The Applicant has conducted special dissolution studies and a PK study (Study PR-08210) of WC3045 capsules compared to Asacol (mesalamine) delayed-release tablets.

The review: The review will focus on the dissolution profile comparisons, dissolution acceptance criteria and the alcohol dose dumping study.

COMMENTS

1. The dissolution profile comparisons demonstrated that the new dosage form, mesalamine delayed-release capsules 400 mg, is similar to the approved Asacol (mesalamine) delayed-release tablets 400 mg.

2. Although the delayed release characteristics are maintained in Phase 1 - 0.1N HCl and Phase 2 –pH 6 when the media contain up to 40% alcohol in the acid stage (Phase I), the profile at Stage 3 (pH 7.2) was affected significantly when the alcohol concentration reached 20% and above. It is also noted that alcohol was only added to the acid stage (Stage 1). At Stage 2 (pH 6.0) and Stage 3 (pH 7.2), no alcohol was present. Because the highest concentrations of alcohol in GI tract are likely to be encountered in the acidic environment of the stomach, the dissolution profiles generated in 0.1 N HCl with different concentrations of alcohol are more clinically relevant (as compared to dissolution profiles generated in dissolution media at other pH's, containing alcohol). Therefore, we consider the study is able address the alcohol induced dose dumping potential. A faster dissolution was shown at pH 7.2 medium when the alcohol concentrations reach 20% or more. However, the delayed release characteristics had not been compromised because the dissolution in Phase 1 - 0.1N HCl and Phase 2 –pH 6 was

zero and the formulation has been designed to release the drug at pH 7. The faster dissolution at pH 7.2 in the presence of high concentration (≥20%) of alcohol may not raise a safety concern.

3. The proposed dissolution specification acceptance criterion at Stage 3 (pH 7.2), Q=80% at 1.5 hrs (using Type II Paddle 50 RPM) is not optimal. An acceptance criterion of Q=80% at 75 minutes seems more appropriate based on the data available. However, since limited data at 75 minutes have been collected, a post-approval commitment is proposed and the agreement is pending (see below Recommendation).

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 204-412 is recommended for approval with a post-marketing commitment as listed below (the agreement is pending).

The dissolution acceptance criteria you proposed below are accepted on an interim basis.

0.1N HCl (Type II Paddle 100 RPM, 2 hrs): No individual value exceeds 1% dissolved
pH 6.0 (Type II Paddle 100 RPM, 1 hr): No individual value exceeds 1% dissolved
pH 7.2 (Type II Paddle 50 RPM): Q=80% at 1.5 hrs

You commit to collect additional dissolution profile data (including the additional 75 min time point) from the stability batches at the scheduled stability time points and from all the batches manufactured during the first year after action date (n=12 for the remaining time points of the ongoing stability protocol; n ≥ 6 for the batch release). These data should be used for setting the final dissolution acceptance criteria.

You commit to provide a report with the complete dissolution information/data and proposed final acceptance criteria under a supplement to the NDA within (b) (4) from action date.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Minerva Hughes, Ph.D. Date
Acting Team Leader
ONDQA Biopharmaceutics

cc: NDA 204-412, *Darrts*

APPENDIX I. Biopharmaceutics Evaluation

1. Introduction

NDA 204-412 provides a new dosage form, mesalamine delayed-release capsules, 400mg. The proposed indication and dosing regimen are the same as the approved Asacol (mesalamine) delayed-release tablets, 400 mg under NDA 19-651. The new dosage form is to address the Agency's concern related to the potential safety issue of dibutyl phthalate (DBP) as an excipient in Asacol products. In the new formulation (WC3045 capsules) dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the plasticizer dibutyl sebacate (DBS) and the tablet is then encapsulated.

A relative bioavailability study, comparing the pharmacokinetic profile and bioavailability of WC3045 capsules to Asacol (mesalamine) delayed-release tablets, 400 mg (Asacol tablets) was conducted based on the FDA's recommendations provided during the November 2, 2010 meeting and the FDA advice on February 15, 2011 for a 3-or 4-period design.

As recommended by FDA in the Advice/Information Request dated December 5, 2011, the Applicant utilized the reference-scaled average BE methodology as described in the Draft Guidance on Progesterone, CDER February 2011. The study revealed that WC3045 capsules have comparable PK profiles and are bioequivalent to Asacol (mesalamine) delayed-release tablets, 400 mg.

A multipoint dissolution profile comparison was performed between WC3045 capsules and Asacol (mesalamine) delayed-release tablets, 400 mg, over a range of pH values (pH 4.5, 6.0, 6.5, 6.8, 7.2 and 7.5) as recommended by FDA in the Type C teleconference between the FDA and Warner Chilcott, held on November 2, 2010. The similarity factors (f2) values were calculated and provided.

2. The Compositions of the proposed 400 mg mesalamine capsule

The composition of WC3045 400 mg mesalamine capsule is detailed in the following table. Each capsule is composed of the following: (b) (4)

Table: Composition of WC3045, Capsule

Component	Quality Standard	Function	Quantity (mg/cap)	Quantity % w/w
(b) (4)				
Mesalamine	USP	Active ingredient	400.0	(b) (4)
Lactose monohydrate	NF			(b) (4)
Sodium starch glycolate	NF			
Talc	USP			
Povidone	USP			
Magnesium Stearate	NF			
Colloidal silicon dioxide	NF			
(b) (4)	USP			
Subtotal				
(b) (4)				

Methacrylic acid copolymer, type B (Eudragit S (b) (4)	-	(b) (4)	
Talc	USP		
Dibutyl sebacate	NF		
Ferric oxide, red	NF		
Ferric oxide, yellow	NF		
(b) (4)	NF		
	USP		
Subtotal			
(b) (4)			
Polyethylene glycol (b) (4)	USP		
(b) (4)	USP		
Subtotal			
(b) (4))			
Hydroxypropyl methylcellulose (HPMC) Capsule, Size (b) (4))	-		
Subtotal			
Total Theoretical Capsule Weight		647.44	100.0

(b) (4)

3. The solubility of mesalamine

The solubility of mesalamine drug substance is shown in the following table.

Table: Mesalamine Solubility

Medium	Solubility (mg/mL)[1]
0.1N Hydrochloric acid	7.6
5% Dextrose	1.4
Sterile water	0.9
Saline	0.8
Methanol	0.1
Methyl-t-butyl ether	0.05
Ethyl ether	0.05
Acetonitrile	0.04
Hexane	0.003
Chloroform	Insoluble

[1] expressed as anhydrous mesalamine

4. Dissolution profile comparisons

To demonstrate the newly formulated test product (WC3045 Capsules) has a dissolution profile comparable to that of the reference: Asacol (mesalamine) Delayed-release Tablets, 400 mg, a multipoint dissolution profile comparison was performed between WC3045 capsules and Asacol® (mesalamine) delayed-release tablets, 400 mg over a range of pH values (pH 4.5, 6.0, 6.5, 6.8, 7.2 and 7.5).

Dissolution evaluation at pH 4.5 and pH 6.0 is detailed in the following table.

Table: pH 4.5 and pH 6.0 Dissolution Method

Parameter	Description
Dissolution Apparatus	USP Dissolution Apparatus II, Paddles, (Vankel-VK7000, or equivalent)
Temperature	37°C ± 0.5°C
Sample size	n=12

Pre treatment Stage	500 mL of 0.1N HCl
Evaluation Stage	900 mL of pH 4.5 Acetate buffer 900 mL of pH 6.0 Phosphate buffer
Paddle Speed	Pre treatment Stage: 100 rpm Evaluation Stage: 50 rpm
Sampling Times	Pre treatment Stage: 120 minutes Evaluation Stage: 0, 10, 20, 30, 45, 60, 75, 90, 120 and 150 minutes

Dissolution evaluation at pH 6.5, pH 6.8, pH 7.2 and pH 7.5 is detailed in the following table.

Parameter	Description
Dissolution Apparatus	USP Dissolution Apparatus II, Paddles, (Vankel-VK7000, or equivalent)
Temperature	37°C ± 0.5°C
Sample Size	n=12
Pre treatment Stages	500 mL of 0.1N HCl 900 mL of pH 6.0 Buffer
Evaluation Stage	900 mL of pH 6.5 Phosphate buffer 900 mL of pH 6.8 Phosphate buffer 900 mL of pH 7.2 Phosphate buffer 900 mL of pH 7.5 Phosphate buffer
Paddle Speed	Pre treatment Stages: 100 rpm Evaluation Stage: 50 rpm
Sampling Times	0.1N HCl Pre treatment Stage: 120 minutes pH 6.0 Buffer Pre treatment Stage: 60 minutes pH 6.5, pH 6.8 and pH 7.5 evaluation Stage: 0, 10, 20, 30, 45, 60, 75, 90, 120 and 150 minutes pH 7.2 evaluation Stage: 0, 15, 30, 45, 60, 75 and 90 minutes

A summary of dissolution profile evaluation stage results and f2 comparison for formulation WC3045 capsules and Asacol (mesalamine) delayed-release tablets, 400 mg at each pH are presented in the following tables.

Table: Comparison of dissolution profile data for WC3045 Capsules and Asacol (mesalamine) Delayed-release Tablets, 400 mg in pH 4.5 Acetate buffer

Product	WC3045 capsules				Asacol (mesalamine) Delayed-release Tablets, 400 mg			
Batch #	508833				444305 S4			
	Amount Dissolved (%LC)				Amount Dissolved (%LC)			
Time	Mean	Min	Max	% RSD	Mean	Min	Max	% RSD
0	0	0	0	N/A	0	0	0	N/A
10	0	0	0		0	0	1	
20	0	0	0		0	0	0	
30	0	0	0		0	0	0	
45	0	0	0		0	0	0	
60	0	0	0		0	0	0	
75	0	0	0		0	0	0	
90	0	0	0		0	0	0	
120	0	0	0		0	0	0	
150	0	0	0		0	0	0	
f2	100							

Table: Comparison of dissolution profile data for WC3045 Capsules and Asacol (mesalamine) Delayed-release Tablets, 400 mg in pH 6.0 Phosphate buffer

Product	WC3045 capsules		Asacol (mesalamine) Delayed-release Tablets, 400 mg	
Batch #	508833		444305 S4	
	Amount Dissolved (%LC)		Amount Dissolved (%LC)	

Time	Mean	Min	Max	% RSD	Mean	Min	Max	% RSD
0	0	0	0	N/A	0	0	0	N/A
10	0	0	0		0	0	0	
20	0	0	0		0	0	0	
30	0	0	0		0	0	0	
45	0	0	0		0	0	0	
60	0	0	0		0	0	0	
75	0	0	0		0	0	0	
90	0	0	0		0	0	0	
120	0	0	0		0	0	0	
150	0	0	0		0	0	0	
f2	100							

Table: Comparison of dissolution profile data for WC3045 Capsules and Asacol (mesalamine) Delayed-release Tablets, 400 mg in pH 6.5 Phosphate buffer

Product	WC3045 capsules				Asacol (mesalamine) Delayed-release Tablets, 400 mg			
Batch #	508833				444305 S4			
Time	Amount Dissolved (%LC)			% RSD	Amount Dissolved (%LC)			% RSD
	Mean	Min	Max		Mean	Min	Max	
0	0	0	0	N/A	0	0	0	N/A
10	0	0	0	80.3*	0	0	0	396.6*
20	0	0	0	466.1*	0	0	0	347.6*
30	0	0	0	273.3*	0	0	2	188.3
45	0	0	2	335.4	2	0	8	160.4
60	0	0	4	347.2	4	0	15	154.8
75	1	0	8	345.7	5	0	21	151.9
90	1	0	15	345.2	7	0	26	150.8
120	3	0	38	345.8	10	0	34	148.7
150	5	0	51	322.5	12	0	41	146.4
f2	68							

*The mean, min and max were rounded and the actual values were between 0 and 0.4%. %RSD's were calculated from the actual values.

Table: Comparison of dissolution profile data for WC3045 Capsules and Asacol (mesalamine) Delayed-release Tablets, 400 mg in pH 6.8 Phosphate buffer

Product	WC3045 capsules				Asacol (mesalamine) Delayed-release Tablets, 400 mg			
Batch #	508833				444305 S4			
Time	Amount Dissolved (%LC)			% RSD	Amount Dissolved (%LC)			% RSD
	Mean	Min	Max		Mean	Min	Max	
0	0	0	0	N/A	0	0	0	N/A
10	0	0	4	214.5	2	0	10	211.5
20	1	0	17	325.0	5	0	24	198.1
30	2	0	28	324.0	9	0	49	199.8
45	5	0	58	316.8	13	0	81	201.1
60	7	0	73	284.6	17	0	88	187.8
75	10	0	83	229.5	19	0	91	178.2
90	16	0	85	158.1	23	0	93	156.4
120	34	2	88	81.1	36	0	97	101.1
150	57	17	93	42.2	53	1	99	65.2
f2	59							

Table: Comparison of dissolution profile data for WC3045 Capsules and Asacol (mesalamine) Delayed-release Tablets, 400 mg in pH 7.2 Phosphate buffer

Product	WC3045 capsules	Asacol (mesalamine) Delayed-release Tablets, 400 mg

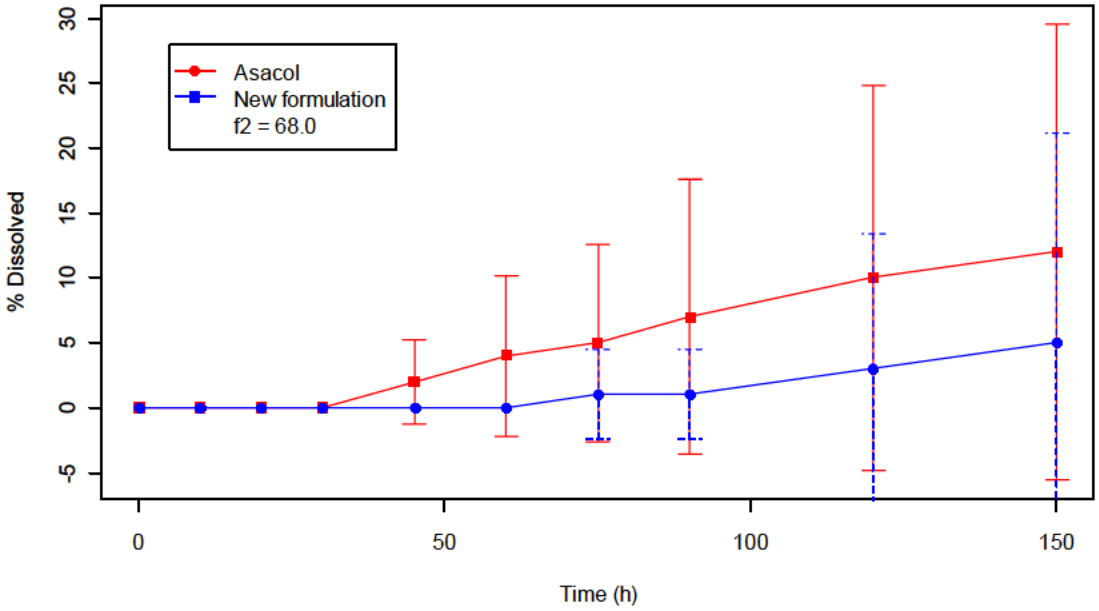
Batch #	508833				444305 S4			
Time	Amount Dissolved (%LC)			% RSD	Amount Dissolved (%LC)			% RSD
	Mean	Min	Max		Mean	Min	Max	
0	0	0	0	N/A	0	0	0	N/A
15	3	0	15	170.1	1	0	6	172.6
30	23	1	57	80.9	15	1	88	160.5
45	63	24	89	33.4	70	49	98	21.6
60	84	66	97	12.5	97	92	101	2.7
75	94	87	100	4.4	100	96	103	1.7
90	97	90	101	2.8	101	98	103	1.4
f2	56							

Table: Comparison of dissolution profile data for WC3045 Capsules and Asacol (mesalamine) Delayed-release Tablets, 400 mg in pH 7.5 Phosphate buffer

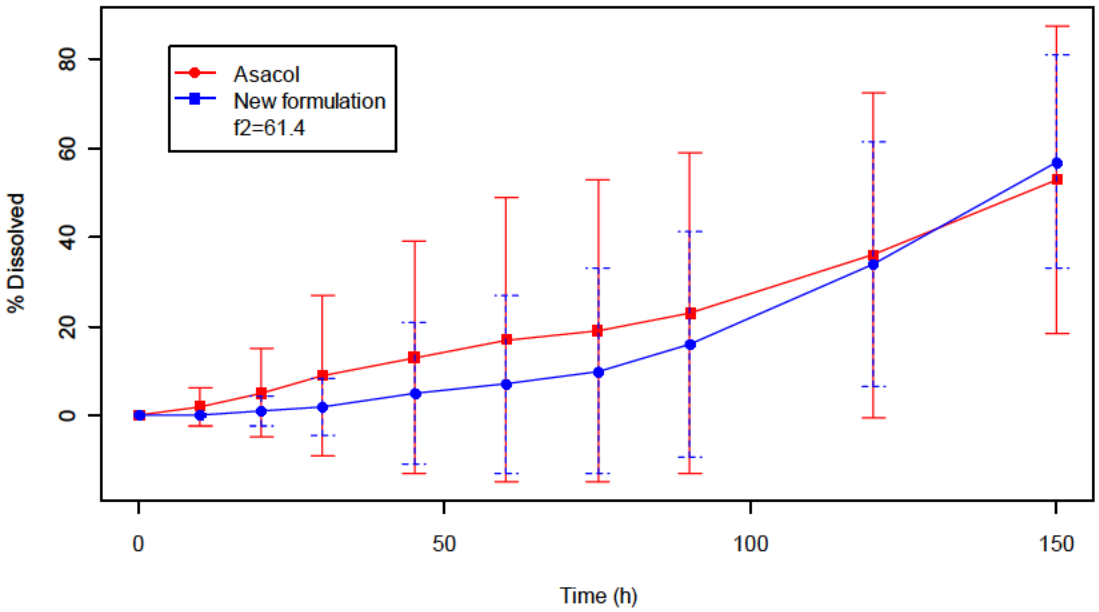
Product	WC3045 capsules				Asacol (mesalamine) Delayed-release Tablets, 400 mg			
Batch #	508833				444305 S4			
Time	Amount Dissolved (%LC)			% RSD	Amount Dissolved (%LC)			% RSD
	Mean	Min	Max		Mean	Min	Max	
0	0	0	0	N/A	0	0	0	N/A
10	1	0	8	285.9	0	0	3	271.5
20	19	2	40	63.6	16	3	33	55.2
30	63	32	85	25.6	62	39	83	24.8
45	87	71	96	8.0	92	87	97	3.6
60	95	89	99	3.3	98	96	100	1.7
75	98	95	101	1.8	100	99	102	1.2
90	99	97	101	1.4	101	99	103	1.0
120	100	98	102	1.4	101	99	103	0.9
150	101	98	103	1.4	101	99	103	0.9
f2	75							

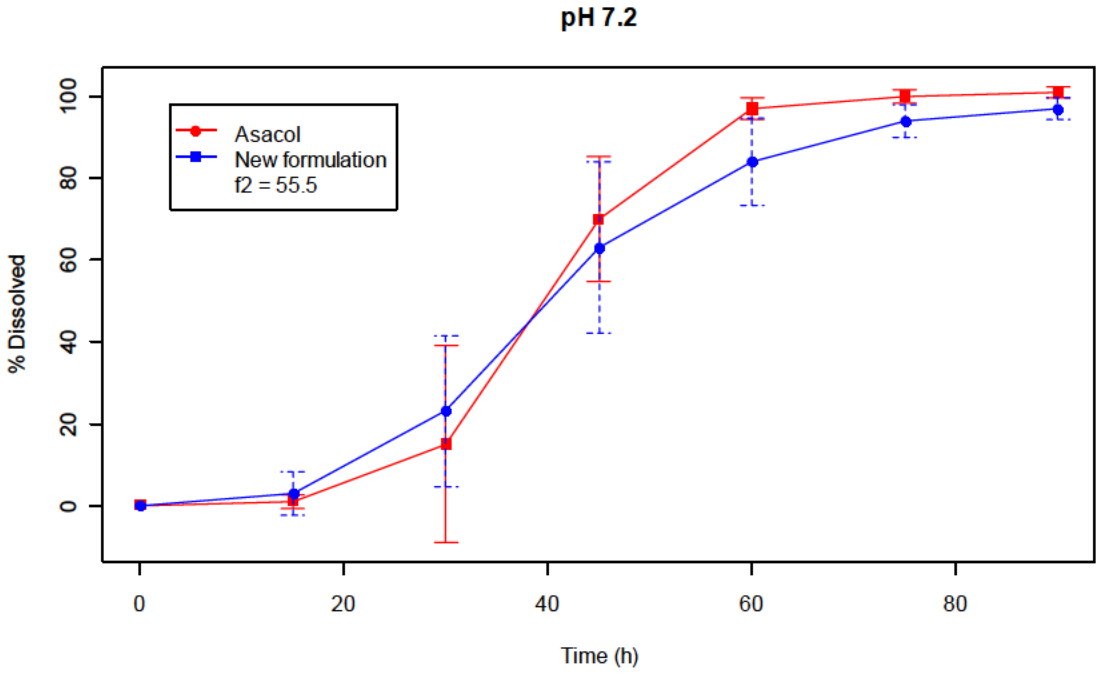
The Reviewer's Comments: *The dissolution profiles for WC3045 capsules are similar to those for the approved Asacol tablets, 400 mg, over a range of pH values, as the similarity factors values (f2) are greater than 50. The reviewer confirmed the results at different pH's although minor differences of f2 values between the Reviewer and the Applicant were observed as shown in the following figures.*

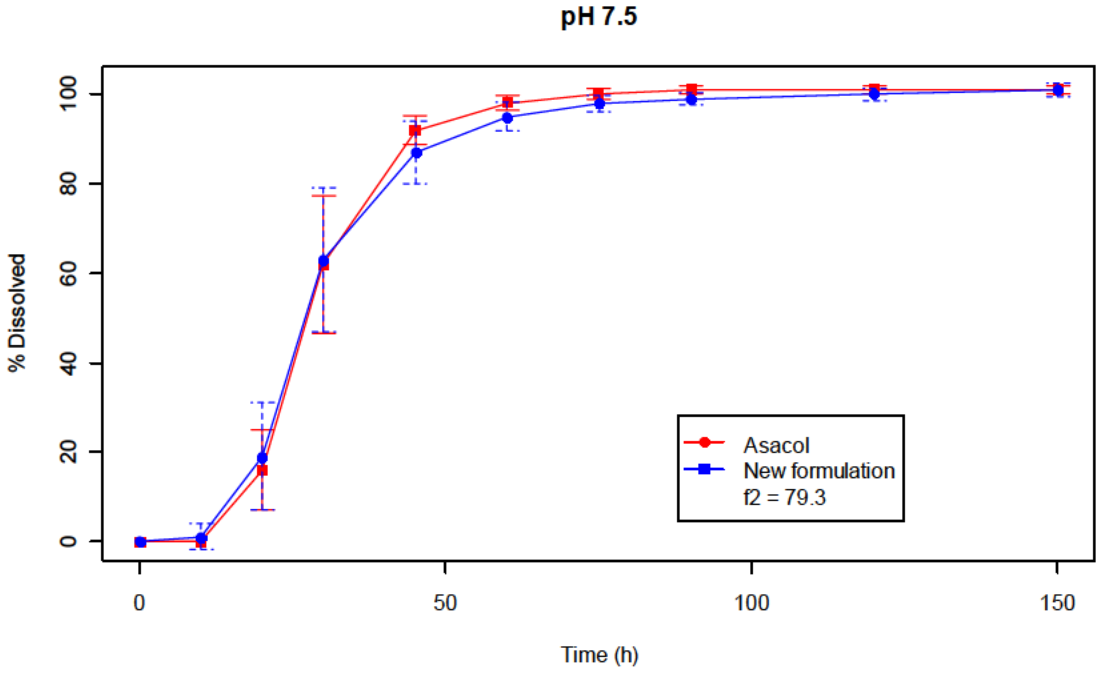
pH 6.5



pH 6.8

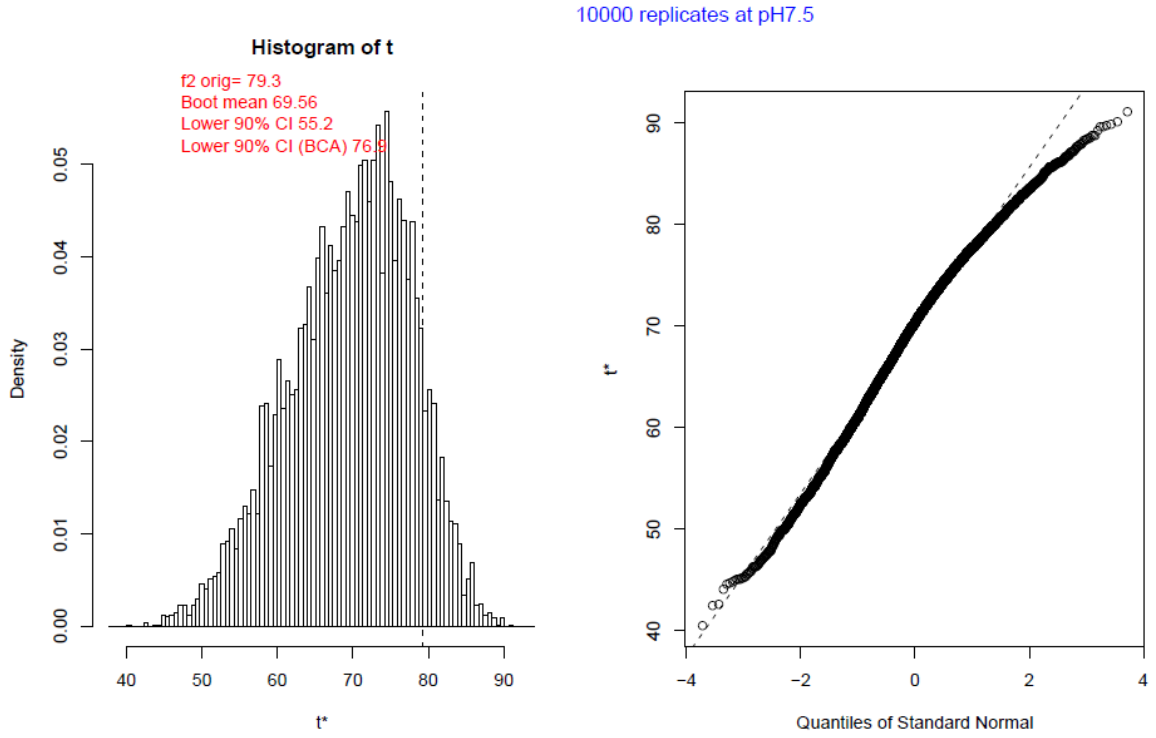


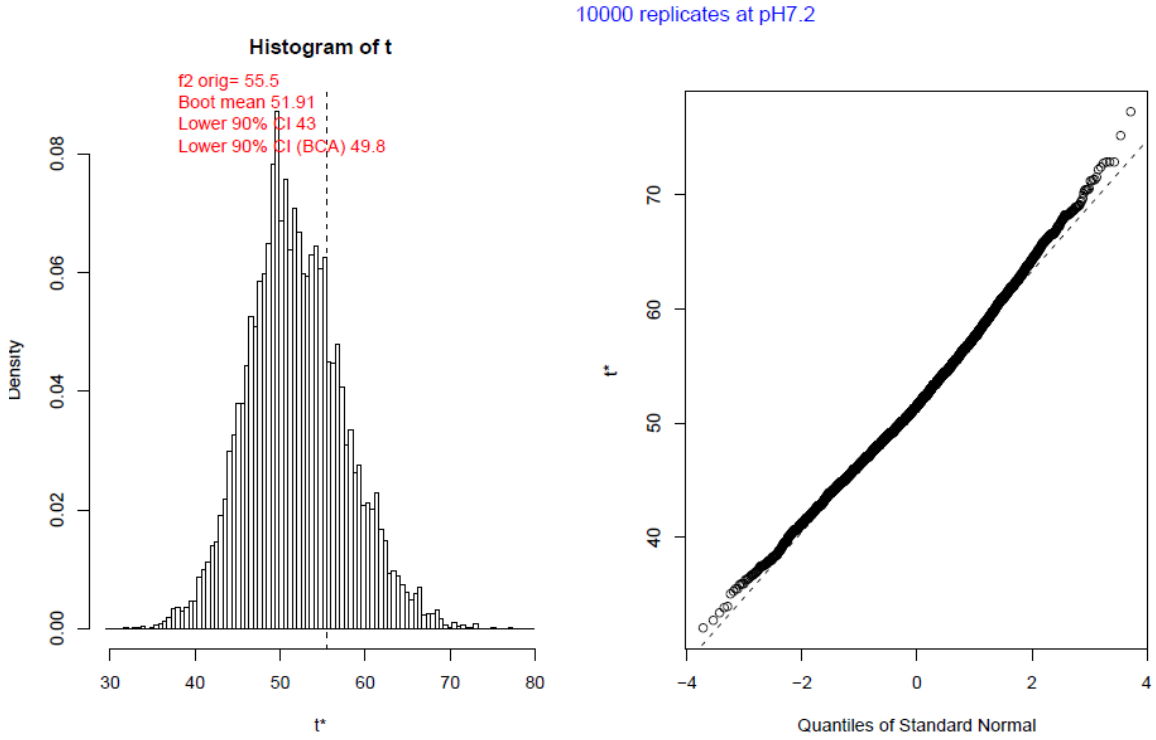


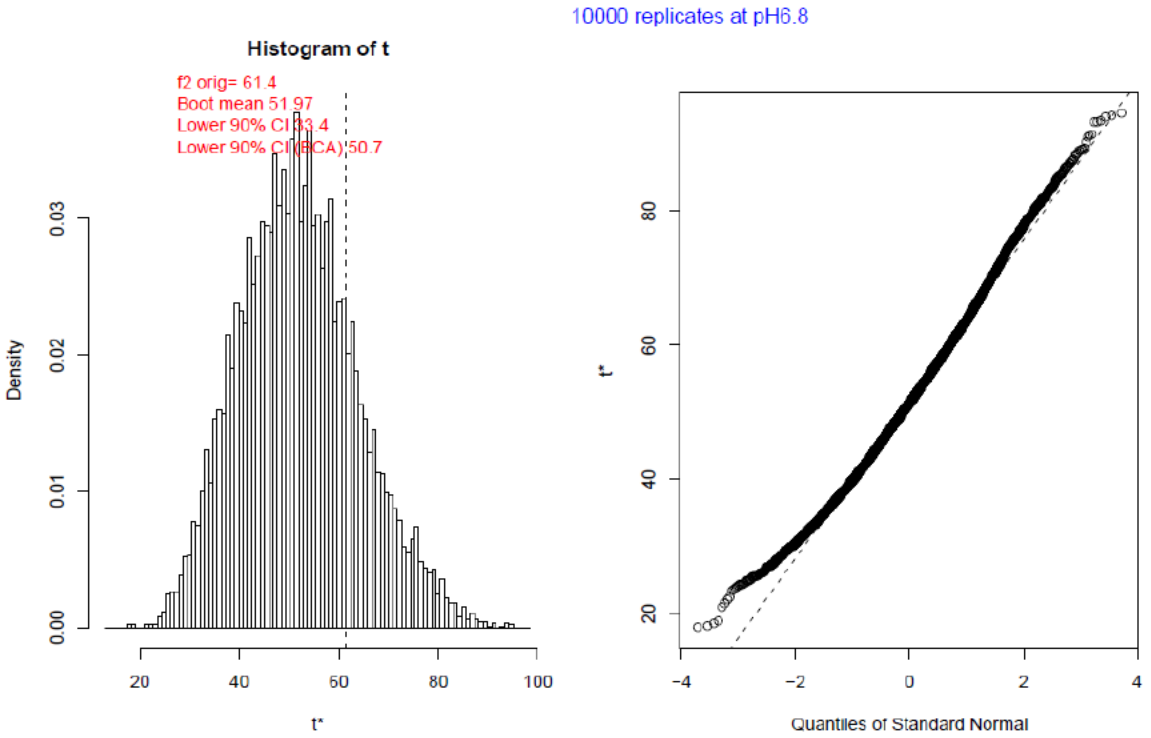


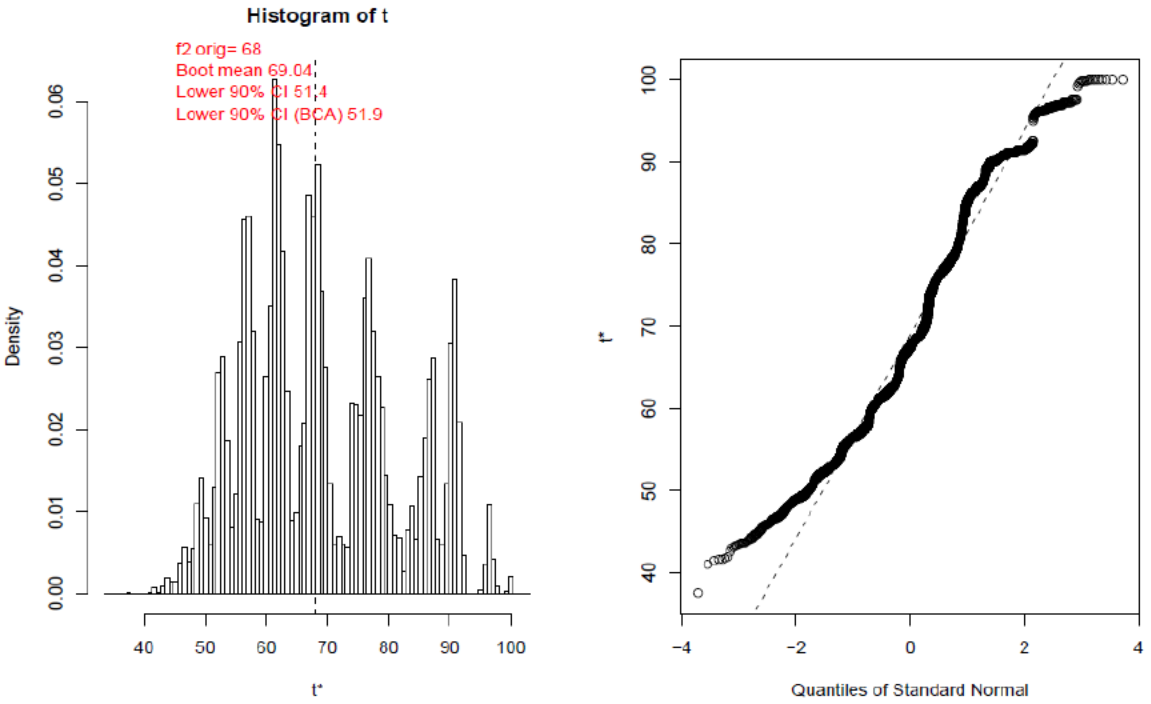
However, the variability is high for either the reference or the test products. In principle, the f2 does not apply when the CV is more than 20% at early time point or more than 10% at later time point. Therefore, bootstrap approach is used to evaluate f2. Twelve (12) dosage units were randomly selected with replacement for reference and test product. The means of these selected units at each time point were obtained and used for f2 calculation. The process was repeated for 10,000 times. The bootstrap mean represents the average over the 10,000 sample means. The distribution of the calculated f2 values was obtained and the 90% confidence intervals were

calculated using percentile and bias-corrected and accelerated (BCA) approaches. The results are shown in the following figures.









Due to the bias, the BCA (bias corrected accelerated) bootstrap method is more reliable. The 90% lower limits of BCA bootstrapped f2 are 50 or more in all the dissolution media tested. Therefore, similarity between the test and reference products was demonstrated even considering the high variability.

5. The comparison of the clinical formulation and the to-be-marketed formulation

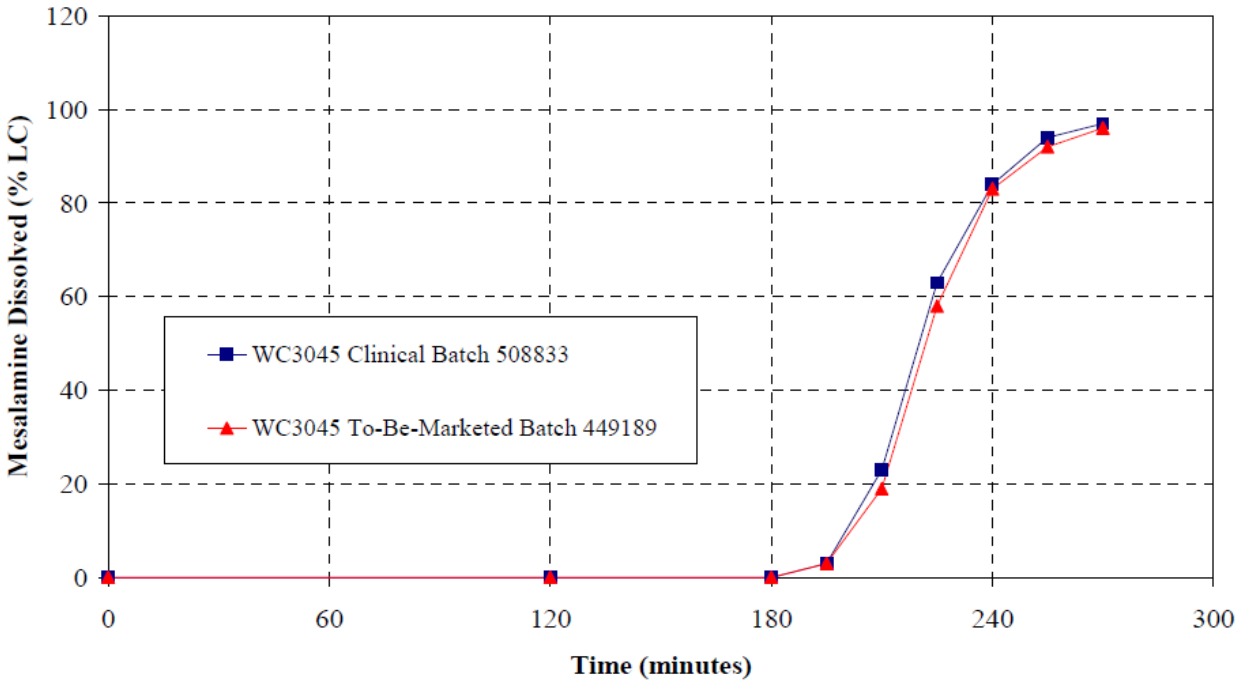
The unit-dose composition and the manufacturing process for the (b) (4) tablets and (b) (4) process between the clinical batch (Material Number 33075301) and to-be-marketed batch

(Material Number 40000024) are [redacted] (b) (4)

[redacted] (b) (4)

The dissolution profiles of the clinical and the to-be-marketed formulations were characterized using the proposed dissolution test method. The mean data are shown in the following figure and table. The dissolution metric f2 was used to show the similarity.

Formulation/ Material Number/ Lot Number	Mean Amount Dissolved (% Label Claim) by pH and Sample Time							
	0.1 N HCl	pH 6.0	pH 7.2					
	2 h	1 h	15 min	30 min	45 min	60 min	75 min	90 min
Clinical Formulation Material Number 33075301 Lot 508745/ 508833/508835	< 1	< 1	3	23	63	84	94	97
To-Be-Marketed Formulation Material Number 40000024 Lot 449189	< 1	< 1	3	19	58	83	92	96



The Reviewer's Comments: *The changes between the clinical and the to-be-marketed formulations are minor and correspond to Level 1 composition changes. The dissolution metric f2 value of 75 for the comparison of the clinical formulation (Material Number 33075301, Batch 508745) to the to-be-marketed formulation (Material Number 40000024, Batch 449189) confirmed that dissolution profiles are similar although the variability is large (bootstrap is not conducted because the mean dissolution profiles are almost overlap each other between the clinical and the to-be-marketed formulations).*

6. Dissolution acceptance criteria

It is proposed to follow the USP method and apparatus for mesalamine delayed release tablets as shown below.

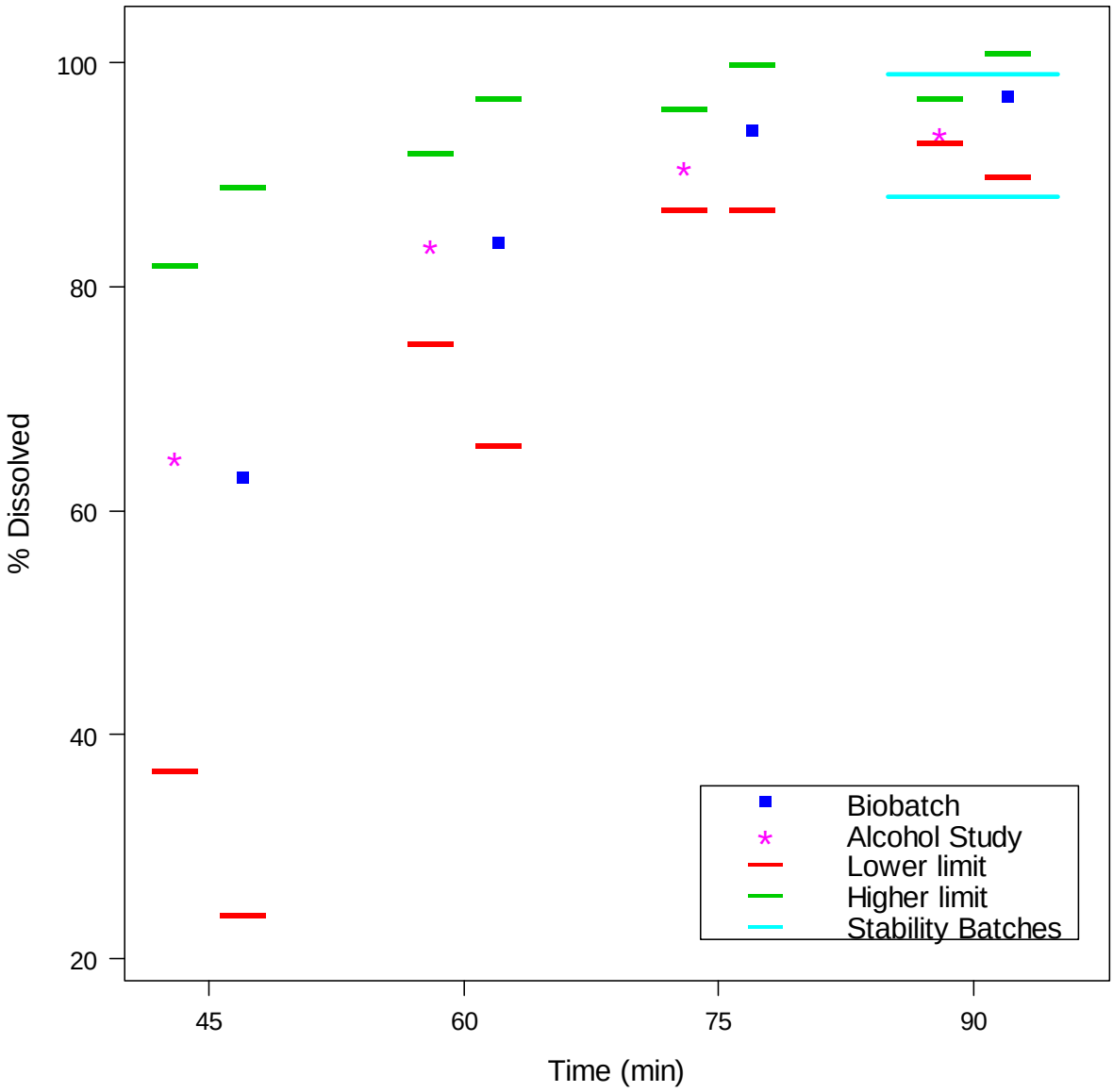
0.1N HCl (Type II Paddle 100 RPM, 2 hrs)
Level 1: No individual value exceeds 1% dissolved
Level 2: Average of the 12 units (L1 + L2) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved.
Level 3: Average of the 24 units (L1 + L2 + L3) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved

pH 6.0 (Type II Paddle 100 RPM, 1 hr)
Level 1: No individual value exceeds 1% dissolved
Level 2: Average of the 12 units (L1 + L2) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved
Level 3: Average of the 24 units (L1 + L2 + L3) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved

pH 7.2, Q=80% (Type II Paddle 50 RPM, 1.5 hrs).

Level 1: Each unit is not less than 85% (Q+5%)
Level 2: Average of the 12 units (L1 + L2) is equal to or greater than 80% (Q), and no unit is less than 65% (Q-15%).
Level 3: Average of the 24 units (L1 + L2 + L3) is equal to or greater than 80% (Q), and not more than two units are less than 65% (Q-15%) and no unit is less than 55% (Q-25%).

The Reviewer's Comments: *The reviewer collected the dissolution information from the submission, which includes the lots for dissolution profile comparisons, alcohol dose dumping study and the stability batches for a range of dissolution at 90 minutes (obtained from stability data). These data are summarized in the following graph. The squares represent the mean for the biobatch and the stars for alcohol study. The green bars are the upper limits and red bars for the lower limits. The long cyan bars enclose the range of dissolution at 90 minutes for the stability batch.*



As seen from the figure, at 90 minutes, the lowest individual dissolution is 88%. The proposed dissolution acceptance criterion of pH 7.2, Q=80% at 1.5 hrs (Type II Paddle 50 RPM) is not optimal. On the other hand, if the criterion is set as Q=80% at 60 minutes, the biobatch would

have to go to Stage 3 with a possibility of failure. Therefore, an acceptance criterion of Q=80% at 75 minutes at the stage of pH 7.2 (Type II Paddle 50 RPM) is recommended. Since limited data at 75 minutes have been collected, a Phase IV commitment is proposed and the agreement is pending.

7. In vitro alcohol dosing dumping study

There is no in vitro alcohol dose dumping study in the original submission dated 7/30/2012. The FDA recommended evaluating alcohol induced dosing dumping potential for WC3045 capsules in NDA 204412 filing communication, issued on September 28, 2012. The Applicant submitted the study report for in-vitro alcohol induced dose dumping of WC3045 capsule on November 15, 2012, in response to the Agency's request.

WC3045 Capsules 400 mg were evaluated using an *in vitro* dissolution method conducted in three stages: Phase 1 - 0.1N hydrochloric acid with varying alcohol concentrations, proceeding to Phase 2 - pH 6.0 phosphate buffer, followed by Phase 3 - pH 7.2 phosphate buffer.

Dissolution data was generated using 12 capsules (n=12) at each of the following alcohol concentrations in the acid pre-treatment stage: 0%, 5%, 10%, 20% and 40%. The results are shown in the following tables.

Table: Dissolution Profile Results for WC3045 Capsule – Control 0% Ethanol

Sample	Capsule Wt (mg)	Drug Release (%LC) at Time (Mins)											
		0.1N HCl Acid				pH 6.0 buffer	pH 7.2 Buffer						
		15	30	60	120	60	0	15	30	45	60	75	90
1	642.68	0	0	0	0	0	0	0	17	80	92	96	97
2	638.58	0	0	0	0	0	0	0	7	37	86	94	96
3	637.36	0	0	0	0	0	0	12	58	82	90	94	95
4	645.40	0	0	0	0	0	0	0	12	50	75	87	93
5	635.11	0	0	0	0	0	0	0	21	75	86	91	93
6	634.56	0	0	0	0	0	0	17	41	67	82	89	94
7	640.63	0	0	0	0	0	0	0	2	44	79	88	96
8	643.49	0	0	0	0	0	0	0	36	75	87	91	93
9	636.28	0	0	0	0	0	0	0	18	65	83	91	96
10	634.06	0	0	0	0	0	0	0	2	60	83	90	93
11	638.72	0	0	0	0	0	0	0	46	72	84	91	94
12	630.36	0	0	0	0	0	0	0	5	68	85	91	93
Mean		**0**	**0**	**0**	**0**	**0**	**0**	**2**	**22**	**65**	**84**	**91**	**94**
Min		0	0	0	0	0	0	0	2	37	75	87	93
Max		0	0	0	0	0	0	17	58	82	92	96	97
SD		N/A						5.6	18.8	14.2	4.7	2.5	1.6

Table: Dissolution Profile Results for WC3045 Capsule – 5% Ethanol

Sample	Capsule Wt (mg)	Drug Release (%LC) at Time (Mins)										
		0.1N HCl Acid				pH 6.0 Buffer	pH 7.2 Buffer					
		15	30	60	120	60	0	15	30	45	60	75	90
1	635.47	0	0	0	0	0	0	0	6	83	95	97	99
2	640.99	0	0	0	0	0	0	0	2	79	96	99	100
3	643.68	0	0	0	0	0	0	0	6	75	90	94	96
4	631.64	0	0	0	0	0	0	0	38	91	98	99	99
5	636.53	0	0	0	0	0	0	0	55	87	96	99	100
6	633.24	0	0	0	0	0	0	0	48	82	92	96	98
7	627.54	0	0	0	0	0	0	0	84	84	96	99	100

8	647.05	0	0	0	0	0	0	0	2	30	69	85	91
9	647.47	0	0	0	0	0	0	0	2	53	85	92	95
10	647.12	0	0	0	0	0	0	0	2	27	61	80	91
11	636.45	0	0	0	0	0	0	0	16	76	97	99	99
12	639.88	0	0	0	0	0	0	0	6	44	72	87	94
Mean		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**22**	**68**	**87**	**94**	**97**
Min		0	0	0	0	0	0	0	2	27	61	80	91
Max		0	0	0	0	0	0	0	84	91	98	99	100
SD		N/A						0.1	27.3	22.8	12.9	6.4	3.4

Table: Dissolution Profile Results for WC3045 Capsule – 10% Ethanol

Sample	**Capsule Wt (mg)**	**Drug Release (%LC) at Time (Mins)**											
		0.1N HCl Acid				**pH 6.0 Buffer**	**pH 7.2 Buffer**						
		15	**30**	**60**	**120**	**60**	**0**	**15**	**30**	**45**	**60**	**75**	**90**
1	645.63	0	0	0	0	0	0	0	1	32	61	87	95
2	646.13	0	0	0	0	0	0	0	18	76	90	98	101
3	639.45	0	0	0	0	0	0	0	21	52	74	94	100
4	641.03	0	0	0	0	0	0	0	53	88	96	98	99
5	641.33	0	0	0	0	0	0	0	65	93	98	100	101
6	635.73	0	0	0	0	0	0	20	83	96	98	99	100
7	636.74	0	0	0	0	0	0	0	9	52	94	98	99
8	647.62	0	0	0	0	0	0	1	26	75	86	92	95
9	646.35	0	0	0	0	0	0	0	3	64	84	91	94
10	638.72	0	0	0	0	0	0	3	51	86	93	97	98
11	648.53	0	0	0	0	0	0	0	3	51	83	91	97
12	645.35	0	0	0	0	0	0	0	4	72	89	94	95
Mean		**0**	**0**	**0**	**0**	**0**	**0**	**2**	**28**	**70**	**87**	**95**	**98**
Min		0	0	0	0	0	0	0	1	32	61	87	94
Max		0	0	0	0	0	0	20	83	96	98	100	101
SD		N/A						5.8	27.8	20.0	10.7	4.1	2.5

Table: Dissolution Profile Results for WC3045 Capsule – 20% Ethanol

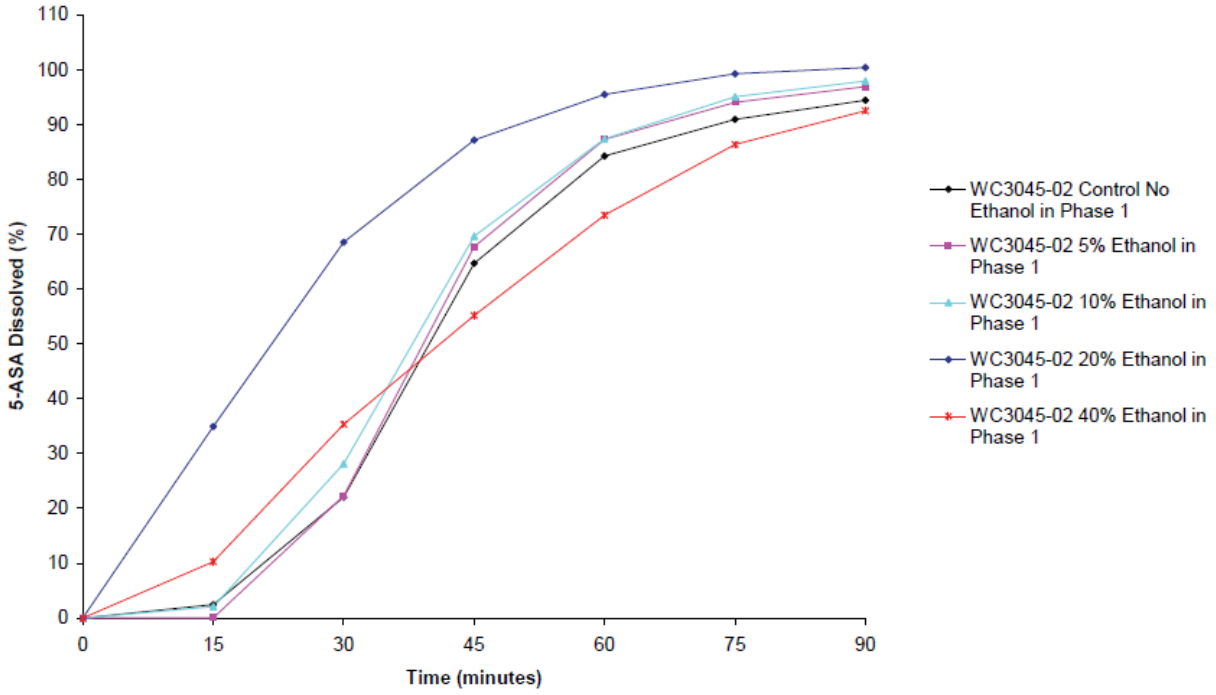
Sample	**Capsule Wt (mg)**	**Drug Release (%LC) at Time (Mins)**											
		0.1N HCl Acid				**pH 6.0 Buffer**	**pH 7.2 Buffer**						
		15	**30**	**60**	**120**	**60**	**0**	**15**	**30**	**45**	**60**	**75**	**90**
1	640.93	0	0	0	0	0	0	24	44	72	89	99	100
2	636.98	0	0	0	0	0	0	43	78	90	94	97	99
3	641.94	0	0	0	0	0	0	56	68	90	99	103	103
4	636.60	0	0	0	0	0	0	70	85	92	100	102	102
5	640.04	0	0	0	0	0	0	33	61	83	94	99	102
6	643.89	1	1	1	1	0	0	16	75	88	93	98	100
7	639.23	0	0	0	0	0	0	15	43	78	94	99	100
8	647.73	0	0	0	0	0	0	8	63	91	99	101	101
9	634.70	0	0	0	0	0	0	42	74	89	95	97	98
10	627.93	0	0	0	0	0	0	59	91	99	100	100	100
11	647.12	0	0	0	0	0	0	14	51	77	88	97	100
12	636.53	0	0	0	0	0	0	40	89	96	99	100	100
Mean		**0**	**0**	**0**	**0**	**0**	**0**	**35**	**69**	**87**	**95**	**99**	**100**
Min		0	0	0	0	0	0	8	43	72	88	97	98
Max		1	1	1	1	0	0	70	91	99	100	103	103
SD		N/A						19.9	16.6	7.9	4.1	1.9	1.3

Table: Dissolution Profile Results for WC3045 Capsule – 40% Ethanol

Sample	**Capsule Wt (mg)**	**Drug Release (%LC) at Time (Mins)**											
		0.1N HCl Acid				**pH 6.0 Buffer**	**pH 7.2 Buffer**						
		15	**30**	**60**	**120**	**60**	**0**	**15**	**30**	**45**	**60**	**75**	**90**
1	648.87	0	0	0	0	0	0	0	48	77	88	94	97
2	638.40	0	0	0	0	0	0	0	1	28	62	82	90
3	642.69	0	0	0	0	0	0	7	28	50	69	84	91

4	640.35	0	0	0	0	0	0	14	44	59	76	92	98
5	638.32	0	0	0	0	0	0	11	34	52	71	83	91
6	645.76	0	0	0	0	0	0	17	39	52	69	82	91
7	647.07	0	0	0	0	0	0	0	21	46	71	81	87
8	642.12	0	0	0	0	0	0	15	39	55	69	86	94
9	635.65	0	0	0	0	0	0	13	35	52	69	87	92
10	639.65	0	0	0	0	0	0	35	56	70	85	91	94
11	649.02	0	0	0	0	0	0	5	42	68	84	94	98
12	637.66	0	0	0	0	0	0	6	37	52	68	81	86
Mean		**0**	**0**	**0**	**0**	**0**	**0**	**10**	**35**	**55**	**73**	**86**	**93**
Min		0	0	0	0	0	0	0	1	28	62	81	86
Max		0	0	0	0	0	0	35	56	77	88	94	98
SD		N/A						9.9	14.0	12.8	8.0	5.0	4.0

The following figure shows For each ethanolic concentration, no mesalamine release was observed after 2 hours in Phase 1 (0.1N HCl) and then a further 60 minutes in Phase 2 (pH 6.0 Buffer), except one tablet from the batch showed 1% release in acid containing 20% ethanol. The following figure shows the results in Phase 3 - pH 7.2 phosphate buffer.



The similarity factors (f2) are summarized in the following table for the comparison between the dissolution in medium with different alcohol concentrations and the medium without alcohol.

Ethanolic Concentration (%)	f2 Value
5%	79
10%	68
20%	27
40%	50

The Reviewer's Comments: *Although the delayed release characteristics are maintained in Phase 1 - 0.1N HCl and Phase 2 –pH 6 when the media contain up to 40% alcohol in the acid stage (Phase I), the profile at Stage 3 (pH 7.2) was affected significantly when the alcohol*

concentration reached 20% and above. It is also noted that alcohol was only added to the acid stage (Stage 1). At Stage 2 (pH6.0) and Stage 3 (pH 7.2), no alcohol was present.
Because the highest concentrations of alcohol in GI tract are likely to be encountered in the acidic environment of the stomach, the dissolution profiles generated in 0.1 N HCl with different concentrations of alcohol are more clinically relevant (as compared to dissolution profiles generated in dissolution media at other pH's). Therefore, we consider the study is able to address the alcohol induced dose dumping potential.

A faster dissolution was shown at pH 7.2 medium when the alcohol concentrations reach 20% or more. However, the delayed release characteristics had not been compromised, because the dissolution in Phase 1 - 0.1N HCl and Phase 2 –pH 6 was zero and the formulation has been designed to release the drug at pH 7. The faster dissolution at pH 7.2 in the presence of high concentration (≥20%) of alcohol may not raise significant safety concern.

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/s/

JOHN Z DUAN
12/28/2012

MINERVA HUGHES
12/28/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204412	Submission Date(s): 08/01/2012, 09/06/2012, 09/18/2012, 09/14/2012, 10/31/2012, 11/27/2012
Brand Name	To be determined
Generic Name	Mesalamine Delayed Release Capsules
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Warner Chilcott
Relevant IND(s)	26,093
Submission/Review Type	Original NDA; Priority Review
Formulation; Strength(s)	Delayed Release Capsules; 400 mg
Indication	Ulcerative Colitis

Table of Contents

1 Executive Summary

1.1 Recommendation

NDA 204412 is acceptable from a Clinical Pharmacology perspective provided an agreement can be reached with the sponsor regarding language in the package insert. The Office of Scientific Investigations (OSI) has identified deficiencies during its inspections for this NDA and has issued Form 483s for which a response from the sponsor to OSI is pending at this time. Once recommendations from OSI are received and reviewed by OCP, an addendum will be entered into DARRTS to communicate our final recommendation.

1.2 Phase IV Commitments

Pediatric post-marketing studies that include PK assessments in all relevant age groups are being considered.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Mesalamine delayed release tablet formulation is currently approved for the treatment of Ulcerative Colitis. To address the Agency's concern related to the potential safety issue of dibutyl phthalate (DBP) as an excipient in Asacol products, Warner Chilcott has developed a new formulation (WC3045 capsules) in which dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the plasticizer dibutyl sebacate (DBS) and the tablet is then encapsulated. Based on communications held with the agency during the drug development, the NDA involves a single dose bioequivalence study PR08210 comparing the test (WC3045 capsules) and reference (Asacol 400 mg) formulations in a fully replicate crossover design, and utilizes the reference-scaled BE approach for highly variable drugs.

Study PR08210 demonstrates bioequivalence of the test and reference mesalamine formulations under the conditions studied (fasting). The primary endpoints for comparison included Cmax, AUC0-tldc as well as a partial AUC parameter AUC8-48. The latter partial AUC was recommended by the agency as it was perceived to reflect drug absorption (and therefore drug availability) at the site of action in the colon. Supportive analyses for other partial AUCs also suggested bioequivalence of the two formulations.

Parameter	Geometric Mean		Within-Subject Standard Deviation		Ratio (Test /Reference)	95% upper confidence bound of the linearized criterion
	Test	Reference	Test	Reference		
Cmax	109.9	99.4	1.167	1.275	1.106	-1.105
AUC8–48	618.3	556.4	1.453	1.490	1.111	-1.514
AUC0–tldc	719.6	648.4	1.464	1.536	1.110	-1.608

Cmax = Maximum plasma concentration (ng/mL); AUC8-48 = Area under the plasma concentration versus time curve from time 8 hours to 48 hours (ng·h/mL); AUC0–tldc = Area under the plasma concentration versus time curve from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)

Due to absence of food-effect information in the NDA for this new delayed release formulation, labeling will need to reflect that dose should be administered under relatively fasted conditions (e.g. 1 h before a meal or 2 h after a meal for this TID

administered drug). Label may be revised if food-effect information becomes available. Approved Asacol can be taken with or without food. NDA also includes in vitro release data at various pH conditions, as well as in vitro alcohol dose-dumping information that is being reviewed by ONDQA Biopharmaceutics Division.

2 Summary of CPB Findings

2.1 General Attributes of the Drug

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Mesalamine 400 mg delayed release tablets (Asacol; NDA 19-651) were approved in 1992 for the treatment of mild to moderately active ulcerative colitis, UC and for maintenance of the remission of UC. The coating of the approved formulation contains a plasticizer dibutyl Phthalate, DBP which has been linked with harmful effects in pregnancy and fertility in preclinical animals when given in very high doses. The sponsor was advised to reformulate the mesalamine delayed release formulation to eliminate DBP. In this regard, sponsor has submitted with this NDA, data supporting the reformulated mesalamine 400 mg delayed release formulation that now includes dibutyl sebacate, DBS instead of DBP as the plasticizer in the enteric coating. The proposed formulation is an over-encapsulated tablet and contains the same release-controlling excipient Eudragit S as approved Asacol delayed release 400 mg tablets.

Several meetings were held with the sponsor during the course of this reformulation. The key agreements made during these meetings and protocol reviews are summarized below:

During a Type C teleconference between the FDA's Division of Gastroenterology Products (DGP) and Warner Chilcott which was held on April 22, 2010, the FDA informed Warner Chilcott that as an alternative to conducting trials with clinical endpoints previously advocated for locally acting GI drug mesalamine, it would be possible to establish bioequivalence between the two formulations through pharmacokinetic (PK) and special dissolution studies.

During a Type C meeting on November 2, 2010, the details of the PK and dissolution requirements were discussed further. During this meeting, the agency agreed with the sponsor regarding the use of partial AUC in addition to the traditional PK parameters (Cmax and AUC) to ensure profile similarity as part of a bioequivalence approach that also includes similarity of dissolution profiles. For partial AUC, agency recommended characterizing the latter portion of the PK profile. FDA also agreed that a reference scaled BE approach for highly variable drugs would be appropriate.

In advice letters dated February 15, 2011 and December 5, 2011, the agency provided further input on the sponsor's proposed study protocol. Agency recommended a fully replicate study design (i.e. both test and reference administered twice), and recommended statistical analyses of Cmax, AUC0-tldc, AUC8-48 in the proposed study. The agency noted that they recommend the partial AUC8-48 hours as opposed to (b) (4) proposed by the sponsor. This time period (8-48 hours) was perceived by the agency at the time to be more clinically relevant and was expected to be able to detect significant differences in product performance. The agency also noted that additional

exploratory parameters, such as [redacted] (0-12 and 12-48 hours, etc.) may be included as secondary endpoints.

A pre-submission meeting was held on June 13, 2012 at which time the agency reiterated that a comparative clinical endpoint study will not be required if bioequivalence and dissolution comparability have been established. Agency also clarified that a reference-scaled BE approach for highly variable drugs can be employed is applicable even when variability (intra-subject %CV) exceeds 100 %.

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?

Drug Product: The composition of WC3045 capsule vs. Asacol is summarized:

Table 1: Unit-Dose Composition of WC3045 Capsules and Asacol Tablets

Ingredient	Unit Quantity (mg/dosage form)	
	WC3045 Capsules Formulation WC3045-02 (Material Number 33075301)	Asacol (mesalamine) Delayed-release Tablets, 400 mg
[redacted]		
5-Aminosalicylic acid (5-ASA, mesalamine), USP	400.0	400.0
Lactose Monohydrate, NF	[redacted]	
Povidone, USP		
Sodium Starch Glycolate, NF		
Magnesium Stearate, NF		
Talc, USP		
Colloidal Silicon Dioxide, NF		
[redacted]		
Methacrylic acid copolymer, NF, type B (Eudragit S [redacted]		
Talc, USP		
Dibutyl sebacate, NF		
Dibutyl phthalate, NF		
Ferric oxide, NF, red		
Ferric oxide, NF, yellow		
[redacted]		
Polyethylene glycol [redacted]		
Subtotal		
HPMC capsule printed with white ink [redacted]		
[redacted]		
TOTAL		

[1]Eudragit S [redacted] methacrylic acid copolymer, NF Type B

Drug Substance: The primary characteristics of mesalamine drug substance are shown:

Drug	Mesalamine
International Nonproprietary Name (INN)	Mesalazine
Chemical Name (CAS)	Benzoic acid, 5-amino-2-hydroxy
Common Name	5-Aminosalicyclic acid 5-ASA
CAS Registry Number	89-57-6
Molecular Formula	$C_7H_7NO_3$
Molecular Weight	153.14

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

WC3045 (mesalamine) delayed-release capsules, 400 mg are indicated for the treatment of mildly to moderately active ulcerative colitis (UC) and for the maintenance of remission of UC.

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.

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

The proposed oral dosing regimen is the same as the approved regimen for Asacol (mesalamine) delayed-release tablets, 400mg (NDA 19-651).

 For the treatment of mildly to moderately active ulcerative colitis: The usual dosage in adults is two 400 mg capsules to be taken three times a day for a total daily dose of 2.4 grams for duration of 6 weeks.

 For the maintenance of remission of ulcerative colitis: The recommended dosage in adults is 1.6 grams daily, in divided doses. Treatment duration in the prospective, well-controlled trial was 6 months.

2.2 General Clinical Pharmacology

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

There are no new clinical pharmacology or clinical studies in this NDA. One bioavailability/ bioequivalence study (Study PR-08210) was conducted to compare the pharmacokinetic profile and mesalamine relative bioavailability of WC3045 capsules to Asacol tablets, 400 mg. The bioavailability study was designed and conducted according to FDA's recommendations, including addition of the partial AUC parameter AUC8-48, and replicate treatment design for both test and reference to evaluate intrasubject variability. Study PR-08210 was an open-label, randomized, single-dose, replicate treatment, four-period, two-sequence, two-formulation crossover study. As recommended by FDA, Warner Chilcott utilized the reference-scaled average bioequivalence methodology as described in the Draft Guidance on Progesterone, CDER February 2011 and an article by Haidar et al (Haidar 2008).

The proposed WC3045 capsules and the approved Asacol tablets are delayed release formulations with a pH-sensitive coating that breaks down at a pH 7.0 or greater. Failure of the pH sensitive component may cause early, unintended release of the drug in the GI tract and thus affect availability at the site of action in the colon. A pH 7.0 is typically achieved in the GI tract at the terminal ileum. In healthy volunteers the transit to this region (and subsequent transfer to cecum) is variable, and may take ~ 5 h (± 1h) on average. Transit time appears somewhat longer in UC patients (6 ± 1.5 h) [Published data for orocecal transit times (OCTT); Waller et al, 1975; Rao & Read, 1990; Bennink et al, 1999; Priebe et al, 2004]. Therefore a partial AUC parameter such as AUC8-48h, that encompasses a time period after drug transit to terminal ileum/cecum may be better reflective of drug absorption and therefore drug availability at colon. Cmax and AUC0-tldc may ensure comparable overall systemic exposures across formulations, but will not identify significant differences in the drug release profile between formulations.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Systemic mesalamine exposure has been evaluated using validated LC-MS/MS methods at (b) (4). The assay validation and sample assay reports appear acceptable. However, a final inspection report for the clinical and bioanalytical facilities and final recommendations by the Office of Scientific Investigations, OSI are pending at this time.

2.2.4 What is the exposure-response relationship for mesalamine in UC?

Systemic exposure-response relationship for efficacy is currently not understood for mesalamine in the treatment of UC. It is generally believed that mesalamine acts topically to reduce inflammation in the colon and the contribution of systemically available drug (estimated at ~ 28 % of dose) on the efficacy outcomes in UC is not known. Safety information generated in the current NDA is following a single dose of the test drug in healthy volunteers of study PR08210 and includes a wide range of mesalamine systemic concentrations due to the high intra- and inter-subject variability associated with the PK

of this drug. Please refer to the medical officer review for additional information related to safety at these exposures.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Dosing recommendations for the proposed reformulation will be the same as for the approved Asacol 400 mg delayed release tablet formulation. There are no revisions to the dose or dosing frequency that require additional consideration in this NDA. Food-effect information on bioavailability is lacking for the new formulation. BE study was conducted under fasted conditions. Drug labeling, if approved has to be restrictive with regard to dosing in relation to food (e.g. dosing 30 minutes prior or 2 h after a meal) until further information can be generated by the sponsor in this regard. Please refer to biopharmaceutics and labeling sections of this review for further information in this regard.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Single dose pharmacokinetics of the proposed (WC3045) delayed release mesalamine capsules 400 mg have been evaluated in the current NDA in healthy volunteers of the BA/BE study PR08210. In this study subjects (n = 238 completers) received a single dose of the proposed formulation (WC3045) and the reference Asacol 400 mg formulation in a crossover manner under fasting conditions. Plasma mesalamine was determined in samples collected at regular intervals at pre-dose and up to 48 hours post-dose and analyzed using validated bioanalytical methods with a lower limit of quantitation of 10 ng/mL for mesalamine. Plasma concentrations and resultant PK of mesalamine were associated with high inter- and intra-individual variability. Formulation comparability is discussed in detail in the biopharmaceutics section of this review.

Mean PK of mesalamine from WC3045 capsules in healthy volunteers of BE study PR-08210 are summarized. PK parameters are from the 238 subjects who received replicate treatments of test and reference formulations. N values shown in table represent total number of measurements contributing to the averages:

Parameter	Test **Mean (SD)**	Reference **Mean (SD)**
Cmax; ng/ml; n = 476	265 (513)	285 (622)
AUC8-48; ng.h/mL; n = 476	1160 (1062)	1111 (1023)
AUC0-tldc; ng.h/mL; n = 476	1419 (1458)	1426 (1587)
AUCinf; n = 254	2349 (2478)	2546 (2013)
Kel; n = 254	0.158 (0.151)	0.182 (0.183)
Tmax; h; **median [range]**	12 [4 – 48]	12 [4 - 48]
Tlag; h; n = 445	10.1 (6.2)	10.7 (6.5)

Metabolite PK was not characterized in this BE study. However, labeling information previously available for the major metabolite in the Asacol labeling will be summarized in the labeling. Additional ADME information is also summarized from approved/proposed labeling and literature:

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

Plasma concentrations of mesalamine (5-aminosalicylic acid; 5-ASA) and its metabolite, N-acetyl-5aminosalicylic acid (N-Ac-5-ASA) are highly variable following administration of mesalamine delayed release formulations. The tmax for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid, is usually delayed, reflecting the delayed release, and ranges from 4 to 12 hours. After intravenous administration, the half-life of elimination for mesalamine was around 40 minutes. After oral administration the elimination for mesalamine and N-acetyl-5-aminosalicylic acid is variable and may include continued absorption in addition to elimination. Label reports that the elimination half life values are usually about 12 hours, but are variable, ranging from 2 to 15 hours. There is a large intersubject variability in the plasma concentrations of mesalamine and N-acetyl-5-aminosalicylic acid and in their elimination half lives following oral administration of mesalamine DR products.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Plasma mesalamine concentrations were determined in healthy volunteers in the BE study PR08210 in which the objective was to compare the relative bioavailability and bioequivalence of the test and reference (Asacol) formulations. Thus PK from patients is not available for this proposed formulation. In general, the presence of an inflamed/damaged colonic mucosa in ulcerative colitis may allow a greater systemic absorption of mesalamine from colonic sites in UC patients compared to healthy volunteers with an intact colon. Theoretically such an increase may not persist with chronic dosing if the mucosal integrity is improved with ongoing anti-inflammatory treatment with mesalamine. The safety and efficacy implications of a potentially greater systemic exposure in UC patients are not understood.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The pharmacokinetics of oral mesalamine appear to be associated with large between- and within-subject variability. The average variability for the test formulation was similar or somewhat smaller compared to the reference formulation in healthy volunteers. The variability information for mesalamine capsules (proposed) in patients with UC is

not known as the study was conducted in healthy volunteers. However, in patients the systemic uptake 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. 0 for drug release to occur as well as the gastrointestinal transit time variabilities across individuals may influence the amount of drug absorbed from the intestine.

	Test (WC3045 Capsules)		Reference (Asacol 400 mg tablets)	
	Inter-Subject % CV	Intra-Subject % CV	Inter-subject CV	Intra-subject CV
Cmax	148 %	170 %	165 %	200 %
AUC0-tldc	81 %	272 %	87 %	306 %
$AUC_{8\text{-}48h}$	70 %	268 %	71 %	286 %
Within-subject CV = [SQRT(EXP(sWR^2)-1)]; sWR is within-subject standard deviation from SAS output				

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

There were no specific specific subpopulation studies in the NDA. Dosage adjustments are not currently recommended in any subgroup. However, cautionary language is included based on approved labeling for Asacol:

Elderly

Clinical studies for mesalamine delayed release products did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing TRADENAME. Reports from uncontrolled clinical studies and post-marketing reporting systems suggest a higher incidence of blood dyscrasias, i.e., agranulocytosis, neutropenia, pancytopenia, in subjects receiving mesalamine delayed release products who are 65 years or older. Caution should be taken to closely monitor blood cell counts during drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when prescribing this drug therapy. As stated in the PRECAUTIONS section, it is recommended that patients have an evaluation of renal function prior to initiation of therapy and periodically while on TRADENAME therapy.

Pediatrics

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

(b) (4)

Hepatic Impairment

(b) (4)

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.

Pregnancy and Lactation

(b) (4)

Mesalamine and its N-acetyl metabolite are excreted into human milk. In published lactation studies, maternal mesalamine doses from various oral and rectal formulations and products ranged from 500 mg to 3 g daily. The concentration of mesalamine in milk ranged from non-detectable to 0.11 mg/L. The concentration of the N-acetyl-5-aminosalicylic acid metabolite ranged from 5 to 18.1 mg/L. Based on these concentrations, estimated infant daily doses for an exclusively breastfed infant are 0 - 0.017 mg/kg/day of mesalamine and 0.75-2.72 mg/kg/day of N-acetyl-5-aminosalicylic acid. Caution should be exercised when TRADENAME is administered to a nursing woman.

2.4 Extrinsic Factors

2.4.2 Drug-drug interactions

[redacted] (b) (4)

2.5 General Biopharmaceutics

2.5.2 Is the proposed mesalamine formulation (WC3045 400 mg capsules) bioequivalent to the reference mesalamine (Asacol 400 mg tablets) formulation?

Bioequivalence Conclusions: The relative bioavailability and bioequivalence of the test (WC3045 DR capsules) and reference (Asacol DR tablets) were evaluated in study PR08210 in healthy volunteers. Data suggests bioequivalence of the WC3045 400 mg capsules and Asacol 400 mg tablets following administration of replicate single dose treatments of test and reference drug products under fasted conditions. Bioequivalence was demonstrated for key PK endpoints Cmax, AUC0-tldc, and AUC8-48 as well as for the supportive partial AUC parameters, AUC10-48 and AUC12-48. Tlag and Tmax values were prolonged as expected for delayed release formulations and were comparable between test and reference products. Terminal elimination phase was not readily identifiable in all individuals and therefore kel, T1/2, AUCinf data was only available for some of the study subjects. The within subject variability was very high for both test and reference formulations, with the variability of the test formulation for the PK various parameters somewhat lower compared to the reference formulation. Approximately 31 subjects in the test group and 38 subjects in the reference group had no detectable drug levels throughout the PK sampling interval (48 hours) in at least one study period. The reason for the absence of drug concentrations was not clear (i.e. whether it is related to lack of drug release or lack of drug absorption), however the incidence was comparable between test and reference formulations. Statistical analyses were conducted with and without these individuals and bioequivalence was demonstrated regardless of imputation.

Bioequivalence Study Summary:

This open-label, randomized, single-dose, replicate treatment, 4-period, 2-sequence, 2-formulation crossover study was conducted under medical supervision in healthy male and female volunteers. All subjects received the following Test and Reference treatments.
• Test: One mesalamine delayed-release capsule (FormulationWC3045-02), 400 mg
• Reference: One Asacol (mesalamine) delayed-release tablet, 400 mg

All treatments were administered orally with 240 mL ambient-temperature water to fasted subjects. Treatment periods were separated by at least 7 days. Subjects were randomly assigned to one of the following 2 treatment sequences:

• Sequence A: Reference – Test – Reference – Test
• Sequence B: Test – Reference – Test – Reference

N = 252 subjects (18 – 60 years) were enrolled and n = 238 completed all four treatments. PK blood samples were collected pre-dose (within 2 hours prior to dosing) and 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 30, 36, and 48 hours post-dose. Plasma mesalamine concentrations were determined using a validated LC-MS/MS method; the bioanalytical work was performed by (b) (4).

Pharmacokinetic analyses: PK analyses were done using non-compartmental analytical methods. The following parameters were calculated:

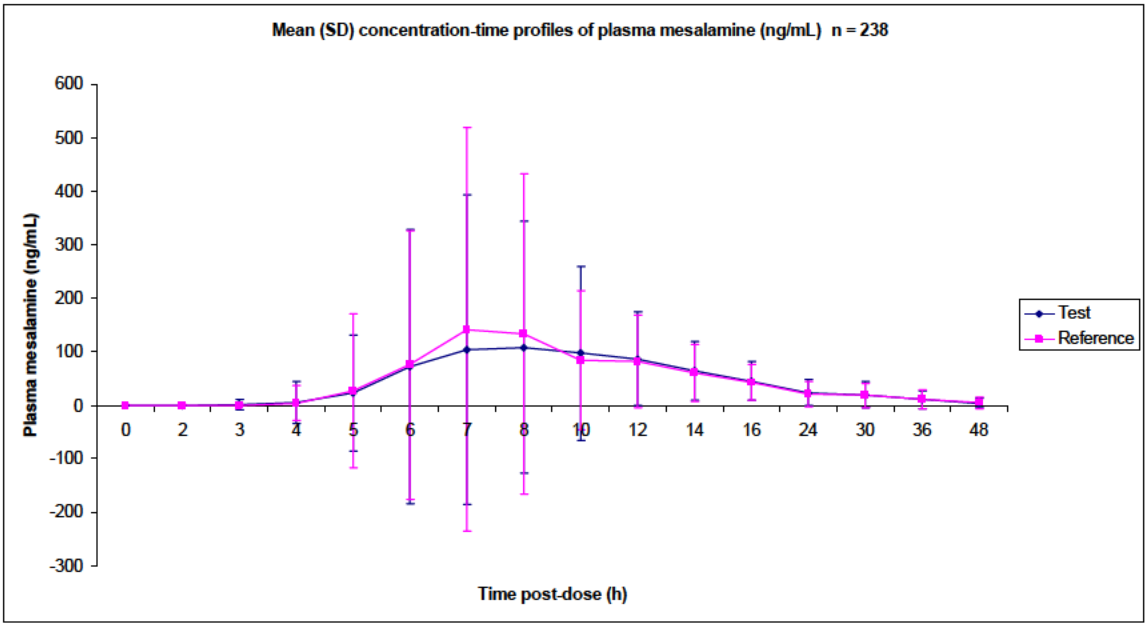
Pharmacokinetic Parameter	Definition
Cmax	Maximum plasma concentration
AUC8–48	The area under the plasma concentration versus time curve, from 8 hours to 48 hours post dose or to the last determinable concentration (tldc), as calculated by the linear trapezoidal method
AUC0–tldc	The area under the plasma concentration versus time curve, from time 0 hours to the tldc, time of last determinable concentration, as calculated by the linear trapezoidal method.
AUC0-inf	The area under the plasma concentration versus time curve, from time 0 hours to infinity, as calculated by the linear trapezoidal method.
tlag	Time postdose to the first measurable concentration
tmax	Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, tmax was defined as the first time point with this value.
kel	Terminal phase rate constant
t½	Terminal phase half-life (0.693/kel)

Pharmacokinetic parameter calculations were performed using SAS (Version 9.2).

PK endpoints for primary analyses: The primary endpoints as agreed during the pre-submission review period for this NDA included AUC8-48 as the partial AUC of interest. All statistical analysis by sponsor was performed using PC/SAS, Version 9.2, with SAS program code prepared specifically for the project. Geometric Mean ratio was calculated as (T/R)=[(T1*T2)/(R1*R2)]1/2. The point estimates of the Test/Reference geometric mean ratio for Cmax, AUC8-48 and AUC0-tldc were calculated. For Cmax, AUC8-48, AUC0-tldc, and AUC0-inf, the within-subject standard deviation for each formulation was estimated from the analysis of variance of the log-transformed parameter using the reference-scaled average bioequivalence procedure as described in the February 2011 Draft Guidance on Progesterone. The same procedure was used to determine the 95% (1-sided) upper-confidence bound on the linearized criterion for these pharmacokinetic parameters.

Results Summary:

Mean plasma concentration-time data for the test and reference mesalamine treatments:



For the formulation comparisons to pass the reference-scaled bioequivalence analysis, the 95% upper confidence bounds of the linearized criterion should be ≤ 0, and the point estimates of the Test/Reference geometric mean ratio should be within 0.80-1.25 for the key PK parameters (in this case Cmax, AUC8-48 and AUC0-tldc).

Imputation: Following administration of Test treatment, 31 subjects had plasma mesalamine concentration values below the limit of quantitation for the entire sampling period. Following administration of Reference treatment, 38 subjects had plasma mesalamine concentration values below the limit of quantitation for the entire sampling period. Values of 5 ng/mL (50% of the 10 ng/mL LLOQ) and 5 ng•h/mL were imputed for Cmax and AUC for those subject treatment periods with mesalamine concentration values below the lower limit of quantitation (LLOQ). Data analyses were conducted with and without imputation (sensitivity analyses) and results suggest formulation bioequivalence regardless of imputation.

Sponsor's analyses of the study data demonstrate bioequivalence of the formulations using the scaled BE approach for HVD. Reviewer's non-compartmental analyses of the plasma mesalamine concentration-time data as well as the statistical analyses using SAS 9.2 provided similar results and will be summarized below the sponsor's analyses of the same for each set of results (primary and supporting PK endpoints).

AUCinf couldn't be determined for all subjects due to the lack of clearly identifiable terminal elimination phase in many patients possibly as the terminal phase noted in the study is a composite of continued drug absorption and not just elimination. While AUCinf data was available for at least 1 study period in 174 individuals, data for all four treatment groups were available in only 27 of subjects. Resultant statistical analyses suggest bioequivalence but would not constitute a primary PK endpoint due to the absence of adequate sample size with quantifiable AUCinf.

Sponsor's analysis of the primary PK endpoints:

Parameter	Geometric Mean		Within-Subject Standard Deviation		Ratio (Test /Reference)	95% upper confidence bound of the linearized criterion
	Test	Reference	Test	Reference		
Cmax	109.9	99.4	1.167	1.275	1.106	-1.105
AUC8–48	618.3	556.4	1.453	1.490	1.111	-1.514
AUC0–tldc	719.6	648.4	1.464	1.536	1.110	-1.608

Cmax = Maximum plasma concentration (ng/mL); AUC8-48 = Area under the plasma concentration versus time curve from time 8 hours to 48 hours (ng·h/mL); AUC0–tldc = Area under the plasma concentration versus time curve from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)

Supportive data in the form of statistical comparison of additional partial AUC parameters was undertaken by sponsor and results in general support bioequivalence of the parameters tested.

Sponsor's analyses of supportive partial AUC parameters AUC10-48 and AUC12-48:

Statistic	AUC10-48 (ng.hr/mL)	AUC12-48 (ng.hr/mL)
Ratio of geometric means (Test/Reference)	1.103	1.090
90% 2-sided confidence interval	0.956, 1.272	0.941, 1.262
95% (1-sided) upper confidence bound on the linearized criterion	-1.448	-1.475

Reviewer analyses of primary, supportive partial AUC parameters also concluded bioequivalence of the test and reference formulations. Note that exploratory statistical comparison of partial AUC parameters corresponding to the early part of the release profile was also conducted (AUC0-2, AUC0-4, AUC0-6 and AUC0-8) and in general did not pass bioequivalence criteria possibly due to the lack of quantifiable concentrations in most individuals at these early time points. Data therefore suggests that the test and reference mesalamine delayed release formulations perform comparably in terms of drug release that occurs primarily in the latter part of the profile as per design, in order to allow drug availability at the site of action in the colon.

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
Primary Statistical Endpoints								
Cmax	1.11	95.12	122.49	1.5156088	1.2311006	-1.030364	Scaled/PE	PASS
AUC_{TLDC}	1.08	90.52	121.76	1.8493626	1.3599127	-1.265287	Scaled/PE	PASS
AUC8-48	1.10	92.89	125.92	2.0725896	1.4396491	-1.41748	Scaled/PE	PASS
Additional Analyses								
AUC6-48	1.10	92.38	126.11	2.1815445	1.4770052	-1.493384	Scaled/PE	PASS
AUC10-48	1.12	94.38	126.79	1.9880089	1.4099677	-1.355735	Scaled/PE	PASS
AUC12-48	1.10	93.90	126.05	1.9860953	1.4092889	-1.35789	Scaled/PE	PASS

Summary of tmax, tlag, elimination rate constant, and half-life values following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) and a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

	TEST				REFERENCE			
Statistic	tmax (h)	tlag (h)	kel (h^{-1})	Half-life (h)[b]	tmax (h)	tlag (h)	kel (h^{-1})	Half-life (h)[b]
N	207	207	80	80	205	204	53	53
Mean	14.298	10.004	0.147	4.699	15.147	10.710	0.202	3.424
Standard Deviation	6.641	4.713	0.116		6.715	4.586	0.153	
Within-subject RMSD[a]	7.828	5.628	0.125		8.810	6.438	0.174	
Median	12.000	9.000	0.119		13.000	10.000	0.173	
Minimum	5.000	4.000	0.020		5.500	4.500	0.013	
Maximum	39.000	28.000	0.512		42.000	27.500	0.562	

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food-effect on the bioavailability of the proposed WC3045 delayed release formulation has not been evaluated under the current NDA. The approved mesalamine drug product, (administered three times daily) is dosed without regard to food based on similar absorption of drug in fasted and fed subjects (based on Asacol 400 mg label). Due to the lack of food-effect information for the proposed delayed release capsule formulation, revised dosing instructions should note the following:

TRADENAME (mesalamine) delayed release capsules should be dosed at least 1 h before a meal or 2 h after a meal.

Food-effect information on this specific formulation if become available can be used to revisit dosing instructions with regard to food intake.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Special in vitro dissolution studies at various pH conditions encountered throughout the GI tract were a requirement for the proposed delayed release capsule product and together with the results of the BE study are expected to govern the final approval. Please see review of the dissolution data by ONDQA Biopharmaceutics discipline (Dr. John Duan).

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma mesalamine concentrations were determined using a validated LC-MS/MS method; the bioanalytical work was performed by (b) (4).

This assay utilizes protein precipitation with HPLC separation and MS/MS detection for the determination of 5-ASA and N-Acetyl-5-ASA in human K3 EDTA plasma using stable labeled (b) (4) as internal standards.

Full validation: The LC/MS/MS method for the determination of 5-ASA and N-Acetyl-5-ASA concentrations in human K3 EDTA plasma was validated according to (b) (4) SOP BC03, Version 1.0, for the concentration range of 10.0 to 1500 ng/mL for 5-ASA and 20.0 to 2500 ng/mL for N-Acetyl-5-ASA. Calibration standards and quality control (QC) samples were prepared by spiking control human plasma with known amounts of 5-ASA and N-Acetyl-5-ASA.

The method validation results are summarized below:

Dilution integrity was demonstrated up to a 40-fold dilution for mesalamine.

Sensitivity: The lower limit of quantitation (LLOQ) of the assay was defined as the lowest calibration standard concentration. Samples prepared at a concentration of 10.0 ng/mL for 5-ASA and 20.0 ng/mL for N-Acetyl-5-ASA were analyzed in replicates of six in Run 1. Precision of 2.13% and accuracy of -0.500% were obtained for 5-ASA. Precision of 4.66% and accuracy of -1.00% were obtained for N-Acetyl-5-ASA. The signal-to-noise ratio for each peak was ≥ 5:1, and therefore met the acceptance criteria.

Inter-Run Precision and Accuracy: Inter-run precision and accuracy were determined by analyzing three concentrations (25.0, 600 and 1200 ng/mL for 5-ASA and 50.0, 1000, and 2000 ng/mL for N-Acetyl-5-ASA) of QC samples in replicates of six over three separate batch runs.

Precision of the method, defined by the percent relative standard deviation (%RSD) [standard deviation/mean × 100], was determined from the interpolated QC sample concentrations. The overall precision for the QC samples at three concentrations of 5-ASA over the three batch runs was ≤ 3.83%. The overall precision for the QC samples at three concentrations of N-Acetyl-5-ASA over the three batch runs was ≤ 2.84%.

Accuracy of the method was defined by the percent relative error (%RE) [(mean observed concentration - nominal concentration) / nominal concentration × 100]. The overall accuracy for the QC samples at three concentrations of 5-ASA over the three batch runs ranged from 4.00% to 5.17%. The overall accuracy for the QC samples at three concentrations of N-Acetyl-5-ASA over the three batch runs ranged from 5.35% to 6.20%.

Recovery (extraction efficiency): An overall mean extraction recovery of 106% was observed for 5-ASA and an overall mean extraction recovery of 114% was observed for N-Acetyl-5-ASA.

Carryover Evaluation: During Run 1, zero calibration standards (human plasma blanks with internal standard added) were analyzed after each high level standard to assess

carryover. The response (peak area) for the zero calibration standards had to be ≤ 20% of the lowest standard to be acceptable. No carryover was observed for 5-ASA or N-Acetyl-5-ASA.

Stability: Mesalamine is stable in human plasma at room temperature for 24 hours and stable for 513 days at -80ºC. The analyte was shown to be stable during 6 freeze-thaw cycles.

Conclusions: The LC/MS/MS analytical method for the determination of 5-ASA and N-Acetyl-5-ASA has been validated for the concentration range of 10.0 to 1500 ng/mL for 5-ASA and 20.0 to 2500 ng/mL for N-Acetyl-5-ASA in human K3 EDTA plasma. The method has been demonstrated to be precise and accurate for analysis of study specimens.

Partial validation: Additionally, a partial validation was conducted to modify the original method to monitor only 5-ASA on the LC-MS/MS system. This method continues to include N-acetyl-5-ASA for all calibration standard and QC preparations; however, this compound is not monitored upon injection onto the LC-MS/MS system. The internal standard for N-Acetyl-5-ASA ((b) (4) has also been removed in this method, and an additional anticoagulant (K2 EDTA) has been validated.

Partial validation summary of K2 EDTA plasma:

Standard Curve	
R2	0.9994
Sensitivity	
LLOQ 10 ng/ml Precision % CV	2.12 %
LLOQ Accuracy % RE	5 %
ULOQ 1500 ng/mL % CV	4.3 %
ULOQ % RE	3 %
Quality controls	
25 ng/Ml % CV % RE **600 ng/mL** % CV % RE **1500 ng/mL** % CV % RE	 2.71 % 0.4 % 4.22 % -0.5 % 2.05 % -1.42 %

Conclusions: The LC/MS/MS analytical method for the determination of 5-ASA (single-analyte monitoring) has been validated with an increased dwell time of 250 msec, for the concentration range of 10.0 to 1500 ng/mL in human K3 EDTA plasma. This method has also been validated for 5-ASA in human K2 EDTA plasma. This method has been demonstrated to be precise and accurate for analysis of study specimens. This new method was employed for analysis of all samples from study PR-08210.

Validation summary from study report (study sample assay) was as follows:

Assay Performance: Calibration standards and quality control (QC) samples, prepared by spiking K2 EDTA human plasma with known amounts of 5-ASA, were routinely analyzed with the test samples. Known amounts of N-Acetyl-5-ASA were also spiked into the standard and QCs, but this analyte was not monitored on the LC/MS/MS system. During analysis of the first several subjects in Runs 1 - 6, it was noticed that the majority of sample concentrations were in the lower half of the curve range. For this reason, and with the Sponsor's approval, a fourth QC level was validated at 100 ng/mL of 5-ASA during Run 7. N-Acetyl-5-ASA was also present in this additional QC level (at 167 ng/mL); although, this analyte was not monitored. This extra QC level was employed for all subsequent runs, in addition to the original three QC levels (25.0, 600, and 1200 ng/mL for 5-ASA).

Assay parameters	
Standard curve	
R2	0.9995
Precision (% CV)	2.14 to 3.23 %
Accuracy (% RE)	-0.933 % to 1.16 %

QC samples	
Precision, %CV:	
25 ng/mL	3.92%
100 ng/mL	2.92%
600 ng/mL	2.67%
1200 ng/mL	2.85%
Accuracy, %RE:	
25 ng/mL	-0.8%
100 ng/mL	3 %
600 ng/mL	1.83%
1200 ng/mL	0.75%
Dilution QCs;	
% CV	3.22 %
% RE	6.54 %

Incurred Sample Reanalysis: The acceptance criterion for confirmatory re-analysis of incurred samples was met for 5-ASA since 821/832 (98.7%) of the ISR samples had results within 20% of the mean values, with a mean overall bias of 1.07%.

3 Detailed Labeling Recommendations

Clinical Pharmacology section incorporating agency recommendations:

2 Dosage and Administration

For the treatment of mildly to moderately active ulcerative colitis, the dose of mesalamine delayed-release capsules in adults is two 400 mg capsules to be taken three times daily (total daily dose of 2.4 g), for a duration of 6 weeks.

For the maintenance of remission of ulcerative colitis, the recommended dose of mesalamine delayed-release capsules in adults is 1.6 g daily, in divided doses.

Swallow whole, do not cut, break, or chew.

TRADENAME should be administered at least 1 h before a meal or 2 h after a meal.

12.3 Pharmacokinetics

Absorption

Approximately 28 percent of the mesalamine in mesalamine delayed-release formulation is absorbed after oral ingestion. The tmax for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid, is usually delayed, reflecting the delayed-release, and ranges from 4 to 12 hours.

The effect of food on the absorption of mesalamine from TRADENAME delayed-release capsules has not been evaluated.

Metabolism

The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver to N-acetyl-5-aminosalicylic acid.

Excretion

Absorbed mesalamine is excreted mainly by the kidney as N-acetyl-5-aminosalicylic acid. Unabsorbed mesalamine is excreted in feces.

After intravenous administration, the half-life of elimination for mesalamine is reported to be around 40 minutes. After oral administration, the terminal elimination half-life of for mesalamine and N-acetyl-5-aminosalicylic acid are usually about 12 hours, but are variable, ranging from 2 to 15 hours. There is a large inter- **and intra-**subject variability in the plasma concentrations of mesalamine and N-acetyl-5-aminosalicylic acid and in their elimination half-lives following administration of mesalamine delayed-release formulations.

4 Appendices

4.1 Individual Study Review

PR-08210: Study evaluated the relative bioavailability and bioequivalence of the new mesalamine delayed release capsule 400 mg (test) to that of the approved Asacol, mesalamine delayed release tablet 400 mg. Due to high variability of the pharmacokinetics of Asacol tablets, study evaluated bioequivalence using the reference-scaled bioequivalence approach (RSABE). The new mesalamine formulation differs from the approved Asacol tablets in that the plasticizer included in the enteric coating is now dibutyl sebacate (DBS) compared to dibutylphthalate (DBP) in the approved formulation. In addition, the new formulation over-encapsulates the enteric coated tablet in order to provide additional stability of the enteric coating. The main excipient that provides the enteric coating and therefore delayed release of the active ingredient has not been altered (Eudragit S).

Regulatory history: In response to a citizen's petition by the sponsors of Asacol and Pentasa, FDA responded that bioequivalence studies would be accepted for oral mesalamine delayed release or modified release formulations as long as appropriate endpoints (including partial AUCs) are identified and reference-scaled bioequivalence analysis for highly variable drugs is used for statistical analysis. The agency at that time communicated that a clinical endpoint comparison would not be necessary and that a scaled BE study using appropriate PK endpoints together with specialized dissolution studies covering the pH range anticipated would address bioequivalence of test and reference formulations. The BE study was to be conducted under both fed and fasted conditions, and due to the lack of proportional PK between different dosage strengths, separate BE studies would be required for each strength of oral mesalamine (e.g. 400 mg, 800 mg).

Study design:

This open-label, randomized, single-dose, replicate treatment, 4-period, 2-sequence, 2-formulation crossover study was conducted under medical supervision in healthy male and female volunteers. All subjects received the following Test and Reference treatments.
 Test: One mesalamine delayed-release capsule (FormulationWC3045-02), 400 mg
 Reference: One Asacol (mesalamine) delayed-release tablet, 400 mg
All treatments were administered orally with 240 mL ambient-temperature water to fasted subjects. Treatment periods were separated by at least 7 days.

Subjects were randomly assigned to one of the following 2 treatment sequences:
 Sequence A: Reference – Test – Reference – Test
 Sequence B: Test – Reference – Test – Reference

Blood samples for determination of plasma mesalamine concentration were collected pre-dose through 48 hours post-dose.

Study sites: This was a multi-center trial and was conducted at the following three locations: Clinical Trials Drug Development Solutions (San Antonio, TX) and Comprehensive Clinical Development (Miramar and Fort Myers, FL).

Study population: 252 healthy males and females were randomized and 238 subjects completed the study. Subjects were between 18- 60 years of age and non-smoking. Concomitant prescription or OTC medications were not allowed. In addition, use of caffeine- or alcohol- containing foods/beverages was not allowed. Grapefruit containing foods or beverages were also not allowed.

A sample size of 250 subjects is estimated to provide approximately 90% power to yield point estimates of Test/Reference ratio of geometric means within the strict bounds of 80% to 125% for all 3 parameters (Cmax, partial AUC8-48 and AUC0-tldc)

Identity of investigational products:

Test Treatment: WC3045 capsules (mesalamine delayed-release capsule) (FormulationWC3045-02), 400 mg	
Package description	Natural HDPE bottle containing 180 capsules per bottle
Dosage form description	Colourless capsule imprinted with "WC 400 mg" in white ink containing one reddish-brown coated tablet
Manufacturer	Warner Chilcott Deutschland GmbH, Dr. Otto Rohm Straße 2-4, D-64331, Weiterstadt, Germany
Date of manufacture	22 August 2011
Batch number	508745
Reference Treatment: Asacol (mesalamine) delayed-release tablet, 400 mg	
Package description	Natural HDPE bottle containing 180 tablets per bottle
Dosage form description	Red-brown, capsule-shaped tablets imprinted with "Asacol NE" in black
Manufacturer	Warner Chilcott Deutschland GmbH, Dr. Otto Rohm Straße 2-4, D-64331, Weiterstadt, Germany
Date of manufacture	25 August 2010
Batch number	444305-A

PK sampling: For determination of plasma mesalamine concentrations, 6 mL of blood was collected into K2-EDTA vacutainers to provide at least 2 to 3 mL of plasma. PK blood samples were collected pre-dose (within 2 hours prior to dosing) and 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 30, 36, and 48 hours post-dose.

Bioanalytical methods: Plasma mesalamine concentrations were determined using a validated LC-MS/MS method; the bioanalytical work was performed by (b) (4)

Pharmacokinetic analyses: PK analyses were done using non-compartmental analytical methods. The following parameters were calculated:

Pharmacokinetic Parameter	Definition
Cmax	Maximum plasma concentration
AUC8–48	The area under the plasma concentration versus time curve, from 8 hours to 48 hours post dose or to the last determinable concentration (tldc), as calculated by the linear trapezoidal method
AUC0–tldc	The area under the plasma concentration versus time curve, from time 0 hours to the tldc, time of last determinable concentration, as calculated by the linear trapezoidal method.
AUC0-inf	The area under the plasma concentration versus time curve, from time 0 hours to infinity, as calculated by the linear trapezoidal method.
tlag	Time postdose to the first measurable concentration
tmax	Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, tmax was defined as the first time point with this value.
kel	Terminal phase rate constant
t½	Terminal phase half-life (0.693/kel)

Pharmacokinetic parameter calculations were performed using SAS (Version 9.2).

PK endpoints for primary analyses: The primary endpoints as agreed during the pre-submission review period for this NDA included AUC8-48 as the partial AUC of interest. The Division felt at the time that the 8 h time point represents a reasonable time for when the dosage form reaches the colon (site of action for mesalamine in UC) and therefore any drug release after this period is most relevant in comparing two different formulations (test vs. reference). The sponsor did not sample beyond 48 hours during this trial. They were advised during the protocol review to extend sampling beyond this time point. During the pre-NDA meeting, the sponsor noted that only 17 % of subjects had detectable levels of drug at the 48 hour time point, and therefore they do not anticipate that sampling beyond this time point would've made any difference. During the earlier meetings, the sponsor was also advised that in addition to any newer partial AUCs, the sponsor should also analyze data for the typically used parameters such as Cmax, AUCt, and AUCinf. Sponsor appears to have done this along with two other partial AUCs, AUC10-48 and AUC12-48h. The AUCinf data was determinable in only few subjects. Only 27 (11%) subjects of 238 subjects had determinable kel and AUC0-inf values in all 4 treatment periods. The terminal log linear phase of the profile couldn't be identified in several individuals perhaps owing to the continued absorption of mesalamine from the site of action.

Statistical analyses:

Data from 238 subjects who completed all four treatments were included in the analysis. Data from other subjects who missed one or more treatments were presented in descriptive statistics but not included in the statistical analyses.

All statistical analysis by sponsor was performed using PC/SAS, Version 9.2, with SAS program code prepared specifically for the project.

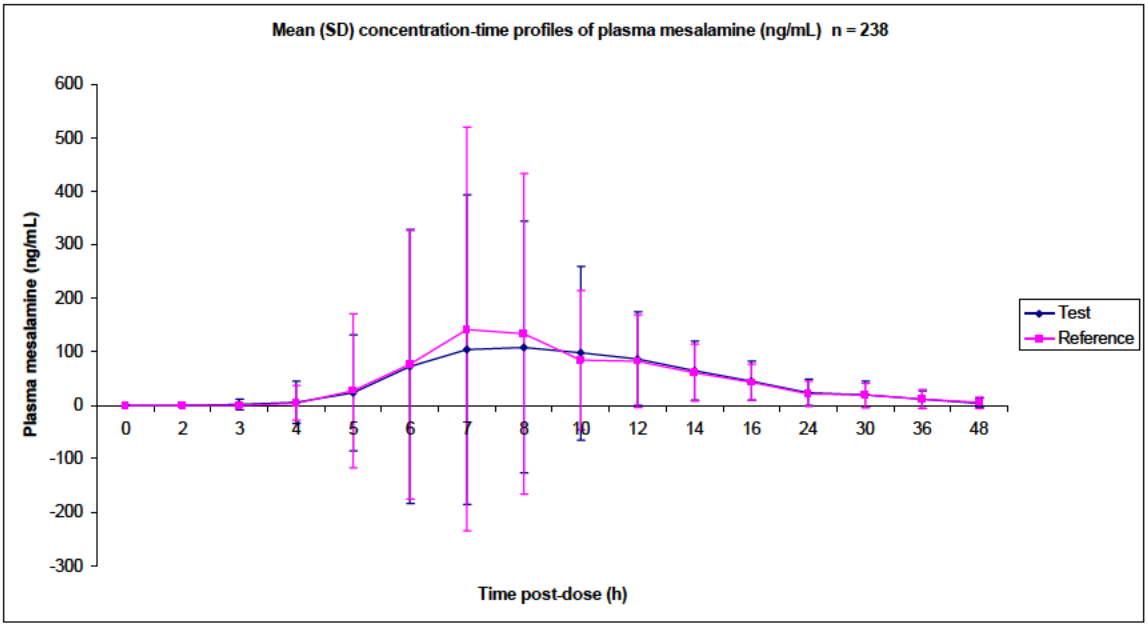
Imputation: Cmax is set to 5 ng/mL for subjects whose plasma mesalamine concentration values are below the limit of quantitation for all samples for a given treatment. Subjects with mesalamine concentration values below the limit of quantitation

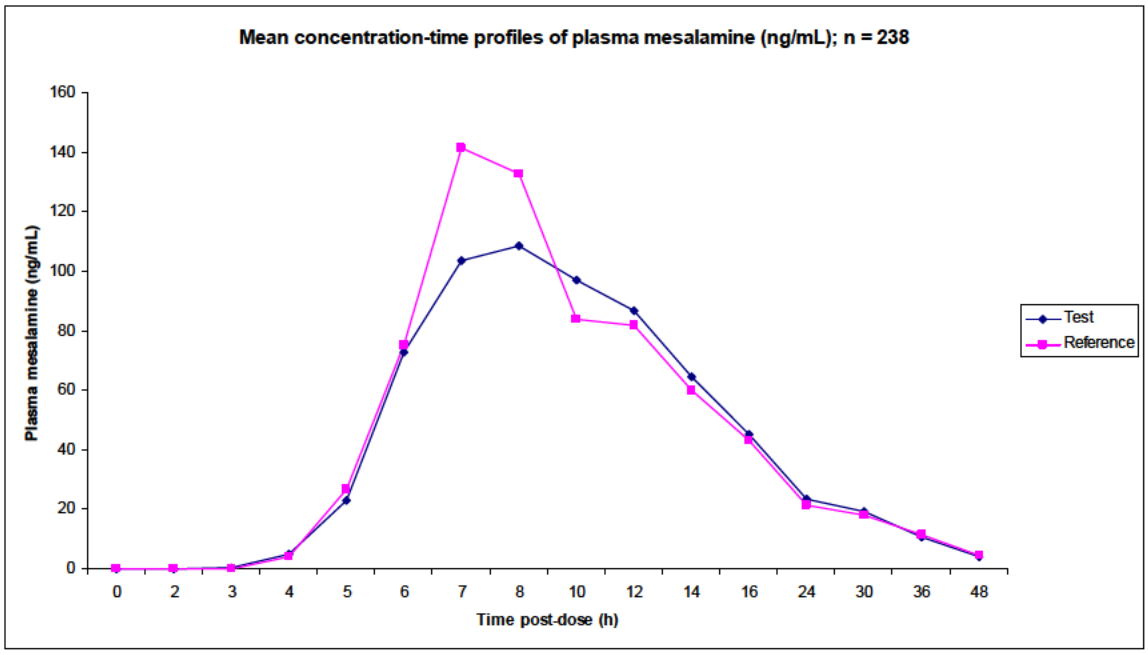
for the entire sampling period were assigned a Cmax value of 5 ng/mL (one-half the limit of detection) and AUC8-48 and AUC0-tldc were assigned values of 5 ng·h/mL. This procedure avoids the indeterminacy of the log of zero without substantial impact on the study outcomes. To assess the effect of the imputation of Cmax, AUC8-48 and AUC0-tldc values, a sensitivity analysis was conducted excluding subjects with plasma mesalamine concentration values below the limit of quantitation for all plasma samples for a given period.

Geometric Mean ratio was calculated as $(T/R)=[(T1*T2)/(R1*R2)]^{1/2}$. The point estimates of the Test/Reference geometric mean ratio for Cmax, AUC8-48 and AUC0-tldc were calculated. For Cmax, AUC8-48, AUC0-tldc, and AUC0-inf, the within-subject standard deviation for each formulation was estimated from the analysis of variance of the log-transformed parameter using the reference-scaled average bioequivalence procedure as described in the February 2011 Draft Guidance on Progesterone. The same procedure was used to determine the 95% (1-sided) upper-confidence bound on the linearized criterion for these pharmacokinetic parameters.

Pharmacokinetic results:

Mean plasma concentration-time data for the test and reference mesalamine treatments:





Descriptive statistics for PK parameters (PK population) are shown:

Parameter	Test Mean (SD)	Reference Mean (SD)
Cmax; ng/ml	265 (513)	285 (622)
AUC8-48; ng h/mL	1160 (1062)	1111 (1023)
AUC0-tldc; ng h/mL	1419 (1458)	1426 (1587)
AUCinf	2349 (2478)	2546 (2013)
Kel	0.158 (0.151)	0.182 (0.183)
Tmax; h; median [range]	12 [4 – 48]	12 [4 - 48]
Tlag; h	10.1 (6.2)	10.7 (6.5)

The within-subject variability of the reference formulation was large (> 30 %) thus justifying the use of scaled BE approach for statistical analysis. The variability associated with the test formulation was also large, albeit somewhat smaller than the test formulation. Variability was the largest for Cmax compared to the AUC parameters. The terminal elimination phase of the PK profile was not readily identifiable for many subjects as for oral mesalamine delayed release formulations the elimination is intermingled with continued absorption from the GI tract. Therefore, the kel (and thus T1/2) and AUCinf values couldn't be estimated for all subjects (as shown by lower 'n' for these parameters in the PK table below). Lag time was noted for both formulations and was similar based on mean, median, minimum and maximum values for this parameter. A lag time is expected as the formulations are designed as delayed-release dosage forms with enteric coating to target the site of action in the colon; these coatings are intended to breakdown and release drug only at pH 7.0 or greater.

The sampling duration was 48 h in these studies. Only few subjects had detectable concentrations at the 48 h time point.

For the formulation comparisons to pass the reference-scaled bioequivalence analysis, the 95% upper confidence bounds of the linearized criterion should be ≤ 0, and the point estimates of the Test/Reference geometric mean ratio should be within 0.80-1.25 for the key PK parameters (in this case Cmax, AUC8-48 and AUC0-tldc).

Sponsor's analysis of the study data provided the following statistical outcomes suggesting bioequivalence of the formulations using the scaled BE approach for HVD:

Parameter	Geometric Mean		Within-Subject Standard Deviation		Ratio (Test /Reference)	95% upper confidence bound of the linearized criterion
	Test	Reference	Test	Reference		
Cmax	109.9	99.4	1.167	1.275	1.106	-1.105
AUC8–48	618.3	556.4	1.453	1.490	1.111	-1.514
AUC0–tldc	719.6	648.4	1.464	1.536	1.110	-1.608

Cmax = Maximum plasma concentration (ng/mL); AUC8-48 = Area under the plasma concentration versus time curve from time 8 hours to 48 hours (ng·h/mL); AUC0–tldc = Area under the plasma concentration versus time curve from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)

Summary of Cmax, AUC8-48, and AUC0-tldc following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) and a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

	TEST			REFERENCE		
Statistic	**Cmax (ng/mL)**	**AUC8-48 (ng.hr/mL)**	**AUC0-tldc (ng.hr/mL)**	**Cmax (ng/mL)**	**AUC8-48 (ng.hr/mL)**	**AUC0-tldc (ng.hr/mL)**
N	238	238	238	238	238	238
Mean	264.882	1160.517	1419.548	285.962	1111.561	1426.859
Standard Deviation	393.480	811.762	1154.923	472.894	784.112	1241.729
Within-subject RMSD[a]	468.706	972.357	1264.712	573.945	929.730	1399.243
% Coefficient of Variation	176.949	83.786	89.093	200.707	83.642	98.065
Median	137.550	979.775	1155.138	123.325	948.150	1148.448
Minimum	8.750	20.050	20.050	5.000	5.000	5.000
Maximum	2691.500	4877.200	7577.271	2805.000	4687.350	6814.850
μ (Geometric LSM)[b]	109.946	618.295	719.557	99.371	556.397	648.351
90% 2-sided lower confidence limit	98.098	544.108	629.472	88.026	484.313	560.040
90% 2-sided upper confidence limit	123.224	702.599	822.535	112.179	639.208	750.587
s2w (within-subject variance, log-transformed parameter)	1.362	2.110	2.142	1.625	2.221	2.358
Within-subject standard deviation	1.167	1.453	1.464	1.275	1.490	1.536

Note: For subjects whose plasma mesalamine concentration values are below the limit of quantitation for all samples for a given treatment, Cmax is set to 5 ng/mL, and AUC8-48 and AUC0-tldc are set to 5 ng.h/mL.

Descriptive statistics are calculated for concentration average for subject/treatment at each time point. N = number of subjects with known average concentrations at this time point.

[a] Within-subject RMSD (root mean square deviation) is estimated using the residual error from the analysis of variance of the untransformed parameter with terms for sequence, subject within sequence, and period within sequence.
[b] Geometric LSM (least squares mean), 90% confidence interval, and within-subject variance are estimated from the analysis of variance of the log-transformed parameter as described in the study report.

Statistic	Cmax (ng/mL)	AUC8-48 (ng.hr/mL)	AUC0-tldc (ng.hr/mL)	AUC0-inf (ng.hr/mL)[a]
Ratio of geometric means (Test/Reference)	1.106	1.111	1.110	0.833
90% 2-sided confidence interval	0.974, 1.257	0.959, 1.288	0.951, 1.296	0.671, 1.033
95% (1-sided) upper confidence bound on the linearized criterion	-1.105	-1.514	-1.608	-0.151

[a] Values are based on results for 27 subjects with determinable elimination rate constant for all study periods.
Note: For subjects whose plasma mesalamine concentration values are below the limit of quantitation for all samples for a given treatment, Cmax is set to 5 ng/mL, and AUC8-48 and AUC0-tldc are set to 5 ng.h/mL.

Reviewer analyses: Using SAS code for a 2 sequence, 2 treatment, 4 period replicate bioequivalence study using reference-scaled BE approach, the following statistical outcomes for scaled BE approach were obtained:

Scaled BE analysis:

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUClast	1.11	93.52	128.34	2.3322963	1.5271857	-1.593986	Scaled/PE	PASS
AUC8-48	1.10	92.89	125.92	2.0725896	1.4396491	-1.41748	Scaled/PE	PASS
CMAX	1.11	96.60	125.07	1.6256326	1.275003	-1.10703	Scaled/PE	PASS

Values obtained by our analysis are similar to the values presented by the sponsor for the reference-scaled BE approach (data from 238 subjects who completed all four treatments was used and imputation was same as that utilized by the sponsor). Data suggests that the point estimates for the T/R ratios of primary PK parameters were within 0.8 to 1.25 and the 95 % upper bounds of the linearized criteria were < 0, thus supporting bioequivalence of the two formulations.

Sensitivity analyses: Following administration of Test treatment, 31 subjects had plasma mesalamine concentration values below the limit of quantitation for the entire sampling period. Following administration of Reference treatment, 38 subjects had plasma mesalamine concentration values below the limit of quantitation for the entire sampling period. As explained earlier, values of 5 ng/mL (50% of the 10 ng/mL LLOQ) and 5 ng·h/mL were imputed for Cmax and AUC for those subject treatment periods with mesalamine concentration values below the lower limit of quantitation (LLOQ).

The effect of this imputation was determined by the sponsor by reanalyzing data after excluding these subjects from the analysis. While the variability was expectedly lower with the deletion of these patients (with low Cmax and AUC values at 5), the overall within subject variability still remained high to support a reference-scaled BE approach for this product. With the exclusion of these below LLOQ data points, the ratio of geometric mean of Test to Reference for Cmax was 1.120; the corresponding ratio values for AUC8-48 and AUC0-tldc were 1.114 and 1.108, respectively; the 95% (1-sided) upper confidence bound on the linearized criterion was ≤ 0 for all 3 parameters. Thus formulation bioequivalence was noted regardless of imputation.

Summary of Cmax, AUC8-48, AUC0-tldc following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) and a 400-mg Asacol (mesalamine)

delayed-release tablet (Reference) to fasted healthy volunteers (Excluding Subjects with Plasma Mesalamine Concentrations Below the Level of Quantitation for all Samples in at Least One Period), Study PR-08210

Statistic	TEST Cmax (ng/mL)	TEST AUC8-48 (ng.hr/mL)	TEST AUC0-tldc (ng.hr/mL)	REFERENCE Cmax (ng/mL)	REFERENCE AUC8-48 (ng.hr/mL)	REFERENCE AUC0-tldc (ng.hr/mL)
N	183	183	183	183	183	183
Mean	307.408	1332.848	1641.303	333.820	1250.951	1628.465
Standard Deviation	423.314	804.758	1171.472	520.340	787.415	1303.345
Within-subject RMSD[a]	506.077	1026.608	1348.736	641.692	977.671	1517.605
Median	159.700	1130.550	1336.250	144.500	1071.500	1288.098
Minimum	17.900	89.800	89.800	20.500	161.850	161.850
Maximum	2691.500	4877.200	7577.271	2805.000	4687.350	6814.850
μ (Geometric LSM)[b]	151.068	967.662	1145.229	134.837	868.574	1034.024
90% 2-sided lower confidence limit	135.937	892.071	1049.602	120.374	795.365	938.355
90% 2-sided upper confidence limit	167.885	1049.660	1249.567	151.037	948.522	1139.446
s2w (within-subject variance, log-transformed parameter)	0.904	0.743	0.727	1.249	0.836	0.917
Within-subject standard deviation	0.951	0.862	0.852	1.118	0.914	0.957

Descriptive statistics are calculated for concentration average for subject/treatment at each time point. N = number of subjects with known average concentrations at this time point.

[a] Within-subject RMSD (root mean square deviation) is estimated using the residual error from the analysis of variance of the untransformed parameter with terms for sequence, subject within sequence, and period within sequence .
[b] Geometric LSM (least squares mean), 90% confidence interval, and within-subject variance are estimated from the analysis of variance of the log-transformed parameter as described in the study report.

Statistic	Cmax (ng/mL)	AUC8-48 (ng.h/mL)	AUC0-tldc (ng.h/mL)
Ratio of geometric means (Test/Reference)	1.120	1.114	1.108
90% 2-sided confidence interval	0.999, 1.257	1.016, 1.221	1.006, 1.219
95% (1-sided) upper confidence bound on the linearized criterion	-0.82627	-0.54905	-0.60529

Analyses of PK parameters obtained from reviewer analyses also suggest bioequivalence of AUCtldc, AUC8-48 and Cmax either when assigning a value of 0 in subjects with no detectable limits across the sampling interval, or by excluding all together data from any subjects who demonstrate below LLOQ values across the sampling duration in one or more of their treatment periods.

Primary endpoints: Zero value assigned for subjects with all values below LLOQ

Parameter	Test	Reference	T/R Ratio	Lower 90% CI	Upper 90% CI	sWR	Criteria Bound	OUTCOME
AUCtldc	1004.88	970.52	1.11	93.80	114.29	0.9621112	-0.61857	PASS
AUC8-48	970.07	934.42	1.10	95.73	112.59	0.7768269	-0.40006	PASS
CMAX	134.63	126.41	1.12	95.18	119.16	1.1179276	-0.836431	PASS

Primary endpoints: Excluding all four periods from individuals with zero values across sampling duration in one or more treatment periods:

Parameter	Test	Reference	T/R Ratio	Lower 90% CI	Upper 90% CI	sWR	Criteria Bound	OUTCOME
AUCtldc	1147.40	1035.06	1.11	99.73	123.22	0.9582041	-0.60808	PASS
AUC8-48	1083.27	984.66	1.10	100.81	120.06	0.7808448	-0.400849	PASS
CMAX	151.19	134.89	1.12	99.17	126.69	1.1234581	-0.837589	PASS

Additional statistical tables from the sponsor's analyses:

Summary of AUC0-inf following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) and a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

	TEST			REFERENCE		
Statistic	**At Least 1 Period[a]**	**Both Periods[b]**	**All Periods[c]**	**At Least 1 Period[a]**	**Both Periods[b]**	**All Periods[c]**
N	174	80	27	170	53	27
Mean	2258.318	2546.836	3201.669	2445.284	2870.272	3507.924
Standard Deviation	1854.119	2185.329	2631.685	1622.434	1877.408	1894.790
Within-subject RMSD[d]	2710.902	2710.902	4064.770	2271.124	2271.124	2776.490
Median	1827.003	2033.619	2527.448	2046.959	2199.131	3108.902
Minimum	347.622	467.944	740.166	465.046	662.688	948.802
Maximum	14688.00	14688.00	14688.00	9369.398	8731.317	6877.234
μ (Geometric LSM)[e]	1848.257	1848.257	2330.871	2189.214	2189.214	2799.762
90% 2-sided lower confidence limit	1650.347	1650.347	1958.253	1913.057	1913.057	2385.550
90% 2-sided upper confidence limit	2069.900	2069.900	2774.392	2505.236	2505.236	3285.894
s2w (within-subject variance, log-transformed parameter)	0.376	0.376	0.497	0.362	0.362	0.451
Within-subject standard deviation	0.613	0.613	0.705	0.601	0.601	0.671

[a] Subject had determinable elimination rate constant in at least one period for given treatment.
[b] Subject had determinable elimination rate constant in both periods for given treatment.
[c] Subject had determinable elimination rate constant for all study periods.

Statistics are calculated for average values for subject/treatment.

[d] Within-subject RMSD (root mean square deviation) is estimated using the residual error from the analysis of variance of the untransformed parameter with terms for sequence, subject within sequence, and period within sequence.
[e] Geometric LSM (least squares mean), 90% confidence interval, and within-subject variance are estimated from the analysis of variance of the log-transformed parameter as described in the study report.

Summary of AUC10-48 and AUC12-48 following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) and a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

	TEST		REFERENCE	
Statistic	**AUC10-48 (ng.hr/mL)**	**AUC12-48 (ng.hr/mL)**	**AUC10-48 (ng.hr/mL)**	**AUC12-48 (ng.hr/mL)**
N	238	238	238	238
Mean	955.033	771.362	896.303	730.391
Standard Deviation	661.809	586.078	641.263	576.384
Within-subject RMSD[a]	793.320	713.784	745.752	637.395
% Coefficient of Variation	83.067	92.535	83.203	87.268
Median	769.650	613.850	766.525	580.062
Minimum	20.050	5.000	5.000	5.000
Maximum	3482.216	3411.216	3297.267	3095.027
μ (Geometric LSM)[b]	501.051	374.921	454.383	343.969
90% 2-sided lower confidence limit	441.644	329.215	397.672	300.789
90% 2-sided upper confidence limit	568.449	426.973	519.181	393.347
s2w (within-subject variance, log-transformed parameter)	2.184	2.226	2.122	2.158
Within-subject standard deviation	1.478	1.492	1.457	1.469

Statistic	**AUC10-48 (ng.hr/mL)**	**AUC12-48 (ng.hr/mL)**
Ratio of geometric means (Test/Reference)	1.103	1.090
90% 2-sided confidence interval	0.956, 1.272	0.941, 1.262
95% (1-sided) upper confidence bound on the linearized criterion	-1.448	-1.475

Reviewer analyses of the additional partial AUC parameters also suggest bioequivalence of the test and reference data using reference-scaled BE approach:

Parameter	Test	Reference	T/R Ratio	Lower 90% CI	Upper 90% CI	sWR	Criteria Bound	OUTCOME
AUC10-48	496.04	457.24	1.11	93.25	126.21	1.4494907	-1.436721	PASS
AUC12-48	367.86	346.20	1.08	91.00	124.07	1.4660854	-1.475162	PASS

Additionally, reviewer reanalyzed the PK concentration-time data using WinNonlin and calculated additional partial AUC parameters to explore whether there might be other PK parameters that can offer better comparisons of the formulations:

Following PK analyses using non-compartmental analysis the partial AUCs were subjected to reference-scaled BE comparison using SAS 9.2:

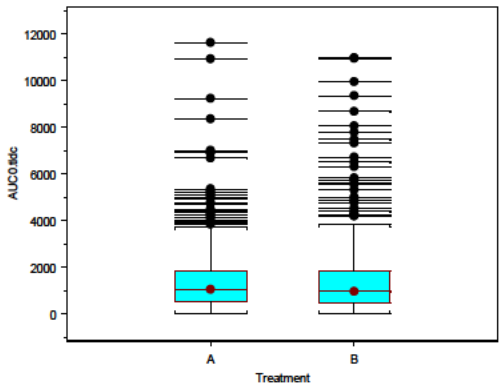
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
Primary Statistical Endpoints								
Cmax	1.11	95.12	122.49	1.5156088	1.2311006	-1.030364	Scaled/PE	PASS
AUC_{TLDC}	1.08	90.52	121.76	1.8493626	1.3599127	-1.265287	Scaled/PE	PASS
AUC8-48	1.10	92.89	125.92	2.0725896	1.4396491	-1.41748	Scaled/PE	PASS
Additional Analyses								
AUC6-48	1.10	92.38	126.11	2.1815445	1.4770052	-1.493384	Scaled/PE	PASS
AUC10-48	1.12	94.38	126.79	1.9880089	1.4099677	-1.355735	Scaled/PE	PASS
AUC12-48	1.10	93.90	126.05	1.9860953	1.4092889	-1.35789	Scaled/PE	PASS
AUC0-2	.	31.24	311.19	0.0011561	0.034001	.	Unscaled	FAIL
AUC0-4	.	57.90	138.00	0.4927233	0.7019425	.	Scaled/PE	FAIL
AUC0-6	0.31	49.67	97.03	2.3954621	1.547728	6.9852195	Scaled/PE	FAIL
AUC0-8	0.52	64.84	107.81	2.6080105	1.6149336	-0.45076	Scaled/PE	FAIL
AUC0-10	0.88	78.46	133.44	3.5029452	1.8716157	-2.134094	Scaled/PE	PASS
AUC0-12	1.30	92.09	133.71	2.0976859	1.448339	-1.224384	Scaled/PE	FAIL

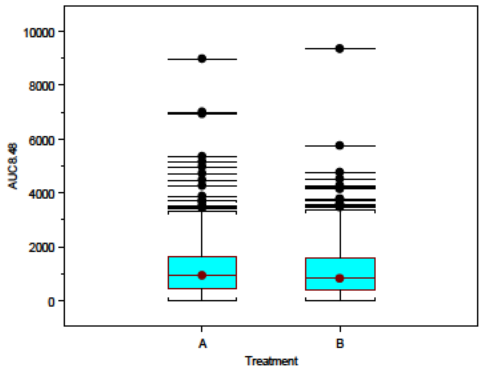
AUC0-2h was not quantifiable in individuals (except one) during all treatment periods; Approximately 4 % of all treatment periods resulted in quantifiable AUC0-4 h; ~ 26 % of all treatment periods had quantifiable AUC0-6h; ~ 48 % had quantifiable AUC0-8h.

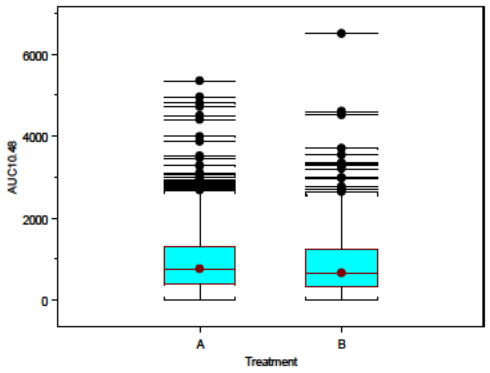
Summary of tmax, tlag, elimination rate constant, and half-life values following replicate single-dose oral administration of a 400-mg WC3045 capsule (Test) and a 400-mg Asacol (mesalamine) delayed-release tablet (Reference) to fasted healthy volunteers, Study PR-08210

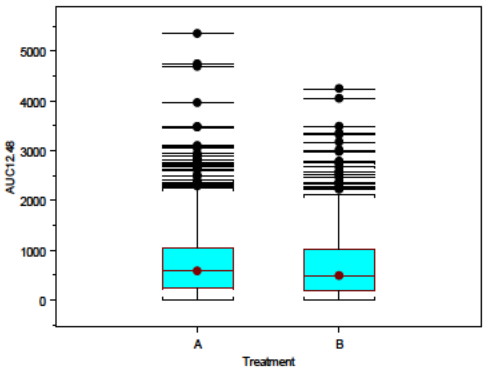
Statistic	TEST				REFERENCE			
	tmax (h)	tlag (h)	kel (h^{-1})	Half-life (h)[b]	tmax (h)	tlag (h)	kel (h^{-1})	Half-life (h)[b]
N	207	207	80	80	205	204	53	53
Mean	14.298	10.004	0.147	4.699	15.147	10.710	0.202	3.424
Standard Deviation	6.641	4.713	0.116		6.715	4.586	0.153	
Within-subject RMSD[a]	7.828	5.628	0.125		8.810	6.438	0.174	
Median	12.000	9.000	0.119		13.000	10.000	0.173	
Minimum	5.000	4.000	0.020		5.500	4.500	0.013	
Maximum	39.000	28.000	0.512		42.000	27.500	0.562	

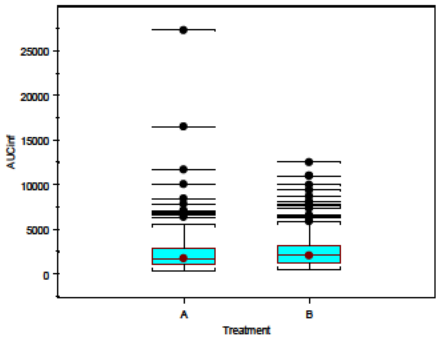
Box plots of PK parameters comparing test and reference treatments (A = Test; B = Reference):

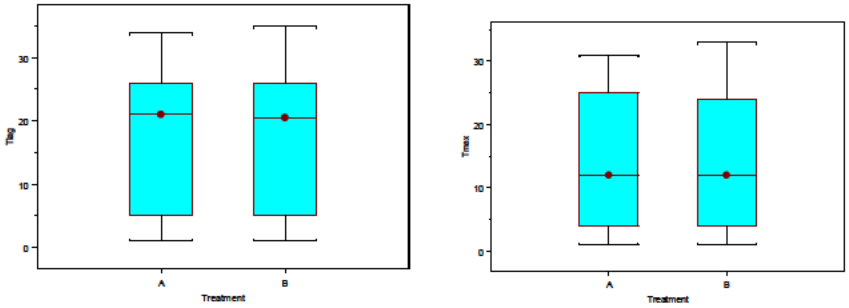












Partial AUC8-48h represented a significant portion of the total AUC (AUC0-tldc) for the test and reference treatments (~ 90 %) on average suggesting that drug release occurred primarily after the 8 h time point as expected for the delayed release test and reference formulations.

The additional partial parameters explored in the study, i.e. AUC10-48h and AUC12-48h, represented ~ 80 % and 70 % of the total AUC0-tldc on average for both the test and reference treatments.

Data supports that the test formulation performs in vivo as per its design (delayed release) characteristics, and this release was comparable to that of the reference Asacol as demonstrated by comparable values for partial AUC values when expressed as % AUCtldc.

4.2 Consult Reviews

Office of Scientific Investigations:

Inspections of the clinical and bioanalytical sites for PR08210- Final review and recommendations from OSI are pending at this time. An addendum will be entered into DARRTS when this information becomes available.

4.3 Cover Sheet and OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**204412**	**Brand Name**	**(b) (4) (proposed)**
OCP Division (I, II, III, IV, V)	**DCPIII**	**Generic Name**	**Mesalamine (WC3045)**
Medical Division	**DGIEP**	**Drug Class**	**Anti-inflammatory (topical action)**
OCP Reviewer	**Sandhya Apparaju**	**Indication(s)**	**Treatment of mild to moderate Ulcerative Colitis, UC; Maintenance of remission in UC**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Delayed release capsules**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Treatment of UC: Two 400 mg capsules taken TID (total daily dose 2.4g) for 6 weeks Maintenance: 1.6 g daily in divided doses**
Date of Submission	**07/30/2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**01/04/2013**	**Sponsor**	**Warner Chilcott**
Medical Division Due Date		**Priority Classification**	**Priority**
PDUFA Due Date	**Feb 1, 2013**	**Reference Drug/NDA**	**Asacol (mesalamine DR tablets); NDA 19-651**

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**			
Tabular Listing of All Human Studies	**X**			**One new BE trial; PR08210**
HPK Summary	**X**			
Labeling	**X**			Labeling has been copied from the Asacol label due to claimed BE
Reference Bioanalytical and Analytical Methods	**X**			LC-MS/MS method for mesalamine in plasma
I. Clinical Pharmacology				No new clinical pharmacology studies were conducted
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				

Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				**One pivotal BE study**
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**X**	**1**		**PR-08210;** compares BA of new formulation with Asacol 400 mg DR tablets; the new formulation replaces plasticizer dibutyl phthalate, DBP with dibutyl sebacate, DBS (due to safety concerns) and also over-encapsulates tablet
traditional design; single / multi dose:				
replicate design; single / multi dose:	**X**			Scaled BE for highly variable drugs
Food-drug interaction studies				None conducted for the new formulation
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	**X**			
Literature References	**X**			**OGD guidance on progesterone; scaled BE publication by Haider et al**
Total Number of Studies	**X**	**1**		**BE study** PR-08210

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Pivotal BE study PR08210
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Cross reference NDA 19651
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			PR-08210
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Same as reference NDA
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	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to			X	

	assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			Food-effect information in labeling will need to be addressed
	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.

- **Comments to sponsor:** Due to the lack of a food effect study, there will be restrictive language in regard to dosing if the NDA is approved.

Sandhya Apparaju, Ph.D.
Reviewing Clinical Pharmacologist Date

Sue Chih Lee, Ph.D.
Team Leader/Supervisor Date

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/s/

SANDHYA K APPARAJU
12/20/2012

SUE CHIH H LEE
12/20/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 204412

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**204412**	**Brand Name**	**(b) (4) (proposed)**
OCP Division (I, II, III, IV, V)	**DCPIII**	**Generic Name**	**Mesalamine (WC3045)**
Medical Division	**DGIEP**	**Drug Class**	**Anti-inflammatory (topical action)**
OCP Reviewer	**Sandhya Apparaju**	**Indication(s)**	**Treatment of mild to moderate Ulcerative Colitis, UC; Maintenance of remission in UC**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Delayed release capsules**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Treatment of UC: Two 400 mg capsules taken TID (total daily dose 2.4g) for 6 weeks Maintenance: 1.6 g daily in divided doses**
Date of Submission	**07/30/2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**01/04/2013**	**Sponsor**	**Warner Chilcott**
Medical Division Due Date		**Priority Classification**	**Priority**
PDUFA Due Date	**Feb 1, 2013**	**Reference Drug/NDA**	**Asacol (mesalamine DR tablets); NDA 19-651**

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**			
Tabular Listing of All Human Studies	**X**			**One new BE trial; PR08210**
HPK Summary	**X**			
Labeling	**X**			Labeling has been copied from the Asacol label due to claimed BE
Reference Bioanalytical and Analytical Methods	**X**			LC-MS/MS method for mesalamine in plasma
I. Clinical Pharmacology				No new clinical pharmacology studies were conducted
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 204412

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				**One pivotal BE study**
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**X**	**1**		**PR-08210;** compares BA of new formulation with Asacol 400 mg DR tablets; the new formulation replaces plasticizer dibutyl phthalate, DBP with dibutyl sebacate, DBS (due to safety concerns) and also over-encapsulates tablet
traditional design; single / multi dose:				
replicate design; single / multi dose:	**X**			Scaled BE for highly variable drugs
Food-drug interaction studies				None conducted for the new formulation
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	**X**			
Literature References	**X**			**OGD guidance on progesterone; scaled BE publication by Haider et al**
Total Number of Studies	**X**	**1**		**BE study** PR-08210

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 204412

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Pivotal BE study PR08210
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Cross reference NDA 19651
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			PR-08210
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Same as reference NDA
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	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of	X			Food-effect information in

	the label?				labeling will need to be addressed
	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.

- **Comments to sponsor:** Due to the lack of a food effect study, there will be restrictive language in regard to dosing if the NDA is approved.

Sandhya Apparaju, Ph.D.

Reviewing Clinical Pharmacologist Date

Sue Chih Lee, Ph.D.

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 204412

Filing summary:

NDA 204412: (b) (4) mesalamine delayed release capsules

NDA Clinical Pharmacology contents: Pivotal BE study PR-08210 in 252 subjects, comparing proposed (b) (4) capsules to Asacol tablets (400 mg);

Formulation: Change in plasticizer in the enteric coating (from DBP to DBS); over-encapsulation of delayed release tablet

Table 1: Unit-Dose Composition of WC3045 Capsules and Asacol Tablets

Ingredient	Unit Quantity (mg/dosage form)	
	WC3045 Capsules Formulation WC3045-02 (Material Number 33075301)	**Asacol (mesalamine) Delayed-release Tablets, 400 mg**
	(b) (4)	
5-Aminosalicylic acid (5-ASA, mesalamine), USP	400.0	400.0
Lactose Monohydrate, NF	(b) (4)	
Povidone, USP		
Sodium Starch Glycolate, NF		
Magnesium Stearate, NF		
Talc, USP		
Colloidal Silicon Dioxide, NF		
(b) (4)		
Methacrylic acid copolymer, NF, type B (Eudragit S (b) (4)		
Talc, USP		
Dibutyl sebacate, NF		
Dibutyl phthalate, NF		
Ferric oxide, NF, red		
Ferric oxide, NF, yellow		
(b) (4)		
Polyethylene glycol (b) (4)		
Subtotal		
HPMC capsule printed with white ink ((b) (4) (b) (4)		
TOTAL		

[1]Eudragit S (b) (4) methacrylic acid copolymer, NF Type B

Bioequivalence study PR-08210: An open-label, randomized, single dose, replicate, four-period, two-sequence, two formulation crossover study was conducted in 252 healthy male and female volunteers (18-60 years; 238 with evaluable PK) to compare the relative bioavailability of WC3045 capsules with Asacol 400 mg DR tablets.

The study utilized a reference-scaled BE methodology (as described in OGD guidance for progesterone formulations) due to the high variability of the reference drug.

Sponsor claims bioequivalence of the two formulations using this approach (pending review).

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 204412

Study No (Report No)	Study Objective	Study Design	Dose / Regimen / Lot Number	Number Enrolled / Completed / Age	Analyte / Parameter	Ratio Test/Ref	95% Upper Confidence Bound to Linearized Criterion	Conclusions
PR-08210 (RR-02412)	To assess the relative bioavailability of WC3045 capsule as compared to Asacol 400-mg tablet	Multiple-center, randomized, single-dose, replicate treatment, 4-period, 2-sequence crossover	400 mg mesalamine / single-dose, replicate treatment Test: one WC3045 capsule (Lot 508745) Reference: one Asacol 400-mg tablet (Lot 444305-A)	252 / 238 18-60 years (238 evaluable for PK analysis)	Mesalamine			The pharmacokinetic profile of WC3045 capsules, 400 mg is similar to that of Asacol tablets. WC3045 capsules, 400 mg are bioequivalent to Asacol tablets, 400 mg. Single oral doses of WC3045 capsules, 400 mg and Asacol tablets, 400 mg were generally well tolerated.
					Cmax	1.106	-1.105	
					AUC8-48	1.111	-1.514	
					AUC0-tldc	1.110	-1.608	

Data: Electronic datasets, Bioanalytical methods/assay reports located.

Inspection: OSI inspection of clinical and Bioanalytical sites will be requested.

Issue: Effect of food on BA was not evaluated for proposed formulation; Approved Asacol can be taken without regard to food, due to absence of food effect on PK.

- if approved, the label for the new formulation may need to indicate dosing on empty stomach (30 min to 1 h before meals?)
- label may be revised if sponsor conducts a food-effect study

Conclusion: NDA can be filed, from a Clinical Pharmacology perspective.

Review issues: Absence of food-effect on PK and labeling of dosing with regard to food intake

- **Comments to sponsor:** Due to the lack of a food effect study, there will be restrictive language in regard to dosing if the NDA is approved.

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/s/

SANDHYA K APPARAJU
09/12/2012

SUE CHIH H LEE
09/12/2012

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

NDA Number	204-412
Submission Date	July 31, 2012
Product name, generic name of the active	Mesalamine Delayed-Release Capsules
Dosage form and strength	Capsule, 400 mg
Applicant	Warner Chilcott, 100 Enterprise Dr. Rockaway, NJ
Clinical Division	Division of Gastrointestinal Drug Products
Type of Submission	Original NDA 505(b)1
Biopharmaceutics Primary Reviewer	John Duan, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

BIOPHARMACEUTICS INITIAL ASSESSMENT

Biopharmaceutics Summary

NDA 204-412 provides a new dosage form, mesalamine delayed-release capsules, 400mg. The proposed indication and dosing regimen are the same as the approved Asacol (mesalamine) delayed-release tablets, 400mg under NDA 19-651. This is to address the Agency's concern related to the potential safety issue of dibutyl phthalate (DBP) as an excipient in Asacol products. The Applicant has developed a new formulation (WC3045 capsules) in which, dibutyl phthalate (DBP) in the tablet enteric coating is replaced with the plasticizer dibutyl sebacate (DBS) and the tablet is then encapsulated.

The Applicant has conducted a special dissolution study and a PK study (Study PR-08210) of WC3045 capsules compared to Asacol (mesalamine) delayed-release tablets.

The Biopharmaceutics review will focus on the dissolution study. This evaluation will include:
1) whether the dissolution method is adequate;
2) whether the acceptance criteria are appropriate;
3) Whether the delayed release claim is suitable.

Critical Review Issues

Critical review issues identified during filing are as follows.

- Suitability of the dissolution test method for dissolution profile comparisons between the proposed and approved products.
- Suitability of the proposed dissolution acceptance criteria

Comments for Day 74-Letter

The following comment should be conveyed to the Applicant:

- We recommend that you evaluate if alcohol induces dose dumping for your product. First, you should conduct the in vitro alcohol induced dose dumping testing. Depending on the result of this testing you may have to follow-up with an in vivo alcohol-dose dumping

study.

The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your MR product:

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the in vitro dissolution studies are recommended in the currently proposed media: 0%, 5%, 10%, 20%, and 40%.
- The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
- The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided for review.

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		
3.	Does the application contain the dissolution method development report?		x	The dissolution methods were discussed and agreed upon during communications between the Agency and the Applicant.
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?		x	
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in *vivo* BA or BE information in the submission?	x		In vivo PK data will be reviewed by the Office of Clinical Pharmacology. The bioequivalence study was conducted to compare the proposed formulation to the approved formulation (Asacol)
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?	x x	 x	

ONDQA - BIOPHARMACEUTICS
Initial Product Quality Assessment and Filing Review

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		Please convey the comment for in vitro alcohol dose dumping described in pages 1 and 2 of this IQA and filing review.

Administrative Block: *{See appended electronic signature page}*

John Duan, Ph.D.
Biopharmaceutics Primary Reviewer
Office of New drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New drug Quality Assessment

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/s/

JOHN Z DUAN
09/10/2012

ANGELICA DORANTES
09/10/2012