OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204412/ S-006	Submission Dates: 11/11/2014, 02/26/2015, 05/28/2015, 06/24/2015, 07/13/2015
Brand Name	Delzicol
Generic Name	Mesalamine
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	DCPIII
OND Division	DGIEP
Sponsor	Warner Chilcott Company LLC
Submission Type; Code	Pediatric Efficacy Supplement
Formulation; Strength(s)	Delayed Release Capsules 400 mg (Four 100-mg delayed release tablets in capsule)
Indication	Mildly to Moderately Active Ulcerative Colitis (UC) in adults and pediatric patients aged 5 years of age and older (Added age range: 5-11 years)
Pediatric Dosing Regimen	• Pediatric Patients ≥ 5 years of age: Total daily dose is weight-based up to a maximum of 2.4 grams/day with or without food (see table below); twice daily dosing for 6 weeks

Weight Group (kg)	Daily Dose (mg/kg/day)	Maximum Daily Dose (grams/day)
17 to <33	36 to 71	1.2
33 to <54	37 to 61	2.0
54 to 90	27 to 44	2.4

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1 Executive Summary

1.1 Recommendation

The application has been reviewed by the Office of Clinical Pharmacology and found to be acceptable from a clinical pharmacology perspective provided that a mutual agreement on label language can be reached between the sponsor and Agency.

1.2 Postmarketing Studies: None

1.3 Regulatory Background

(A) Approved Delzicol Capsules 400 mg (WC3045): NDA 204412 for Delzicol (mesalamine 400 mg delayed release) capsules were initially approved on February 1, 2013. This formulation was intended to replace Asacol 400 mg delayed release tablets, due to a potential safety concern with the plasticizer in Asacol coating (dibutylphthalate). The clinical program for Delzicol Capsules (WC3045) consisted of one reference-scaled bioequivalence study (Study PR-08210) to demonstrate bioequivalence of Delzicol capsules 400 mg to Asacol tablets 400 mg. In the approval letter, the Agency waived pediatric study requirements for children 0 to less than 5 years and deferred submission of PREA required pediatric studies in children aged 5 to 17 years.

Subsequently, FDA approved use of Asacol tablets 400 mg in pediatric patients down to 5 years of age for mildly to moderately active ulcerative colitis. Based on the established bioequivalence to Asacol tablets, Delzicol capsules received the same indication on April 28, 2014 but only in patients aged 12 years and older because WC3045 was not considered an age-appropriate formulation for patients < 12 years of age.

(B) Proposed Delzicol Capsules 400 mg (WC3079): To fulfill the PREA requirement for the approved Delzicol capsules, sponsor has developed a new delayed release formulation (phthalate-free just like the original Delzicol), also referred to as WC3079. This proposed capsule formulation contains four 100-mg tablets. Patients may either swallow the capsule intact or, in case of swallowing difficulties (particularly in younger children), open the capsule and swallow the individual 100 mg tablets. Note that the proposed WC3079 capsule is a clear, uncolored capsule printed with 'WC 400mg' in black ink containing four reddish-brown coated round tablets. Thus, the proposed Delzicol capsules differ in appearance from the approved Delzicol capsules. (b) (4)

To support the approval of the proposed Delzicol formulation in UC patients aged 5 years and older, the sponsor submitted a relative bioavailability study PR-07513

(WC3079 versus Asacol 400 mg) conducted in healthy adult subjects and a swallowability study PR-00514 (using placebo formulation) conducted in pediatric subjects 5 to 11 years of age. This review focuses on the bioavailability study (Study PR-07513) only.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability Study (Study PR-07513):

The objectives of the study were to assess the bioavailability of the proposed Delzicol Capsules 400 mg relative to the approved Asacol Tablets 400 mg under fasted conditions as well as the food effect for the former. Due to the high variability of mesalamine pharmacokinetics, the sponsor utilized a reference-scaled bioequivalence approach and conducted a 4-sequence, 5-period, crossover study, which is not in alignment with the study designs recommended for reference scaled BE analyses of highly variable drugs (see OGD draft progesterone guidance in this regard).

In the data analyses, the sponsor eliminated treatments that were not relevant to the particular analysis in question and renumbered the study periods. This data handling assumed absence of period effects. The sponsor concluded that all PK parameters (Cmax, AUC8-48h, & AUC0-tld) met the BE criteria using the reference-scaled BE methodology. Advised by DBVI, the sponsor subsequently provided additional analyses to derive unbiased estimates of relative bioavailability without discarding any of the test or reference replicate treatment data. However, DBVI concluded that the study design and data features render it impossible to apply appropriate statistical methods to assess the relative bioavailability. Please refer to the review by Dr. Zhuang Miao dated 8/3/15.

As such, we examined various aspects of the study and conducted further analyses of the data. These included one analysis using PK data from fasted periods for sequences (Sequences #C & D) that had the fed treatment on the same study period (i.e., Period 3) without renumbering the periods. Using the reference-scaled BE testing, all PK parameters met the BE criteria. We concluded that the bioavailability of the proposed Delzicol Capsules 400 mg is comparable to that for the Asacol Tablets 400mg because of the reasons listed below. Note that for future studies, sponsors should adhere to the balanced, fully or partially replicated study designs to avoid the above statistical issues.

1. The sponsor's analysis using PK data for all treatments under fasted conditions assuming no period effect and the reviewer's analysis using data from Sequences C and D (or Sequences 3 and 4) showed that the proposed Delzicol formulation met the reference-scaled bioequivalence testing criteria. The washout period of 7 days in the study was long enough to avoid carry-over effect between study periods based on the elimination half-life of mesalamine. Therefore, the assumption of no period effect is considered reasonable.

2. We did not exclude subjects with no or low systemic exposure from the bioequivalence analyses. Rather, these data were included in the analyses as part of the PK variability. This is because most subjects with zero exposure in one study period had high concentrations when the same dosage form was given in another period.

3. The proposed Delzicol Capsules 400 mg is not bioequivalent to the approved Delzicol Capsules 400 mg. According to ONDQA/Biopharm, the dissolution testing at pH 6.5 failed the f2 test, which is part of the BE testing for mesalamine delayed-release products. However, this does not preclude the approval of the proposed product because the individual dissolution data showed that more dosage units of Asacol tablets dissolved at pH 6.5 compared to the proposed product although both formulations were designed to release drug at pH 7 and above.

Conclusion: By establishing the comparable bioavailability between the proposed product and Asacol Tablets, the pediatric indication approved for Asacol Tablets may be extended to the proposed product (WC3079). Regarding food effect, a high fat meal increased the mesalamine systemic exposure by approximately 30-45% following administration of the proposed product. This is similar to what was observed for the approved Delzicol Capsules (WC3045). As such, the proposed product can be administered without regard to food.

2 Review of Study PR-07513

"A Study to Assess the Relative Bioavailability and the Effect of Food of a New Delayed-Release Mesalamine Formulation (WC3079-19F) in Healthy Volunteers, Study PR-07513"

Study objectives:

- To assess the relative bioavailability of the proposed formulation (WC 3079-19F; over-encapsulated 4 x 100 mg delayed release, DR tablets), as compared to Asacol DR tablets, 400 mg
- To assess the effect of food on the bioavailability of mesalamine from the proposed DR formulation (WC3079-19F, 400 mg)

Study design:
Single center, open-label, randomized, single dose, replicate treatment, 5-period, 4-sequence, 2-formulation crossover study in N = 160 healthy male and female volunteers.

Subjects:
One hundred and forty-six healthy subjects completed the study, and 14 subjects 4 discontinued prematurely. Reasons for premature withdrawal from the study were: subject withdrew consent (6 subjects), AE (4 subjects), positive cotinine or drug test

result (2 subjects), and other reason (2 subjects, 1 for personal reasons and 1 for lack of compliance/reliability).

Treatments:
Treatments and treatment sequences are as shown below. All treatments were administered with 240 mL water, after overnight (at least 10 h) fasting (except treatment 3), with 7-days between treatment administrations. As the intra-subject variability of mesalamine PK is very high, a reference-scaled bioequivalence approach has been used by the sponsor (this approach was also used in the original approval of Delzicol 400 mg DR tablet (encapsulated) and in the food-effect PK study for Delzicol capsule).

Treatment 1: One Asacol (mesalamine) delayed-release tablet, 400 mg (fasted)
Treatment 2: One mesalamine delayed-release capsule (WC3079-19F); 400 mg (fasted)
Treatment 3: One mesalamine delayed-release capsule (WC3079-19F); 400 mg with food
Subjects were randomly assigned to one of the following 4 treatment sequences:
Sequence A: Treatment 1 – Treatment 3 – Treatment 2 – Treatment 1 – Treatment 2
Sequence B: Treatment 2 – Treatment 1 – Treatment 2 – Treatment 3 – Treatment 1
Sequence C: Treatment 1 – Treatment 2 – Treatment 3 – Treatment 1 – Treatment 2
Sequence D: Treatment 2 – Treatment 1 – Treatment 3 – Treatment 2 – Treatment 1

Food-effect component:
At 30 minutes prior to dosing, subjects randomized to receive one WC3079 (mesalamine) delayed-release capsule, 400 mg with food (Treatment 3) were given a high-fat (approximately 50% of total caloric content of the meal), high calorie (800 to 1000 calories) breakfast. The meal ended within 5 minutes prior to dose administration.

PK sampling:
Blood samples were collected at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 30, 36, 48, and 72 hours post-dose. All samples were stored at -70°C or colder pending shipment for assay.

Analytical method:

Plasma mesalamine concentrations were determined using a validated liquid chromatography with tandem mass spectrometry method; the bioanalytical work was performed by ICON Development Solutions.

The assay method had a lower quantification limit of 2 ng/mL. Dilution integrity was demonstrated for a 25-fold dilution. Precision (% CV) for the calibration standards ranged from 2.43 % to 3.17 %, while precision for the quality controls ranged from 3.67 % to 4.07 %. Accuracy (% RE or bias) ranged from -2.22 % to 2 % for calibration standards, and 0.5 % to 8.83 % for quality controls. The method was linear with R^2 value of 0.9993. No interfering peaks were noted at the expected retention time of the analyte or internal standard. Overall mean recovery of mesalamine at 25, 600 and 1200 ng/mL was 90.3 %, 125 % and 102 %, respectively. Stability of mesalamine was demonstrated to be 92 days at -70^{o}C, and 378 days at -80^{o}C in K2 EDTA human plasma. Stability was shown over four freeze-thaw cycles. No matrix interference was noted. Acceptance

criteria were met for incurred sample reanalysis as (b) (4) % of ISR samples had results within (b) (4) % of their mean value.

PK analyses:

PK parameters calculated for mesalamine using non-compartmental analyses are listed below. In previous discussions and Delzicol submissions, Cmax, AUC8-48h and AUC0-tldc were identified as primary criteria for reference-scaled BE analyses.

Pharmacokinetic parameter	Definition
Cmax	Maximum plasma concentration
tmax	Time of the maximum measured plasma concentration. If the maximum value occurred at more than 1 time point, tmax was defined as the first time point with this value
AUC8–48	The area under the plasma concentration (AUC) versus time curve, from 8 hours to 48 hours postdose or to the last determinable concentration (tldc), as calculated by the linear trapezoidal method
AUC0–tldc	AUC from 0 hours to the last determinable concentration (tldc), as calculated by the linear trapezoidal method
AUC0-inf	The AUC from time 0 to infinity, calculated as the sum of AUC0–tldc plus the ratio of the last measurable plasma concentration to the terminal phase rate constant.
kel	Terminal phase rate constant
t½	Terminal phase half-life = 0.693/kel
AUC%extrap	100* (1- (AUC0-tldc/AUC0-inf))

Statistical methods:

Per the sponsor, "pharmacokinetic data from subjects who completed both Treatment 1 (reference) and Treatment 2 (test) replicate treatments were included in the relative bioavailability assessment. Pharmacokinetic data from subjects who completed both Treatment 2 (reference) replicate treatments and Treatment 3 (with food; test) were included in the food effect assessment. The point estimates of the Test/Reference geometric mean ratio for Cmax, AUC8-48, and AUC0-tldc were calculated for each study objective. For Cmax, AUC8-48, and AUC0-tldc, 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:

PK parameters generated by the sponsor could be replicated by reviewer using non-compartmental PK analyses of the sponsor-provided mesalamine plasma concentration-time data (Pharsight Phoenix).

Table: Arithmetic mean (SD), and geometric mean data for key pharmacokinetic parameters (N=146)

Arithmetic Mean (SD) Geometric Mean	C_{max} (ng/mL)	$AUC_{8\text{-}48h}$ (ng h/mL)	AUC_{tldc} (ng h/mL)	Tlag (h)	Tmax (h) Mean/Median
Reference R1	159 (337) 55.4	882 (803) 453	1083 (1021) 531	8.1 (4.7)	17.6 (12.7)
Reference R2	157 (286) 63.6	889 (670) 352	1144 (955) 644	7.7 (4.8)	16.6 (11.7)
Test T1	207 (323) 78.6	701 (620) 487	1035 (987) 667	6.2 (4.3)	13.6 (11.5)
Test T2	201 (422) 60.6	712 (866) 445	1007 (1222) 574	6.8 (4.3)	15.4 (13.0)
Test with food, F	214 (320) 90.8	948 (853) 679	1128 (974) 780	9.9 (4.1)	17.6 (11.1)

Sponsor's bioequivalence analysis:

The sponsor used reference-scaled BE methodology to analyze the BE data. In the analyses, matching sequences were collapsed after removal of food-effect treatment 3 from each sequence as shown in the schematic below, which resulted in 2 sequences rather than the original 4 and that geometric mean and ratio estimates were based on patients with no missing values for the 2 test and 2 reference variables.

	Period p_j				
Sequence g_i	1	2	3	4	5
1	Trt_1	~~Trt_3~~	Trt_2	Trt_1	Trt_2
2	Trt_2	Trt_1	Trt_2	~~Trt_3~~	Trt_1
3	Trt_1	Trt_2	~~Trt_3~~	Trt_1	Trt_2
4	Trt_2	Trt_1	~~Trt_3~~	Trt_2	Trt_1

Trt_1 = Asacol, fasted; Trt_2 = Delzicol, fasted; ~~Trt_3 = Delzicol, fed~~

The sponsor concluded bioequivalence of the proposed Delzicol formulation to the approved Asacol formulation as for all three key PK parameters tested (i.e., Cmax, AUC8-48 and AUC0-tldc) the 95% upper confidence bounds of the linearized criterion were < 0, and the point estimates of the Test/Reference geometric mean ratio were within 80.00 and 125.00%.

		Within-Subject SD (%CV)		Geometric Mean (LSM)		Ratio (%)	95% Upper Bound of the Linearized
PK Parameter	N	Test	Reference	Test	Reference	(T / R)	Criterion
Cmax	146	1.20 (179)	1.31 (214)	68.9	59.4	115.96	-1.11
AUC8-48	146	0.739 (85.2)	1.52 (301)	465	484	96.07	-1.54
AUC0-tldc	146	0.833 (100)	1.52 (301)	618	586	105.52	-1.53

Cmax = Maximum plasma concentration (ng/mL);
AUC8-48 = AUC from time 8 hours to 48 hours (ng·h/mL);
AUC0–tldc = AUC from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)
Test(T) = WC3079 capsule fasted; Reference(R) = Asacol tablet fasted.
Ratio = The ratio of geometric means.
PK = Pharmacokinetic; SD = standard deviation; %CV=100*sqrt(exp(SD**2)-1); LSM = least squares mean from ANOVA model.

The above analyses involved elimination of fed period, which assumed absence of period effects. In contrast, the two designs (full and partial replicated, respectively) recommended in the OGD draft guidance (as shown below) do not require any assumptions on period effect.

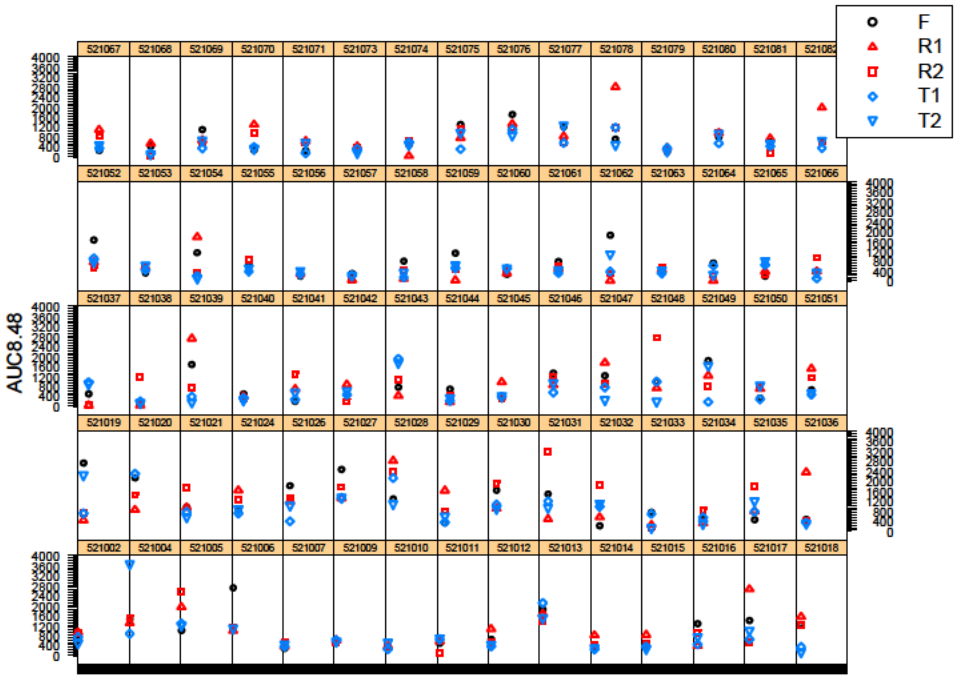
Trt_R = Reference treatment; Trt_T = Test treatment

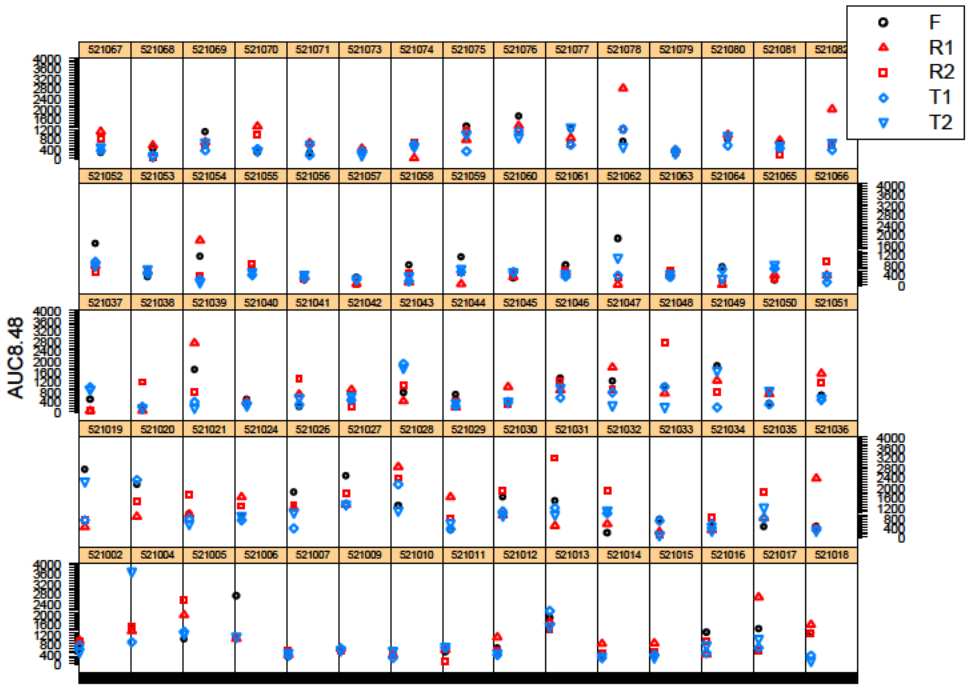
	Period p_j			
Sequence g_i	1	2	3	4
1	Trt_T	Trt_R	Trt_T	Trt_R
2	Trt_R	Trt_T	Trt_R	Trt_T

	Period p_j		
Sequence g_i	1	2	3
1	Trt_T	Trt_R	Trt_R
2	Trt_R	Trt_T	Trt_R
3	Trt_R	Trt_R	Trt_T

Thus, on the advice of statisticians from the Office of Biometrics, DBVI, the sponsor conducted additional analyses to identify unbiased estimates of the relative bioavailability. Subsequently, DBVI determined that the study design is uninterpretable and the WC3079 and Asacol responded differently. The following are DBVI comments provided in their review: "The bioequivalence cannot be concluded due to the following reasons: First, the proposed estimators will not make up for the deficiency of the design. We found one unbiased estimator using weight different the sponsor's weight, whose point estimate is smaller than 0.8. Second, there are no proper statistical methods for calculating the confidence interval for $(\mu_T - \mu_R)^2 - (\theta\sigma_{WR})^2$. Third, there are more cases with the small number of nonzero concentrations ($\leq$3) for the reference product than those for the test product and the point estimate of μ_T / μ_R for nonzero group is 0.72. Therefore, the test product WC3097 and reference product Asacol are not bioequivalent."

Individual subject $AUC_{8\text{-}48}$ data by treatment/replicate:





**subject IDs 521006, 521020,521055, 521128, 521134 had at least one value exceeding 4000 and therefore that data is not seen in the plots above*

***Examination of observed zero exposures (Reviewer's analysis)**:*

Fifteen subjects in the reference group and 2 in the test group (1 common subject) had all zero concentrations throughout the 72 hour sampling window. For the purpose of statistical analyses, the sponsor assigned a value of 1 to Cmax and AUC parameters. The following table shows AUC_{8-48} data for each of these patients across the treatments and for the replicates within treatments (C_{max} and AUC_{tldc} were similarly assigned value of 1 in presence of zero concentrations and hence not shown here). Since these are observed values, reviewer agrees that data should be included in the analyses and not deleted as outliers.

Data shows that for the majority of individuals, the zero concentrations were noted in only one of the two replicates of test or reference treatments. This demonstrates the intra-subject, intra-occasion variability of mesalamine plasma pharmacokinetics. In addition, the new formulation (test) had fewer instances of zero concentrations so there is less concern on this issue. It is likely (although cannot be conclusively proven) that presence of four individual 100 mg units in the new capsule formulation would reduce the incidence of complete product failure to release drug in the colon, as opposed to having one unit as in the reference formulation.

ID	**R1** AUC_{8-48}	**R2** AUC_{8-48}	**T1** AUC_{8-48}	**T2** AUC_{8-48}
521037	1	5.1	936.4	801.2
521038	1	1134	158	59.3
521062	1	275	365	1018
521064	1	223	604.4	195.5
521074	1	623	557	405
521098	1	684	260	445
521143	1	825	1077	450
521149	1	812	369	12.8
521160	1	1147	326	1416
521057	30.2	1	213	156
521097	958	1	162	416
521124	456	1	572	289
521129	791	1	16.3	213
521137	422	1	69	206
521146	691	1	2	1
521114	969	387	1	43

***Additional Bioavailability analyses by Reviewer**:*

We utilized only the data from sequences 3 and 4 above (or C and D per original study design) to run the BE analyses. In both these sequences, food-effect treatment 3 was placed in the third period and therefore discounting this period from both these sequences

prior to analyses would have a similar effect on both Test and Reference formulations and no renumbering of periods was necessary.

Sequence C: R1 – T1 – Fed- R2 – T2
Sequence D: T1 – R1 – Fed- T2 – R2
where, Reference (R1 &R2) is the reference Asacol tablets 400 mg and Test (T1 & T2) is the proposed Delzicol capsules 400mg.

Using this data set, statistical analyses were conducted again using SAS 9.3 which generated the following output, suggesting that all three key PK parameters passed the BE criteria:

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
$LAUC_{TLDC}$	0.92	.	.	2.6431803	1.6257861	-1.636809	Scaled/PE	PASS
$LAUC_{8-48}$	0.87	.	.	2.6813033	1.6374686	-1.642708	Scaled/PE	PASS
LCMAX	0.97	.	.	1.8334341	1.3540436	-1.142678	Scaled/PE	PASS

Food-effect on PK:

The second objective of the present study was to assess the food effect on the PK of mesalamine from the new Delzicol (WC3079) formulation. Thus, the PK of mesalamine after the proposed formulation is administered under fed and fasted conditions were compared to estimate the magnitude of any food-effect on absorption. This again, involved assumptions related to absence of period effects, and collapsing of identical sequences (3 and 4 below) in the original analyses.

	Period p_j				
Sequence g_i	1	2	3	4	5
1	~~Trt_1~~	Trt_3	Trt_2	~~Trt_1~~	Trt_2
2	Trt_2	~~Trt_1~~	Trt_2	Trt_3	~~Trt_1~~
3	~~Trt_1~~	Trt_2	Trt_3	~~Trt_1~~	Trt_2
4	Trt_2	~~Trt_1~~	Trt_3	Trt_2	~~Trt_1~~

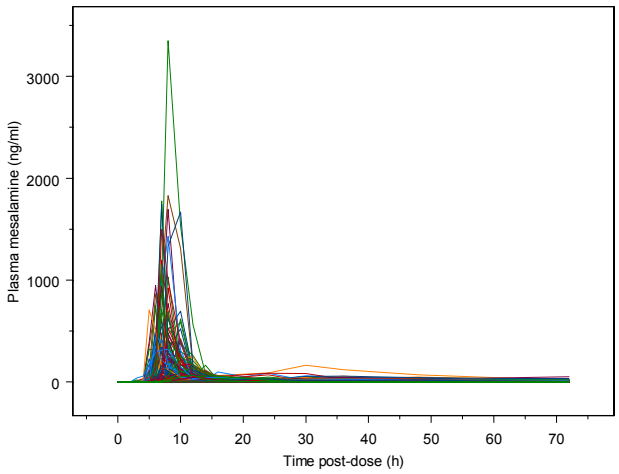
~~Trt_1 = Asacol, fasted~~; Trt_2 = Delzicol, fasted; Trt_3 = Delzicol, fed

The results from this original food effect analyses are shown below and suggest an increase in Cmax, AUC8-48 and AUCtldc by 32 %, 46 % and 29 %, respectively when administered with a high fat meal:

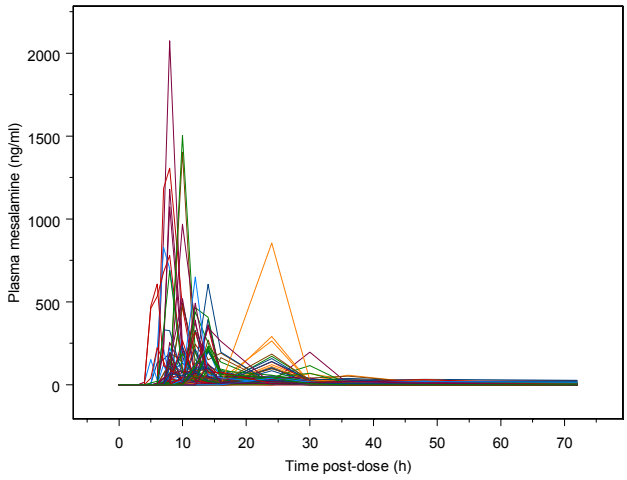
		Within-Subject SD (CV%)		Geometric Mean (LSM)		Ratio (%)	95% Upper Bound of the Linearized
PK Parameter	N	Test	Reference	Test	Reference	(T / R)	Criterion
Cmax	146	NA	1.20 (179)	91.1	69.0	132.11	-0.825
AUC8-48	146	NA	0.738 (85.1)	681	466	146.22	-0.152
AUC0-tldc	146	NA	0.831 (99.7)	802	620	129.39	-0.354
AUC0-inf	99	NA	0.575 (62.6)	1227	1087	112.90	-0.183

Cmax = Maximum plasma concentration (ng/mL);
AUC8-48 = AUC from time 8 hours to 48 hours (ng·h/mL);
AUC0–tldc = AUC from time 0 to the time of last determinable concentration (tldc) (ng·h/mL)
Test(T) = WC3079 capsule with food; Reference(R) = WC3079 capsule fasted.
Ratio = The ratio of geometric means. NA = not applicable
BE = Bioequivalence; SD = standard deviation; CV%=100*sqrt(exp(SD**2)-1); LSM = least squares mean from ANOVA model

Fasted- New formulation



Fed- new formulation



3 Labeling Comments:

- The PK parameters for the new Delzicol product should be reflected in the label.
- The label should indicate that the proposed product can be administered with or without food.

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/s/

SUE CHIH H LEE
08/12/2015