Received: 26 June 2019 | Revised: 15 June 2020 | Accepted: 6 July 2020

DOI: 10.1111/bcp.14479

ORIGINAL ARTICLE

Similar pharmacokinetics of three dosing regimens comprising two oral delayed-release mesalamine formulations in healthy adult volunteers: Randomised, open-label, parallel-group study

Niels Vande Casteele[1] | Abhijeet Jakate[2] | Brian McNamee[3] | William J. Sandborn[1]

[1]University of California, San Diego, La Jolla, CA, USA

[2]Allergan plc, Jersey City, NJ, USA

[3]Allergan Biologics Ltd, Liverpool, UK

Correspondence
Niels Vande Casteele, University of California, San Diego, 9500 Gilman Drive #0956, La Jolla, CA 92093, USA.
Email: nvandecasteele@ucsd.edu

Funding information
American Gastroenterological Association, Grant/Award Number: Research Scholar Award; Warner Chilcott US, LLC, an indirect subsidiary of Allergan plc

Aims: Mesalamine is the first-line therapy for treating mild-to-moderate ulcerative colitis. Multiple mesalamine formulations are available, with similar safety and efficacy profiles. Mesalamine is commonly administered as divided dosing, although once-daily dosing may provide benefits for patients. We evaluated the pharmacokinetics of three dosing regimens of two oral delayed-release mesalamine formulations in healthy adult volunteers.

Methods: A randomised, open-label, parallel-group study of mesalamine pharmacokinetics following Lialda 2 × 1.2 g once daily (QD) (dose A), Asacol 6 × 400 mg QD (dose B), or Asacol 2 × 400 mg three times daily (TID) (dose C) over 7 days. Assessments included 5-aminosalicylic acid (5-ASA) and *N*-acetyl 5-aminosalicylic acid (N-Ac-5-ASA, primary metabolite) pharmacokinetics (A_e(%), $AUC_{0\text{-}24}$ and C_{max}), safety and tolerability.

Results: All enrolled volunteers (n = 37) completed the study. Steady state was achieved for all treatments by day 4. Ratios (95% CI) of means for steady-state $AUC_{0\text{-}24}$ (dose A *vs* B 90.3% [39.8, 204.8], dose A *vs* C 123.5% [55.3, 275.7], dose B *vs* C 136.8% [61.3, 305.5]) and C_{max} (dose A *vs* B 106.0% [46.4, 242.2], dose A *vs* C 133.0% [59.1, 299.0], dose B *vs* C 125.5% [55.8, 282.1]) were similar for all 5-ASA treatments. Mean urinary excretion of 5-ASA plus N-Ac-5-ASA was comparable between treatments (dose A 21.3%, dose B 20.2%, dose C 17.9%). All treatment regimens were well tolerated; no safety issues were observed.

Conclusions: Plasma and urine pharmacokinetics for Asacol TID, Asacol QD, and Lialda QD are similar, suggesting similar daily systemic exposures can be obtained with either TID or QD dosing. NCT00751699.

KEYWORDS

clinical pharmacology, Inflammatory bowel disease, 5-ASA

The authors confirm that the Principal Investigator for this manuscript is Stuart Harris, MD, PhD, and he had direct clinical responsibility for the patients.

Some of these data have been previously published in abstract format, as follows: Sandborn WJ, Balan G, Kuzmak B, Hanauer SB. Comparable pharmacokin-etics (PK) of two delayed release formulations of oral mesalamine. Am J Gastroenterol 2007; 102 (Suppl 2): S465 (abstract 944); and Sandborn W, Balan G, Kuzmak B, Hanauer S. Comparable pharmacokinetics of two delayed release formulations of oral mesalamine: P-043. Inflamm Bowel Dis 2008; 14: S23-24.

1 | INTRODUCTION

Ulcerative colitis is a chronic inflammatory gastrointestinal disorder characterised by relapsing and remitting inflammation of the colon. During a relapse, disease activity can be classified as mild, moderate or severe,[1,2] with symptoms including diarrhoea, rectal bleeding and abdominal pain. Patients may also suffer from extraintestinal manifestations affecting the joints, skin, mouth and eyes.[3–5] Patients with ulcerative colitis are at increased risk of developing colorectal cancer, with a risk of 2% at 10 years of disease duration, increasing to a risk of 30% by 30 years of disease duration.[6,7]

Oral or topical mesalamine (5-aminosalicylic acid [5-ASA]) is established as first-line therapy for mildly to moderately active ulcerative colitis and is effective in inducing and maintaining disease remission.[3,8] Multiple formulations of oral delayed-release mesalamine have been developed with the aim of optimising delivery to the colonic mucosa and minimising systemic absorption.[8,9] Mesalamine is acetylated in the liver and intestine to produce the inactive metabolite *N*-acetyl-5-ASA (N-Ac-5-ASA), with both 5-ASA and N-Ac-5-ASA being excreted in the urine and faeces.[10,11]

Asacol (Allergan plc, Dublin, Ireland) is an enteric-coated mesalamine formulation and Lialda (Norga Pharma, Dublin, Ireland) is a multi-matrix formulation, both of which are designed to release mesalamine in the terminal ileum and colon.[9] Both Asacol and Lialda are indicated for the treatment of mildly to moderately active ulcerative colitis and for maintenance of remission.[12,13] The efficacies for the induction and maintenance of remission of the different available mesalamine formulations have been shown to be broadly similar, with all formulations showing similar safety and tolerability.[14,15] Selection of therapy for an individual patient is therefore influenced by factors such as disease distribution, tolerability, adherence and cost-effectiveness.[9]

Mesalamine was originally identified as the active metabolite of sulfasalazine, which has been used to treat ulcerative colitis since the 1940s.[16] The inactive metabolite of sulfasalazine, sulfapyridine, is associated with side effects such as allergy and dyspepsia, and is poorly tolerated by around 20% of patients[9,17]; sulfasalazine was therefore administered using four-times-daily dosing in order to reduce these side effects by reducing the maximum plasma concentration (C_{max}) of sulfapyridine absorbed from the colon.[18,19] The practice of divided dosing of sulfasalazine for ulcerative colitis was initially carried forward to the dosing of mesalamine as well, although it has subsequently been demonstrated that once-daily (QD) dosing with mesalamine is as safe and effective for both the induction and maintenance of remission as divided dosing.[18,20] QD dosing may provide an advantage for the management of ulcerative colitis versus divided dosing, as needing to take multiple doses per day has been associated with poorer medication adherence.[21–23]

Here we report the results of a study in healthy volunteers evaluating the relative bioavailability of three dosing regimens of two oral delayed-release mesalamine formulations: Asacol 2 × 400 mg three times daily (TID), Asacol 6 × 400 mg QD and Lialda 2 × 1.2 g QD.

What is already known about this subject

- The efficacy and safety of the different available mesalamine formulations for the induction and maintenance of remission in patients with ulcerative colitis are similar.
- Needing to take multiple doses per day has been associated with poorer medication adherence and thus once-daily dosing may benefit management of ulcerative colitis.

What this study adds

- In healthy volunteers, the pharmacokinetics of two oral delayed-release mesalamine formulations, Asacol and Lialda, were broadly similar, irrespective of dosing regimen.
- The data therefore suggest that a similar systemic exposure of oral delayed-release mesalamine can be achieved with either once-daily or three-times-daily dosing.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a randomised, open-label, parallel-group study evaluating the relative bioavailability of mesalamine following multiple-dose oral administration of three regimens of delayed-release mesalamine 2.4 g per day in healthy adult volunteers, in line with the approved dosing for Asacol for the induction of remission and Lialda for the induction and maintenance of remission in ulcerative colitis.[12,13] Treatment was administered for 7 days; the study was conducted over approximately 10 days (Figure 1). The drug nomenclature conforms to the IUPHAR/BPS Guide to Pharmacology nomenclature classification.[24]

The study was conducted in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice and received approval from the Independent Investigational Review Board (Plantation, FL, USA). All volunteers provided written informed consent in accordance with the Declaration of Helsinki. The study is registered with www.clinicaltrials.gov (NCT00751699).

2.2 | Study population

Volunteers were healthy males and females aged 18-45 years, defined as having good general health based on medical history, physical

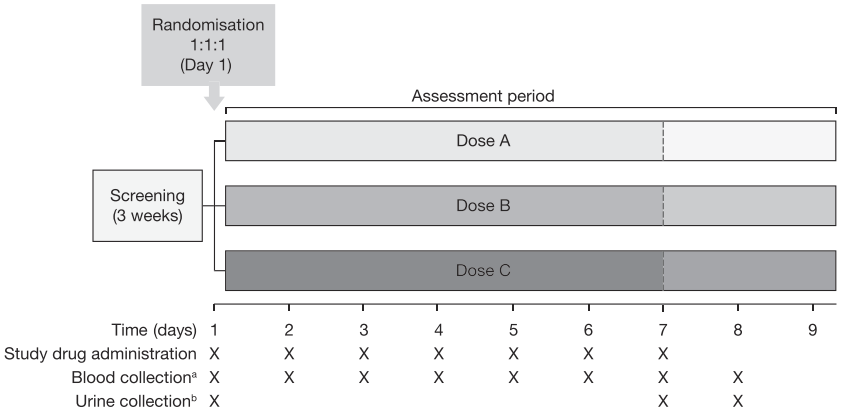

FIGURE 1 Study design. [a]Pharmacokinetic blood collections: 0 (pre-dose on day 1), 24 (day 2), 48 (day 3), 72 (day 4), 96 (day 5), 120 (day 6) and 144 (day 7) hours after the first dose on day 1, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, 18, 19, 20, 22, 24, 30, 36 and 48 hours after the first morning dose on day 7. [b]Pharmacokinetic urine collections: pre-dose on day 1 and pooled over 0-8, 8-16 and 16-24 hours after the first morning dose on day 7

examination and clinical laboratory assessments, and with a body mass index between 18 and 32 kg/m^2. Volunteers were excluded if they had participated in any other investigational drug study within 30 days before the first day of dosing, or if they had a history or presence of any of the following: gastrointestinal condition or surgery causing malabsorption or affecting gastrointestinal motility; uncontrolled acute disease or surgical operation requiring hospitalisation within 1 month of screening; diabetes, syncope or cardiovascular, hepatic or renal disease; uncontrolled chronic disease such as hypertension, systemic lupus erythematosus or rheumatoid arthritis; or hypersensitivity to salicylates or any component of Asacol or Lialda tablets.

2.3 | Drug selection and doses

Eligible volunteers were randomised 1:1:1 to receive Lialda 2 × 1.2 g QD (dose A), Asacol 6 × 400 mg QD (dose B) or Asacol 2 × 400 mg TID (dose C) for 7 days. The study drug was administered with water and within 30 minutes after starting a meal or snack. Volunteers were instructed to swallow the tablets whole. QD doses were administered at approximately 7 AM and TID doses were administered at approximately 7 AM, 3 PM and 11 PM.

2.4 | Pharmacokinetic assessments

Blood samples for measurement of plasma 5-ASA and N-Ac-5-ASA concentration were collected pre-dose on days 1 through 7 and at the following time points after dosing on day 7: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, 18, 19, 20, 22, 24, 30, 36 and 48 hours (Figure 1). Urine samples were collected pre-dose on day 1 and then pooled during the following time intervals after dosing on day 7: 0-8 hours, 8-16 hours and 16-24 hours.

Plasma and urine concentrations of 5-ASA and N-Ac-5-ASA were determined by previously developed and validated methods based on liquid chromatography with tandem mass spectrometry. The nominal range of quantitation was 10-1500 ng/mL for plasma 5-ASA, 20-2500 ng/mL for plasma N-Ac-5-ASA, 50-10 000 ng/mL for urine 5-ASA and 150-150 000 ng/mL for urine N-Ac-5-ASA, based on a sample volume of 50 μL (unpublished data on file, Study 2,007,011, Abhijeet Jakate, Allergan plc, Madison, NJ, USA, abhijeet.jakate@allergan.com).

Plasma and urine concentration data for 5-ASA and N-Ac-5-ASA were analysed by standard noncompartmental methods using WinNonlin version 5.1.1 (Certara USA, Inc., Princeton, NJ, USA) and/or SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA). The C_{max} of 5-ASA or N-Ac-5-ASA was determined by direct observation from the plasma concentration data, the area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) was estimated by linear trapezoidal approximation and the percentage of dose excreted in urine (A_e(%)) as 5-ASA or N-Ac-5-ASA was estimated using the total amount excreted over the 24-hour period on day 7. All pharmacokinetic parameters were estimated using plasma concentration data over the 24-hour period starting immediately prior to the first AM dose on day 7.

2.5 | Statistical analyses

All volunteers randomised to the trial were analysed for pharmacokinetic and safety data. Primary endpoints were plasma 5-ASA and N-Ac-5-ASA $AUC_{0\text{-}24}$ and 5-ASA A_e(%) for day 7; secondary endpoints included other pharmacokinetic parameters for 5-ASA and N-Ac-5-ASA, such as C_{max}. Treatment comparisons were conducted using analysis of variance (ANOVA) methods; $AUC_{0\text{-}24}$ and C_{max} were log-transformed before analysis, and other pharmacokinetic parameters were assessed for adherence to the assumptions of the ANOVA model on both the log and the original scale, with the scale best satisfying the assumptions being used for the analysis. An ANOVA model with terms for treatment, subject, subject (treatment), day and treatment by day was used to compare trough concentrations and determine the time point at which steady state was attained for 5-ASA and N-Ac-5-ASA.[25] Body weight corrections were not made to the pharmacokinetic data.

The sample size was not based upon statistical considerations of power for comparative inference. The study was expected to enrol approximately 42 volunteers, with 14 volunteers per treatment group. Based on this expected sample size, the ratio of two treatments was estimated within a factor of 66% on the multiplicative scale for

$AUC_{0\text{-}24}$ with a 95% confidence interval (CI). For example, if the observed ratio was 1.0 then the CI was expected to be approximately (0.60, 1.66). The difference of two treatments was estimated within 2.72 units on the additive scale for A_e(%) with a 95% CI. For example, if the observed difference was 0.0 then the 95% CI was expected to be approximately (−2.72, 2.72).

2.6 | Safety assessments

Adverse events were monitored throughout the 3-week screening period, at study admission and throughout the study duration.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Volunteer disposition, demographics and baseline characteristics

Thirty-seven volunteers were enrolled and randomised to treatment; all enrolled volunteers completed the study. Volunteer demographics were balanced between treatment groups; 23 (62.2%) volunteers were male and mean age was 30.7 years (Table 1).

TABLE 1 Volunteer demographics

	Dose A (n = 12)	Dose B (n = 12)	Dose C (n = 13)	Overall population (n = 37)
Mean age, years (SD)	32.7 (9.7)	28.1 (6.9)	31.4 (6.2)	30.7 (7.7)
Male, n (%)	8 (66.7)	7 (58.3)	8 (61.5)	23 (62.2)
Race, n (%)				
Caucasian	5 (41.7)	7 (58.3)	10 (76.9)	22 (59.5)
Black	7 (58.3)	5 (41.7)	3 (23.1)	15 (40.5)
Ethnicity, n (%)				
Hispanic or Latino	8 (66.7)	8 (66.7)	11 (84.6)	27 (73.0)
Not Hispanic or Latino	4 (33.3)	4 (33.3)	2 (15.4)	10 (27.0)
Mean height, cm (SD)	170.2 (9.8)	170.5 (10.2)	169.4 (9.0)	170.0 (9.4)
Mean weight, kg (SD)	74.1 (14.6)	72.8 (14.1)	75.6 (10.8)	74.2 (12.9)

Randomised set.
SD, standard deviation.

3.2 | Pharmacokinetics

3.2.1 | Steady-state analysis

Least-squares geometric mean trough plasma concentrations for 5-ASA and N-Ac-5-ASA on days 2-7 were generally stable over time (Figure 2), indicating that steady-state with respect to 5-ASA and N-Ac-5-ASA was achieved for all three treatments by day 4. Comparisons of trough concentrations on day 4 to day 7 suggest higher trough 5-ASA and N-Ac-5-ASA concentrations with dose C relative to dose A (5-ASA, P = 0.129; N-Ac-5-ASA, P = 0.107) and dose B (5-ASA, P = 0.225; N-Ac-5-ASA, P = 0.297), although differences were not statistically significant. Intra-subject variability based on each subject's

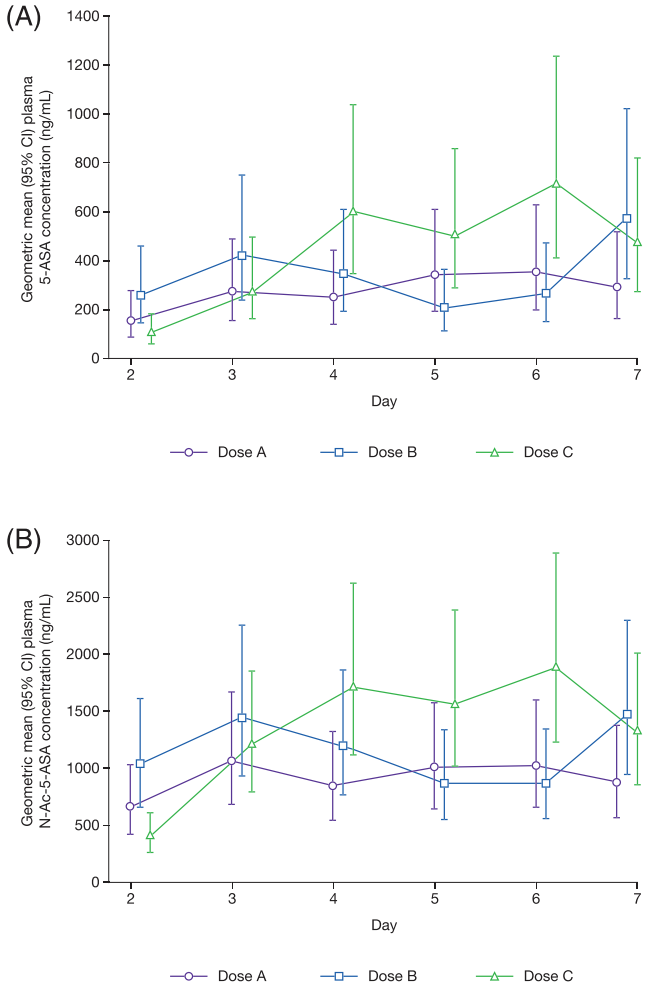

FIGURE 2 (A) Steady-state analysis of 5-ASA by treatment. (B) Steady-state analysis of N-Ac-5-ASA by treatment. Day 2 is 24 hours after the first dose on day 1. Data shown as least-squares geometric means and 95% CIs obtained from a model with independent variable ln(trough concentration) and terms for subject(treatment*sex), day, sex, treatment and treatment*day. BLQ concentrations were set to 5-ASA 1/2 BLQ = 5 ng/mL and N-Ac-5-ASA 1/2 BLQ = 10.2 ng/mL. 5-ASA, 5-aminosalicylic acid; BLQ, below level of quantification; CI, confidence interval; N-Ac-5-ASA, *N*-acetyl-5-aminosalicylic acid

mean 5-ASA trough concentration (days 4 to 8) was compared for the three treatments; the coefficient of variation (%CV) values were 70-82% for dose A, 66-102% for dose B and 70-135% for dose C. Inter-subject variability based on mean 5-ASA trough concentrations on each study day was also compared for the three treatments; the %CV values were 14-160% for dose A, 26-178% for dose B and 26-153% for dose C. The N-Ac-5-ASA trough concentration inter- and intrasubject variability values were equally comparable for the three treatments.

3.2.2 | Pharmacokinetic parameters

Ratios (95% CI) of means for steady-state $AUC_{0\text{-}24}$ were broadly similar between treatments for both 5-ASA (dose A *vs* B 90.3% [39.8, 204.8]; dose A *vs* C 123.5% [55.3, 275.7]; dose B *vs* C 136.8% [61.3, 305.5]) and N-Ac-5-ASA (dose A *vs* B 95.8% [57.4, 160.0]; dose A *vs* C 104.3% [63.1, 172.4]; dose B *vs* C 108.8% [65.9, 179.9]), with ratios of means generally within 40% (Table 2). Similarly, ratios (95% CI) of means for steady-state C_{max} were similar overall between treatments for 5-ASA (dose A *vs* B 106.0% [46.4, 242.2]; dose A *vs* C133.0% [59.1, 299.0]; dose B *vs* C 125.5% [55.8, 282.1]) and N-Ac-5-ASA (dose A *vs* B 97.4% [61.9, 153.3]; dose A *vs* C 114.8% [73.6, 179.2]; dose B *vs* C117.9% [75.6, 184.0]) (Table 2). Ratios of means (90% CI) for steady-state $AUC_{0\text{-}24}$ and C_{max} are also provided and show a similar trend (Supporting Information Table S1). The median observed time of maximum plasma concentration (t_{max}) values ranged from 6 to 16 hours across the three doses, reflecting the delayed-release nature of these formulations. However, all pharmacokinetic parameters, including $AUC_{0\text{-}24}$, t_{max} and C_{max}, had large intersubject variability across treatments, with the coefficient of variation for the geometric mean generally between 50% and 150%, much larger than the variability typically associated with highly variable drug products.[26]

3.2.3 | Plasma concentration-time profiles

Mean plasma 5-ASA concentration-time profiles for the 48 hours after dose administration on day 7 are presented in Figure 3A. Maximum plasma 5-ASA concentrations were observed at 8-16 hours post-dose, reaching mean C_{max} values of 1272 and 1465 ng/mL for dose A and dose B, respectively. Mean post-dose 5-ASA plasma concentrations for dose C showed a flatter profile versus dose A and dose B, with concentrations ranging from 469 to 870 ng/mL on day 7.

Similar trends were observed for the mean plasma N-Ac-5-ASA concentration-time profiles. Dose A and dose B showed similar profiles and a mean C_{max} of approximately 2100 ng/mL at 10-14 hours post-dose on day 7 (Figure 3B). The mean N-Ac-5-ASA concentration-time profile for dose C was flatter than for dose A and dose B; plasma concentrations ranged from 1208 to 1713 ng/mL on day 7.

3.2.4 | Urinary excretion

The least-squares mean total urinary excretion of 5-ASA plus N-Ac-5-ASA was similar between all treatments, and was also similar between treatments for both 5-ASA and N-Ac-5-ASA separately (Table 3).

TABLE 2 5-ASA and N-Ac-5-ASA plasma pharmacokinetic parameters and 95% CI on ratios; steady state at day 7

				Ratio expressed as percentage (95% CI)		
Parameter	**Dose A (n = 12)**	**Dose B (n = 12)**	**Dose C (n = 13)**	**Dose A *vs* B**	**Dose A *vs* C**	**Dose B *vs* C**
5-ASA						
$AUC_{0\text{-}24}$, μg × h/mL	12.39	13.73	10.03	90.3 (39.8, 204.8)	123.5 (55.3, 275.7)	136.8 (61.3, 305.5)
C_{max}, μg/mL	1.458	1.375	1.096	106.0 (46.4, 242.2)	133.0 (59.1, 299.0)	125.5 (55.8, 282.1)
t_{max}[d], h	7.9 (5.0-12.0)	8.5 (0.0-17.0)	15.9 (0.0-24.0)	–	–	–
$t_{1/2}$, h	10.21[a]	9.591[a]	8.528[a]	106.5 (49.0, 231.4)	119.7 (55.1, 260.2)	112.5 (52.2, 242.2)
N-Ac-5-ASA						
$AUC_{0\text{-}24}$, μg × h/mL	31.32	32.67	30.02	95.8 (57.4, 160.0)	104.3 (63.1, 172.4)	108.8 (65.9, 179.9)
C_{max}, μg/mL	2.316	2.378	2.017	97.4 (61.9, 153.3)	114.8 (73.6, 179.2)	117.9 (75.6, 184.0)
t_{max}[d], h	8.5 (5.0-12.0)	10.0 (0.0-19.0)	6.0 (0.0-24.0)	–	–	–
$t_{1/2}$, h	9.416[b]	17.65	19.19[c]	53.3 (25.0, 113.6)	49.1 (23.0, 104.5)	92.0 (44.9, 188.5)

Analysis set includes volunteers evaluable for pharmacokinetics.

Data shown as least-squares geometric means.

Abbreviations: 5-ASA, 5-aminosalicylic acid; $AUC_{0\text{-}24}$, area under the plasma concentration-time curve from 0 to 24 hours; CI, confidence interval; C_{max}, maximum plasma concentration; N-Ac-5-ASA, *N*-acetyl-5-aminoaslicylic acid; $t_{1/2}$, half-life; t_{max}, time of maximum plasma concentration.

[a]n = 11.

[b]n = 10.

[c]n = 12.

[d]Data shown as median (minimum – maximum).

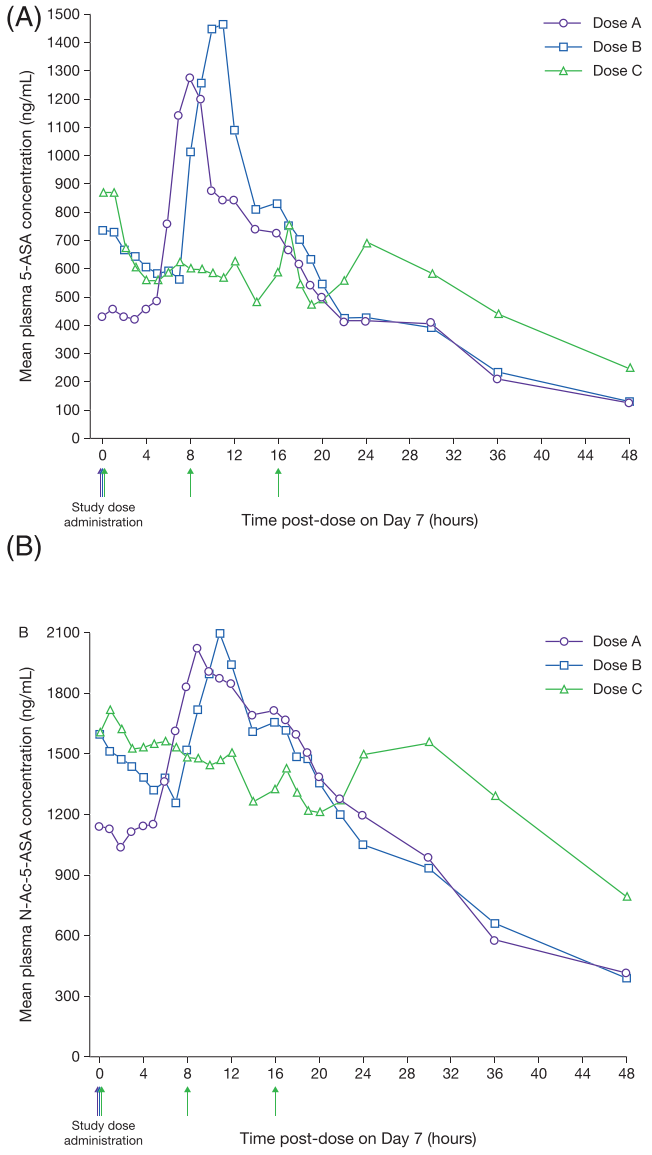

FIGURE 3 (A) Mean plasma 5-ASA concentration-time profiles on day 7 following multiple-dose oral administration of three treatment regimens of two formulations of mesalamine. (B) Mean plasma N-Ac-5-ASA concentration-time profiles on day 7 following multiple-dose oral administration of three treatment regimens of two formulations of mesalamine. 5-ASA, 5-aminosalicylic acid; N-Ac-5-ASA, *N*-acetyl-5-aminosalicylic acid

3.3 | Safety

All three treatment regimens were well tolerated and no safety issues were observed. Four adverse events were reported during the study: one (8.3%) with dose A, two (16.7%) with dose B and one (7.7%) with dose C (Table 4). All four adverse events were judged by the investigator as unlikely to be related to study medication. No serious adverse events, withdrawals due to an adverse event or deaths occurred.

4 | DISCUSSION

The pharmacokinetics of three regimens of oral delayed-release mesalamine, Lialda 2 × 1.2 g QD (dose A), Asacol 6 × 400 mg QD (dose B) and Asacol 2 × 400 mg TID (dose C), were assessed in a randomised, open-label study in healthy adult volunteers. All three dosing regimens showed similar pharmacokinetic profiles following multiple dosing and were well tolerated, with no safety signals observed. Following multiple-dose administration, steady state with respect to 5-ASA and N-Ac-5-ASA was achieved by day 4 for all treatments. While TID dosing (dose C) resulted in higher trough concentrations, trials have not consistently demonstrated statistically significant differences in the prespecified primary endpoints for one agent over another in the treatment of ulcerative colitis.[8]

Dose A and dose B had similar plasma 5-ASA and N-Ac-5-ASA concentration-time profiles and urinary excretion data. Additionally, Asacol and Lialda are both designed to release mesalamine in the same region of the gastrointestinal tract, namely the terminal ileum and colon.[27–29]

The summary pharmacokinetic parameters ($AUC_{0\text{-}24}$ and C_{max}) for 5-ASA with Asacol are broadly similar to those previously reported. The mean C_{max} value in the present study was 1419 ng/mL, compared to the previously reported mean C_{max} range of 321-1608 ng/mL.[8] The observed urinary excretion of 5-ASA plus N-Ac-5-ASA with Asacol is also similar to previously reported values for urinary excretion of 5-ASA alone.[8] Given that 5-ASA is thought to be more nephrotoxic than N-Ac-5-ASA, it is worth noting that the urinary excretion of the individual components was also similar.

These data also confirm previous findings demonstrating the similarity in pharmacokinetics following QD versus TID dosing with Asacol.[19] Furthermore, results following Lialda administration are similar to previously reported steady-state kinetics following multiple administration.[30] A high degree of intersubject variability was observed for all pharmacokinetic parameters across all treatments in the present study, resulting in a degree of variability in the summary pharmacokinetic parameters between treatment groups. However, this degree of variability is in line with previous findings in studies identifying similarity between different mesalamine formulations.[8,19] This variability is characteristic of delayed- and extended-release mesalamine formulations, and, more broadly, a high degree of inter- and intrasubject variability is a common feature of drugs acting in the gastrointestinal tract due to variability in gastrointestinal transit times.[8,19,31]

The results of this study should be interpreted with some caution. The enrolled study population was relatively small, and this was not a statistically powered bioequivalence study. Moreover, mesalamine is considered to be a highly variable drug product and a degree of variability among different mesalamine formulations has been reported in previous pharmacokinetic studies.[8,19] Highly variable drugs such as mesalamine require a considerably larger population size and a reference-scaled average bioequivalence study design to draw firm conclusions regarding the comparative bioavailability of different treatments and dosing regimens, as outlined by global

TABLE 3 Urinary excretion of 5-ASA and N-Ac-5-ASA

Parameter	Dose A (n = 12)	Dose B (n = 12)	Dose C (n = 13)	Ratio expressed as percentage (95% CI)		
				Dose A *vs* B	Dose A *vs* C	Dose B *vs* C
5-ASA						
A_e(%)[a]	2.74	2.97	1.37	139.6 (42.3, 754.4)	157.3 (59.8, 911.1)	84.7 (31.4, 204.9)
N-Ac-5-ASA						
A_e(%)	17.45	15.89	14.86	117.4 (80.6, 174.0)	107.0 (71.7, 160.4)	109.8 (75.6, 161.3)
5-ASA and N-Ac-5-ASA						
A_e(%)	21.3	20.2	17.9	119.0 (77.9, 186.1)	112.8 (72.8, 177.9)	105.4 (69.8, 160.3)

Analysis set includes volunteers evaluable for pharmacokinetics.
Data shown as least-squares arithmetic means.
Abbreviations: 5-ASA, 5-aminosalicylic acid; A_e(%), percentage urinary excretion; CI, confidence interval; N-Ac-5-ASA, *N*-acetyl-5-aminoaslicylic acid; QD, once daily; TID, three times daily.
[a]Data shown are median values.

TABLE 4 Summary of adverse events

n (%)	Dose A (n = 12)	Dose B (n = 12)	Dose C(n = 13)
Any adverse event	1 (8.3)	2 (16.7)	1 (7.7)
Serious adverse events	0	0	0
Adverse events leading to withdrawal	0	0	0
Incidence of adverse events by preferred term			
Back pain	0	1 (8.3)	0
Musculoskeletal stiffness	0	1 (8.3)	0
Pain in extremity	0	0	1 (7.7)
Pruritus	1 (8.3)	0	0

regulatory agencies.[26,32,33] However, this study was not designed or powered to demonstrate bioequivalence; rather, it was designed to determine relative bioavailability of various formulations and/or regimens of mesalamine.

Furthermore, the data were analysed using descriptive statistics and no inferential analyses were conducted, limiting the interpretation of the data. Finally, although this study was conducted in healthy volunteers, the urinary excretion of 5-ASA following Asacol administration has been shown to be comparable between healthy volunteers and patients with inactive ulcerative colitis, suggesting that findings from healthy volunteers in the present study are likely to reflect mesalamine bioavailability in patients with ulcerative colitis.[8] Pharmacokinetic parameters in this study were also evaluated at steady state, providing data that may be more reflective of real-world maintenance usage of mesalamine in adults with ulcerative colitis, in particular patients in remission.

In conclusion, these data demonstrate that three regimens of oral delayed-release mesalamine, Lialda 2 × 1.2 g QD, Asacol 6 × 400 mg QD and Asacol 2 × 400 mg TID, display generally similar pharmacokinetics and are well tolerated in healthy volunteers.

ACKNOWLEDGEMENTS

The authors would like to thank Helen Woodroof, PhD, of Complete HealthVizion, for writing and editorial assistance in the writing and revision of the draft manuscript on the basis of detailed discussion and feedback from all the authors; this assistance was funded by Allergan plc. This work was supported by Warner Chilcott (US), LLC, an indirect subsidiary of Allergan plc. The authors received no compensation related to the development of the manuscript. NVC holds a Research Scholar Award from the American Gastroenterological Association (AGA).

COMPETING INTERESTS

N.V.C. has received consultancy fees from Boehringer Ingelheim, Pfizer, Takeda and UCB Pharma. A.J. is an employee of and holds stock/stock options in Allergan plc. B.M. is an employee of Allergan Biologics Ltd. W.J.S. reports personal fees from Actavis, Actogenix NV, Adherion Therapeutics, Akros Pharma, Ambrx, Am Pharma BV, Ardelyx, Arena Pharmaceuticals, Avaxia Biologics, Baxter Healthcare, Biogen, Catabasis Pharmaceuticals, Celgene, Celgene Cellular Therapeutics, Chiasma, Cosmo Pharmaceuticals, Dr August Wolff, Eisai, Eli Lilly, Ferring Pharmaceuticals, Ferring Research Institute, Forward Pharma, Galapagos, Immune Pharmaceuticals, Index Pharmaceuticals, Ironwood Pharmaceuticals, Kyowa Hakko Kirin, Lexicon Pharmaceuticals, Lipid Therapeutics GmbH, Luitpold Pharmaceuticals, MedImmune (AstraZeneca), Mesoblast, Millennium Pharmaceuticals, Nestlé, Novo Nordisk, Orexigen, Palatin, Qu Biologics, Regeneron, Ritter Pharmaceuticals, Salix Pharmaceuticals, Santarus, Seattle Genetics, Seres Health, Shire, Sigmoid Biotechnologies, Teva Pharmaceuticals, Theradiag, Theravance, TiGenix, Tillotts Pharma, Toray Industries, UCB Pharma, University of Western Ontario (owner of Robarts Clinical Trials), Vascular Biogenics, Vertex Pharmaceuticals, Warner Chilcott and Zyngenia; grants and personal fees from AbbVie, Amgen, Atlantic Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Nutrition Science Partners, Pfizer, Prometheus Laboratories, Receptos and Takeda; and grants from Exact Sciences.

CONTRIBUTORS

All authors meet the International Committee of Medical Journal Editors authorship criteria and agree to be accountable for all aspects of the work. W.J.S. contributed towards study design and data analysis, and W.J.S., N.V.C., A.J. and B.M. contributed towards the writing of the manuscript. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Niels Vande Casteele https://orcid.org/0000-0003-0854-0274

REFERENCES

1. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American college of gastroenterology, practice parameters committee. *Am J Gastroenterol*. 2010;105(3):501-523.
2. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet*. 2012;380(9853):1606-1619.
3. Adams SM, Bornemann PH. Ulcerative colitis. *Am Fam Physician*. 2013;87(10):699-705.
4. Ricart E, Panaccione R, Loftus EV Jr, et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis*. 2004;10(3):207-214.
5. Veloso FT. Extraintestinal manifestations of inflammatory bowel disease: do they influence treatment and outcome? *World J Gastroenterol*. 2011;17(22):2702-2707.
6. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48(4):526-535.
7. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer: a population-based study. *N Engl J Med*. 1990;323(18):1228-1233.
8. Sandborn WJ, Hanauer SB. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther*. 2003;17(1):29-42.
9. Ye B, van Langenberg DR. Mesalazine preparations for the treatment of ulcerative colitis: are all created equal? *World J Gastrointest Pharmacol Ther*. 2015;6(4):137-144.
10. Desreumaux P, Ghosh S. Review article: mode of action and delivery of 5-aminosalicylic acid - new evidence. *Aliment Pharmacol Ther*. 2006;24(Suppl 1):2-9.
11. Hanauer SB. Aminosalicylates in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2004;20(Suppl 4):60-65.
12. US Food and Drug Administration. Asacol. Highlights of prescribing information. 2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/019651s025lbl.pdf (accessed 9 December 2016).
13. US Food and Drug Administration. Lialda. Highlights of prescribing information. 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022000s013lbl.pdf (accessed 9 December 2016).
14. Wang Y, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2016;4:CD000543.
15. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2016;5:CD000544.
16. Ham M, Moss AC. Mesalamine in the treatment and maintenance of remission of ulcerative colitis. *Expert Rev Clin Pharmacol*. 2012;5(2):113-123.
17. Nielsen OH. Sulfasalazine intolerance: a retrospective survey of the reasons for discontinuing treatment with sulfasalazine in patients with chronic inflammatory bowel disease. *Scand J Gastroenterol*. 1982;17(3):389-393.
18. Hawthorne AB, Stenson R, Gillespie D, et al. One-year investigator-blind randomized multicenter trial comparing asacol 2.4 g once daily with 800 mg three times daily for maintenance of remission in ulcerative colitis. *Inflamm Bowel Dis*. 2012;18(10):1885-1893.
19. Hussain FN, Ajjan RA, Kapur K, Moustafa M, Riley SA. Once versus divided daily dosing with delayed-release mesalazine: a study of tissue drug concentrations and standard pharmacokinetic parameters. *Aliment Pharmacol Ther*. 2001;15(1):53-62.
20. Li W, Zhang ZM, Jiang XL. Once daily *vs* multiple daily mesalamine therapy for mild to moderate ulcerative colitis: a meta-analysis. *Colorectal Dis*. 2016;18(7):O214-O223.
21. Shale MJ, Riley SA. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2003;18(2):191-198.
22. Yen L, Wu J, Hodgkins P, Cohen RD, Nichol MB. Medication use patterns and predictors of nonpersistence and nonadherence with oral 5-aminosalicylic acid therapy in patients with ulcerative colitis. *J Manag Care Pharm*. 2012;18(9):701-712.
23. Kane S. Does treatment schedule matter? Once daily versus divided doses of 5-ASAs. *Dig Dis*. 2010;28(3):478-482.
24. Alexander SPH, Kelly E, Marrion NV, et al. The concise guide to pharmacology 2017/18: overview. *Br J Pharmacol*. 2017;174(Suppl 1):S1-S16.
25. Crowder MJ, Hand DJ. *Analysis of repeated measures*. Boca Raton, FL: Chapman & Hall/CRC; 1990.
26. Health Canada. Notice: Policy on bioequivalence standards for highly variable drug products. 2016. Available at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-policy-bioequivalence-standards-highly-variable-drug-products.html (accessed 2 January 2020).
27. D'Incà R, Paccagnella M, Cardin R, et al. 5-ASA colonic mucosal concentrations resulting from different pharmaceutical formulations in ulcerative colitis. *World J Gastroenterol*. 2013;19(34):5665-5670.
28. Goyanes A, Hatton GB, Merchant HA, Basit AW. Gastrointestinal release behaviour of modified-release drug products: dynamic dissolution testing of mesalazine formulations. *Int J Pharm*. 2015;484(1-2):103-108.
29. Stobaugh DJ, Deepak P, Thorpe M, Hannon B, Ehrenpreis ED. Simulated comparison of topical and oral formulations of 5-aminosalicylate for the treatment of ulcerative colitis. *Inflamm Bowel Dis*. 2013;19(2):301-308.
30. US Food and Drug Administration. Lialda (mesalamine) delayed-release tablets clinical pharmacology biopharmaceutics review. 2006. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022000s000_ClinPharmR.pdf (accessed 9 December 2016).
31. Coupe AJ, Davis SS, Wilding IR. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. *Pharm Res*. 1991;8(3):360-364.
32. US Food and Drug Administration. Clinical pharmacology data to support a demonstration of biosimilarity to a reference product. 2016. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-data-support-

demonstration-biosimilarity-reference-product (accessed 31 October 2019).

33. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): Guideline on the investigation of bioequivalence. 2010. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf (accessed October 31, 2019).

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Vande Casteele N, Jakate A, McNamee B, Sandborn WJ. Similar pharmacokinetics of three dosing regimens comprising two oral delayed-release mesalamine formulations in healthy adult volunteers: Randomised, open-label, parallel-group study. *Br J Clin Pharmacol*. 2021;87:1141–1149. https://doi.org/10.1111/bcp.14479