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Original Article

Pharmacology Section

A Fully Replicate, Cross-over, Bioequivalence Study to Compare Two Prolonged Release, Multi-matrix Tablet Formulations of Budesonide in Healthy Indian Adults

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ABSTRACT

Introduction: Budesonide is a synthetic, non halogenated corticosteroid, structurally related to 16α-hydroxyprednisolone, which is approved as first-line therapy for various gastrointestinal disorders. Budesonide prolonged-release tablets incorporating multi-matrix technology {Cortiment® 9 mg: Reference product (R)} were approved in India for induction of remission in adult patients with mild-to-moderate active ulcerative colitis.

Aim: To assess the bioavailability, safety and tolerability of a single dose of generic budesonide prolonged-release tablets 9 mg {Cortirowa™ OD; Test product (T)} and demonstrate their bioequivalence to Reference product (R) in healthy Indian adults under fasting conditions.

Materials and Methods: In this randomised, open-label, single-dose, balanced, 2-treatment, 2-sequence, 4-period, fully replicate, cross-over bioequivalence study was conducted from 12th July 2021 to 8th August 2021 at Ecron Acunova Limited, Manipal, India. Total 56 participants were randomly allocated (1:1) to treatment sequences Test-Reference-Test-Reference (TRTR) or Reference-Test-Reference-Test (RTRT). After a 10-hour overnight fasting, participants were administered a single oral dose of T or R along with 240 mL of water. After each dose, a total of 26 venous blood samples (each 4 mL) were collected from each participant, at hourly intervals until 20 hours, and at 24, 30, 36, 48, and 72 hours. Plasma budesonide concentrations were analysed using a validated Liquid Chromatography-Tandem-Mass Spectrometry (LC-MS/MS) method. Based on the randomisation sequences, the treatment periods were defined as test product treatment Period-1 (T1), test product treatment Period-2 (T2), reference product treatment Period-1 (R1), and reference product treatment Period-2 (R2). The primary pharmacokinetic parameters were peak plasma concentration (C_{max}) and area under the concentration-time curve from time zero to the last sample with quantifiable concentration (AUC_{0-t}).

Results: Test and reference products were comparable in terms of mean (standard deviation) C_{max} {pg/mL: T1=2163.0 (1423.9) and T2=2456.25 (1346.035) vs R1=2301.59 (1582.995) and R2=2437.62 (1437.665)} and AUC_{0-t} {hr.pg/mL: T1=27938.0 (16431.23) and T2=33629.58 (18407.253) vs R1=25882.41 (17250.267) and R2=33146.25 (19350.222)}. As the within-subject Standard Deviation (SD) of R (SWR) for C_{max} and AUC_{0-t} was ≥0.294, the reference-Scaled Average Bioequivalence (SABE) approach was used. The bioequivalence criteria prespecified using the Scaled Average Bioequivalence (SABE) approach was met as the 95% upper confidence bound for $(\mu T-\mu R)^2 - \theta s^2_{WR}$ of C_{max} (-0.255371831) and AUC_{0-t} (-0.445865013) were both ≤0, and the point estimate (T/R) geometric mean ratio of C_{max} (0.97) and AUC_{0-t} (1.06) were both within 0.80 and 1.25. While 10 Adverse Events (AEs) were reported in the study, all were of mild intensity.

Conclusion: Cortirowa™ OD was bioequivalent to Cortiment® 9 mg in healthy Indian adults under fasting conditions. Both the products were found to be well-tolerated.

Keywords: Corticosteroids, Multi-matrix technology, Pharmacokinetics, Ulcerative colitis

INTRODUCTION

Ulcerative colitis is a chronic, idiopathic inflammatory disease, with a significant impact on physical and mental health with a reported annual incidence of 1.2-24.3 cases/100,000 persons [1-4].

Budesonide is a synthetic glucocorticoid with 15 times greater affinity for the glucocorticoid receptor than prednisolone [5]. It has higher topical activity than prednisolone and lower bioavailability due to substantial first-pass elimination (90%), but it is cost-effective compared with prednisolone [5-7]. Budesonide inhibits many inflammatory processes including cytokine production, inflammatory cell activation, and expression of adhesion molecules on endothelial and epithelial cells [6]. Budesonide is available in three oral formulations: a pH-dependent-release formulation designed to deliver the drug at pH ≥6.4, pH and time-dependent controlled-release formulation designed to dissolve at pH ≥5.5, and a prolonged release multi-matrix formulation [8].

The multi-matrix structure in budesonide prolonged-release tablets is covered by a gastro-resistant coating that only dissolves in intestinal fluids having a pH >7. Once the coating is dissolved, the hydrophilic matrix polymers on contact with the intestinal fluids start to swell until a viscous gel matrix is formed. The solvent that penetrates the gel matrix dissolves the active ingredient from the lipophilic matrices. Budesonide is then released into the intestinal tract at a controlled rate throughout the colon [6].

The multi-matrix structure confers several advantages in ensuring targeted drug delivery to the colon. It enables release of high concentrations of active drugs, especially into the distal colon, which is the most difficult to reach in significant amounts with oral drug administration [9]. Multi-matrix formulation is associated with very low systemic absorption and very low rates of AEs [9-12]. In addition, the once-daily dosing favours patient adherence [9,11-13].

Budesonide prolonged-release tablets {Cortiment®, Ferring Pharmaceuticals Pvt. Ltd., United Kingdom (reference product)}

are approved in the European Union for induction of remission in patients with mild-to-moderate active ulcerative colitis where 5-aminosalicylic acid treatment is not sufficient, and for induction of remission in patients with active microscopic colitis [7]. In India, the drug is indicated for induction of remission in adult patients with mild-to-moderate active ulcerative colitis [14].

The present study was conducted to assess the bioavailability, safety and tolerability of a single dose of generic budesonide prolonged release tablets 9 mg {Cortirowa™ OD; test product (T)} and demonstrates its bioequivalence with reference product (R), in healthy Indian adults under fasting conditions.

MATERIALS AND METHODS

This was a randomised, open-label, single-dose, balanced, 2-treatment, 2-sequence, 4-period, fully replicate, cross-over bioequivalence study (NCT05519514) conducted from 12th July 2021 to 8th August 2021 at Ecron Acunova Limited, Manipal, India.

The study protocol and relevant study-related documents were approved by the Manipal Academy of Higher Education (MAHE) Ethics Committee (Reg. No. ECR/191/Inst/KL/2013/RR-19). The study was conducted in accordance with the principles of Declaration of Helsinki, International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice, Indian Council of Medical Research guidelines [15], United States Food and Drug Administration (USFDA) guidelines and recommendations for bioavailability/bioequivalence studies [16], Central Drugs Standard Control Organisation guidelines for bioavailability and bioequivalence studies, and New Drugs and Clinical Trials Rules 2019 [17]. All participants provided written informed consent before entering the study.

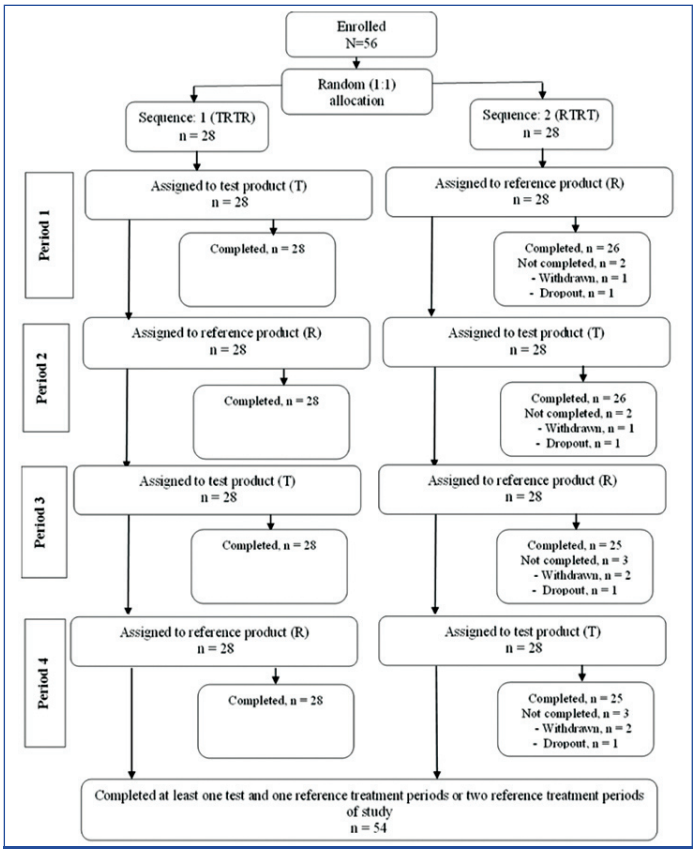
Inclusion criteria: The study included healthy adults aged 18-45 years, with body mass index of 18.5-30 kg/m^2, and with negative test results for alcohol and drugs of abuse in urine. Other criteria included negative results for urine pregnancy test during screening and negative beta human chorionic gonadotropin-test at the time of check-in for women volunteers; use of an acceptable method of contraception by women of child-bearing potential for atleast two days prior to first dosing, during the study and for three days following the last dose; use of condoms for additional protection against conception by male volunteers and husbands of female volunteers throughout the study, irrespective of previous vasectomy or spermicide treatment.

Exclusion criteria: Key exclusion criteria were significant illness; systolic blood pressure <90 mmHg or >140 mmHg or diastolic blood pressure <60 mmHg or >90 mmHg; positive test for COVID-19; hypersensitivity to budesonide or any component of the formulation and/or to any other related drug; significant alcohol dependence or drug abuse within the past one-year, current alcohol abuse (>5 units/week, 1 unit=10 mL or 8 g of pure alcohol) or suspected abuse; daily smoking habit or consumption of tobacco products; donation in excess of 350 mL of blood in the last 90 days; or use of prescription medications over the counter products, or topical medications within 14 days prior to first dosing.

Sample size calculation: Assuming an intrasubject Coefficient of Variation (CV) of approximately 45%, T/R ratio of 90%, and ≥90% power, 44 subjects were required to prove bioequivalence between the two formulations. Considering an additional maximum of three subjects per treatment sequence to account for withdrawals and dropouts, the sample size was determined to be 56.

Enrolled participants (N=56) were randomly allocated (1:1) to one of two treatment sequences (Group 1: TRTR or Group 2: RTRT) [Table/Fig-1]. The randomisation schedule was generated using SAS® version 9.4 (SAS® Institute Inc., United States). The investigator and participants were unblinded to treatment group, while the bioanalytical team remained blinded to treatment to avoid bias.

There were four treatment periods in each treatment sequence [Table/Fig-1]. A washout period of atleast three days were maintained between each treatment period to minimise the possibility of a carry-over effect. Participants were housed from atleast 11 hours before administration of the drug in Period-1 until 72 hours after administration of the drug in Period-4. After a 10-hour overnight fast, participants received a single, oral dose of T or R as per randomisation schedule with 240 mL of water at room temperature. Compliance was ensured by checking the oral cavity to confirm medication and fluid consumption. The bioanalytical operations team was blinded to the randomisation schedule and all pharmacokinetic samples in order to avoid bias during analysis.



[Table/Fig-1]: Study design and participant disposition.
R: Reference product (Cortiment®); T: Test product (Cortirowa™ OD)

One subject in sequence RTRT withdrew consent in the study prior to Period-1 dosing. One subject withdrew from the study due to AE (headache) prior to dosing in Period-1 and another subject withdrew from Periods-3 and 4 due to AE (cough) prior to dosing in Period-3. Thus, 54 subjects completed atleast one test and one reference treatment periods or atleast two reference treatment periods of the study.

Study Procedure

Participants were instructed not to consume tobacco-containing products, xanthine-containing food and beverages, and alcohol, grapefruit or its juice, or cranberry juice, for atleast 48 hours prior to dosing in Period-1 and throughout the study. They were also instructed to not take any recreational drugs for atleast 14 days preceding administration of test product in Period-1 of the study and for the entire duration of study. For participants who required any other treatment during the study, the investigator decided on their continuation in the study based on the timing of medication administration, and the pharmacology and pharmacokinetic interaction of the concomitant medication with treatment.

The T was supplied as white, round, biconvex, coated tablets, plain on both sides in an appropriate package to maintain its integrity. R (white, round, biconvex, coated tablets, plain on one side and debossed "MX 9" on other side) was supplied in the manufacturer's original containers. Both products were stored at a temperature of 15-25°C and relative humidity of 30%-60%.

Outcome Parameters

Drug concentration measurements: In each study period, a total of 26 venous blood samples (4 mL each) were collected from each participant in vacuum tubes containing dipotassium ethylenediaminetetraacetic acid at predose (0 hour), at hourly intervals until 20 hours postdose, and at 24, 30, 36, 48 and 72 hours postdose. The predose sample was collected within two hours before dosing in Period-1 and within 10 minutes before dosing in Periods-2, 3, and 4. All blood samples were centrifuged at 3000 rpm under refrigeration at 4°C for 10 minutes within 45 minutes of collection. After centrifugation, the separated plasma sample was divided into two aliquots such that the first aliquot contained ≥1.2 mL of plasma and stored upright in a deep freezer at -70°C±10°C.

Plasma budesonide concentrations were analysed using a validated LC-MS/MS method (Xevo TQ-S by Waters Corporation) [18]. To 0.5 mL of sample, 0.025 mL of internal standard working stock solution was added, and vortexed to mix. To this, 0.5 mL of buffering agent (100 mM sodium hydrogen carbonate) was added and vortexed, followed by 4.0 mL of extraction solution {methyl-t-butyl ether: dichloromethane (70%:30% v/v)}, and the sample was vortexed for five minutes and centrifuged at 3500 rpm at 4°C for five minutes. The supernatant was separated by flash freezing and evaporated to dryness under a nitrogen stream at 40ºC. The analyte residue was reconstituted with 0.3 mL of reconstitution solution {acetonitrile: water (70%:30% v/v)}, and 10.0 µL of the reconstituted solution was injected into the LC-MS/MS. The instrument was calibrated over a range of 10.201 to 4040 pg/mL for budesonide. Sample values below the lower limit of quantification (10.201 pg/mL) were set to zero for all pharmacokinetic and statistical evaluation.

Pharmacokinetic assessments: The primary pharmacokinetic parameters were peak plasma concentration (C_{max}) and area under the concentration-time curve from time zero to the last sample with quantifiable concentration (AUC_{0-t}), calculated using the linear trapezoidal method [19]. Secondary pharmacokinetic parameters included time to peak concentration C_{max} (t_{max}), terminal elimination half-life calculated as $0.693/K_{el}(\lambda_z)$ ($t_{½}$), apparent elimination rate constant ke/F (t_{lag}), elimination rate constant (K_{el}), total area under concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), and area under concentration-time curve from time 8 to 48 hours calculated using the linear trapezoidal method (AUC_{8-48}). The pharmacokinetic parameters were assessed using Phoenix WinNonlin 8.1.

Safety assessments: Participants were monitored for AEs and serious AEs, with their severity and relationship to study drug during the entire study. Vital signs and well-being were measured before check-in of Period-1, within 2 hours prior to dosing in each study period, and prior to check-out in Period-4 (Day 13). Vital signs were also measured at 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 60 (±1) hours postdose in each period. Laboratory parameters were assessed at screening and again at the end of the study. Clinically significant parameters were documented as an AE and measured until reported clinically non significant in the follow-up visits.

STATISTICAL ANALYSIS

Plasma budesonide concentrations and pharmacokinetic parameters were summarised descriptively.

The within-subject SD of R, termed as SWR, was evaluated using PROC MIXED in SAS® for log-transformed pharmacokinetic parameters. For the primary pharmacokinetic parameters (C_{max} and AUC_{0-t}), if SWR was <0.294, average bioequivalence approach was used, and log-transformed pharmacokinetic parameters were analysed using an Analysis of Variance (ANOVA) test with treatment, period, and sequence as main effects and subjects nested within sequence as random effect. If SWR was ≥0.294, reference-SABE approach was used, and log-transformed pharmacokinetic parameter values were analysed using one-way Analysis of Variance (ANOVA) model with the main effect of sequence as fixed effect. Inclusion of subjects for SWR analysis was based on completion of all four study periods, completion of three periods including two reference periods and one test period, or completion of two reference periods. Inclusion of subjects for SABE analysis was based on completion of all four study periods. Inclusion of subjects for average bioequivalence analysis was based on completion of all four study periods, completion of three periods including two reference periods and one test period, completion of three periods with two test periods and one reference period, or completion of two periods including one reference and one test period.

The sequence effect was tested at 0.10 level of significance using the 'subjects nested within sequence' mean square from the ANOVA as the error term. All other main effects were tested at 0.05 level of significance against the residual error (mean square error) from the ANOVA as the error term. The ANOVA included calculation of Least-Square Means (LSMs), the difference between the adjusted formulation means, and the standard error associated with the difference. The above analysis was done using SAS version 9.4 (SAS® Institute Inc., United States).

The T was considered as bioequivalent to R if log-transformed primary pharmacokinetic parameters C_{max} and AUC_{0-t} satisfied the following criteria: if SWR was <0.294, then 90% confidence interval (CI) for the geometric LSM ratio (T/R) must fall within 80% to 125% (both inclusive). If SWR was ≥0.294, then the 95% upper confidence bound for $(\mu T-\mu R)^2-\theta\ s^2_{WR}$ must be ≤0, where µT and µR were mean of T and R on log-transformed scale, respectively, and $\theta=\{\ln(1.25)/\sigma W0\}^2$ (SABE limit); where $\sigma W0=0.25$ (regulatory limit). The point estimate of reference/R geometric mean ratio must fall within 0.80 and 1.25.

RESULTS

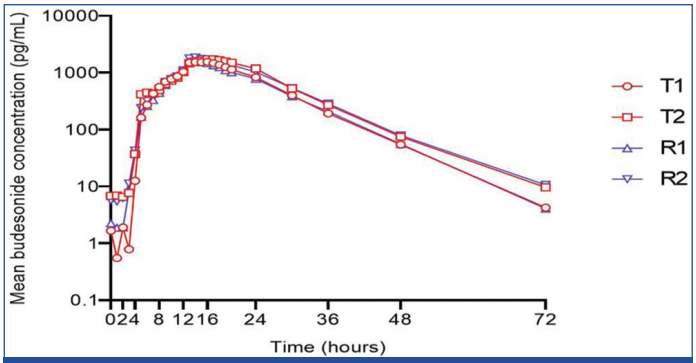
Subject demographics: Of 56 enrolled participants, 28 each were assigned to treatment sequences TRTR or RTRT. Of these, all 28 participants in sequence TRTR completed the study up to end of Period-4 [Table/Fig-1]. In sequence RTRT, one participant withdrew consent prior to dosing in Period-1, another was withdrawn from the study due to an AE (headache) prior to dosing in Period-1, and the third was withdrawn due to an AE (cough) after dosing in Period-2. Thus, 25 subjects completed the study upto end of Period-4 in sequence RTRT.

Participants were all men with a mean (SD) age of 34.3 (6.4) years and mean (SD) Body Mass Index (BMI) of 24.28 (2.67) kg/m^2.

Pharmacokinetics of Budesonide: Plasma samples of the 54 participants who completed atleast one test and one reference treatment periods or atleast two reference treatment periods of the study were analysed for plasma concentration of budesonide, and the same was considered for pharmacokinetic and statistical analysis.

The two formulations had similar mean plasma concentration time profiles [Table/Fig-2]. The mean pharmacokinetic parameters of T and R following first and second dose administration are summarised in [Table/Fig-3].

Because the SWR of C_{max} (0.659) and AUC_{0-t} (0.873) was ≥0.294, the SABE approach was considered for determining bioequivalence. The 95% upper confidence bound for $(\mu T-\mu R)^2-\theta\ s^2_{WR}$ of C_{max}



[Table/Fig-2]: Comparative mean semi (log) linear graph of budesonide.
R: Reference product; T: Test product

occurred prior to dosing in Period-1 and 09 occurred after dosing. All 10 AEs were of mild intensity. There were no deaths, serious AEs, or other significant AEs reported during the study. There were no abnormalities in vital signs and physical examination findings during the study.

DISCUSSION

The study demonstrated bioequivalence of T and R based on prespecified criteria in healthy Indian adults under fasting conditions. The test and reference products had similar mean plasma concentration time profiles and similar mean pharmacokinetic parameters following first and second dose administration. Previous in-vitro dissolution studies have demonstrated a similar dissolution profile for both products, with close to 100% of the active drug being released from both at 12 hours post dissolution in pH 7.2 phosphate buffer containing 0.5% macrogol (data not shown).

	C_{max} (pg/mL)	AUC_{0-t} (hr.pg/mL)	$t_{1/2}$ (hr)[a]	K_{el} (L/hr)	t_{max} (hr)[a]	AUC_{0-inf} (hr*pg/mL)	AUC_{8-48} (hr*pg/mL)	t_{lag} (hr)[a]
Test product administered first time (T1)								
n	54	52	50	50	54	50	54	52
Mean (SD)	2163.0 (1423.90)	27938.0 (16431.23)	5.91 (3.615-8.190)	0.12 (0.023)	14.50 (0.000-36.000)	28684.17 (16304.164)	25333.60 (15722.210)	4.00 (0-12.000)
CV%	65.8	58.8	17.57	18.94	39.14	56.84	62.06	60.33
Reference product administered first time (R1)								
n	54	54	53	53	54	53	54	54
Mean (SD)	2301.59 (1582.995)	25882.41 (17250.267)	5.84 (2.741-92.440)	0.12 (0.036)	13.00 (5.000-36.000)	25426.50 (16468.119)	24423.47 (16167.432)	3.00 (0-5.000)
CV%	68.78	66.65	153.59	30.60	38.23	64.77	66.20	45.90
Test product administered second time (T2)								
n	53	52	51	51	53	51	53	52
Mean (SD)	2456.25 (1346.035)	33629.58 (18407.253)	6.66 (4.439-13.953)	0.11 (0.023)	15.00 (0.000-36.000)	33773.65 (18589.988)	30585.83 (17480.802)	3.00 (0-8.000)
CV%	54.80	54.74	26.27	21.93	37.46	55.04	57.15	86.88
Reference product administered second time (R2)								
n	53	52	51	51	53	51	53	52
Mean (SD)	2437.62 (1437.665)	33146.25 (19350.222)	6.35 (1.692-11.610)	0.12 (0.049)	14.00 (0.000-36.000)	32660.43 (18818.314)	30332.74 (18280.158)	2.00 (0-5.000)
CV%	58.98	58.38	28.64	42.47	36.88	57.62	60.27	84.90

[Table/Fig-3]: Pharmacokinetic parameters of test and reference product.
a median (min-max) values are presented instead of mean (SD)
CV: Coefficient of variation; NE: Not estimable; SD: Standard deviation

(-0.255371831) and AUC_{0-t} (-0.445865013) were both ≤0. Also, the point estimate T/R geometric mean ratios of C_{max} (0.97) and AUC_{0-t} (1.06) were both within 0.80 and 1.25 [Table/Fig-4]. Hence, T was considered bioequivalent to R.

Parameter	Intrasubject SD	95% upper confidence bound[a]	Geometric mean ratio[b]
C_{max}	0.659	-0.255371831	0.97
AUC_{0-t}	0.873	-0.445865013	1.06

[Table/Fig-4]: Bioequivalence summary.
[a]Data was available for 50 participants; bData was available for 47 participants
For the calculation of geometric mean, subjects who did not complete all the periods of the study were excluded. However, for 95% upper confidence bound calculation, only those subjects who did not complete atleast two reference product periods of the study were excluded.
SD: Standard deviation

For C_{max}, the intrasubject CV was 66.57. For AUC_{0-t}, the intrasubject CV was 88.12, and power was 60.4%. The ANOVA of log-transformed C_{max}, AUC_{0-t} levels demonstrated that sequence and treatment had no significant effect, while period had a significant effect (p=0.0339 for C_{max} and 0.0347 for AUC_{0-t}). However, this did not influence the bioequivalence outcome considering the statistical model applied for the determination of bioequivalence, with the point estimates of the ratios being direct results and CIs constructed around these point estimates using the estimated mean square error of the model.

Safety outcomes: Ten AEs were reported in eight participants over the course of the study [Table/Fig-5]. Of these, one AE

Adverse effects	Upto end of study period-4		After study completion	
	Test product (T) N=56	Reference product (R) N=56	Test product (T) N=54*	Reference product (R) N=56*
Any AE, n (E)	2 (3)	1 (1)	5 (5)	1 (1)
Cough	1	-	-	-
Fever	1	-	-	-
Sore throat	1	-	-	-
Nausea	-	1	-	-
Elevated ALT	-	-	4 (4)	-
Elevated random blood glucose	-	-	1 (1)	-
Headache	-	-	-	1 (1)
AE related to treatment, n (E)	0 (0)	0 (0)	0 (0)	0 (0)
AE by intensity				
Mild	2 (3)	1 (1)	5 (5)	1 (1)

[Table/Fig-5]: Incidence of Adverse Events (AE) during and after study.
AE: adverse event; n: number of subjects experiencing AE; E: event
*Number of subjects who reported for poststudy analysis

A >50% intrasubject variability in pharmacokinetic parameters of T and R was observed in this study, which is consistent

with the values reported for R in previous studies (intrasubject CV ranging from 39% to 71%) [20-22]. The study was conducted under fasting conditions as it is considered to be the most sensitive to detect potential differences between T and R [23]. The demonstration of bioequivalence and definition of standardised bioequivalence criteria for locally acting gastrointestinal drugs are in general more difficult and challenging than for systemically absorbed products. As a result, novel bioequivalence criteria are recommended by regulatory agencies for these drugs [24].

Budesonide, a drug acting locally in the colon, is considered a highly variable drug because the intrasubject variability for C_{max} is approximately 36%, which is larger than the defined criteria for variability of 30% for a pharmacokinetic parameter [25]. For highly variable drugs such as budesonide, proving bioequivalence through conventional trials would require a large sample size [25,26]. Hence, for these drugs, the US FDA and European Medicine Agency guidance recommends a replicate cross-over study design (either partial or fully replicate), which has the advantage of using fewer subjects compared to a non replicate design, although each subject in the study would receive more treatments [23,26,27]. Hence, the present study was designed as a fully replicate, 4-way cross-over study.

The additional advantages of the fully replicate design is that it allows comparisons of within-subject variances for T and R, indicates, whether T exhibits higher or lower within-subject variability in the bioavailability measures when compared to R, and provides more information about the intrinsic factor underlying formulation performance [28].

For highly variable drugs, the USFDA also recommends a SABE approach, where the variability of R can be used to set appropriate limits on the generic-reference difference. This involves use of the expanded 90% confidence intervals of geometric mean ratio for bioequivalence assessment [27]. According to these recommendations, a highly variable generic drug product must meet the scaled bioequivalence limit and a point estimate constraint [29]. The SABE approach is specifically recommended in the USFDA guidance on generic budesonide [27]. Accordingly, in the present study, the SABE approach was chosen for demonstrating bioequivalence of T and R.

Both T and R were well-tolerated during the study. The AEs reported were few, mild in nature, and unrelated to study drug. This finding is consistent with safety results reported for R in previous studies [6].

Limitation(s)

A limitation of the study is that only male volunteers were enrolled, although the study was planned for enrolment of both sexes, due to lack of availability of female volunteers who complied with protocol requirements.

CONCLUSION(S)

The generic budesonide formulation, Cortirowa™ OD developed using multi-matrix technology had similar pharmacokinetic profile and was bioequivalent to the reference product in healthy Indian adults under fasting conditions with good safety and tolerability profiles. Thus, similar to Cortiment® 9 mg tablets, the generic prolonged-release budesonide tablets, could effectively deliver budesonide throughout the colon, with good efficacy, safety and tolerability, while offering pharmacoeconomic benefits in Indian patients in ulcerative colitis.

Conflict of Interest: All authors are employees of Abbott. Rajan Verma and Sachin Joshi are shareholders of Abbott.

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