

Bioequivalence of a Hydroxyurea Oral Suspension (100 mg/mL) and Xromi® 100 mg/mL Oral Solution (100 mg Hydroxycarbamide) under Fasting Conditions: A Randomised, Open-label, Single-dose, Two-period Crossover Study

SUNIL JAISWAL¹, ARUN CHAUDHARY², MAMTA SHARMA³, MANSINGH RAJPUT⁴,
BADRINATH SANGLE⁵, KAMLESH LONDHE⁶



ABSTRACT

Introduction: Hydroxyurea oral suspension is approved as an adjunctive treatment for Sickle Cell Disease (SCD) and Myeloproliferative Disorders (MPD). Oral liquid formulations ensure accurate dose administration, improve ease of use in patients with difficulty swallowing solid dosage forms, and may be administered with or without food. As patient-friendly formulations are increasingly needed, there is growing demand for a bioequivalent alternative to the marketed reference hydroxyurea oral solution.

Aim: To evaluate the bioequivalence of hydroxyurea oral suspension (100 mg/mL) compared with the reference product, Xromi® (hydroxycarbamide oral solution 100 mg/mL), under fasting conditions.

Materials and Methods: This open-label, two-treatment, two-period, two-sequence, single-dose crossover bioequivalence study was conducted under fasting conditions over six days at Vivotech Research Lab Pvt., Ltd., Navi Mumbai, Maharashtra, India. Healthy subjects were randomised to receive a single oral dose of 500 mg hydroxyurea as either the Test (Hydroxyurea Oral Suspension 100 mg/mL) or the Reference (Xromi®, Hydroxycarbamide Oral Solution 100 mg/mL), with a 3-day washout period. Plasma hydroxyurea concentrations were measured up to 24 hours using a validated

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Pharmacokinetic parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) were summarised using descriptive statistics and analysed by Analysis of Variance (ANOVA) on log-transformed data. Bioequivalence was assessed using geometric mean ratios (Test/Reference) and corresponding 90% confidence intervals (90% CIs).

Results: Twenty-eight subjects completed both study periods and were included in the pharmacokinetic analysis. The geometric mean ratios (test/reference) and corresponding 90% CIs were 100.57% (93.49-108.18) for C_{max} , 97.87% (93.82-102.09) for AUC_{0-t} , and 97.85% (93.84-102.02) for $AUC_{0-\infty}$. The 90% CIs for all three primary bioequivalence parameters were within the predefined bioequivalence acceptance range of 80.00-125.00%, demonstrating comparable rates and extents of absorption between the test and reference formulations. Both formulations were well tolerated, and all Adverse Events (AE) were mild and transient.

Conclusion: Hydroxyurea oral suspension (100 mg/mL) was bioequivalent to the reference product, Xromi® (Hydroxycarbamide Oral Solution 100 mg/mL), under fasting conditions. Both formulations were safe and well tolerated, supporting the oral suspension as an effective alternative for patients requiring a liquid oral dosage form.

Keywords: Bioavailability, Crossover studies, Drug absorption, Pharmacokinetics, Therapeutic equivalence

INTRODUCTION

Hydroxyurea is a small, non-chiral, highly water-soluble antimetabolite that has been used for several decades in the management of haematological disorders. It is primarily indicated for the prevention of vaso-occlusive complications in patients with SCD and for cytoreductive therapy in MPD including polycythaemia vera and essential thrombocythemia [1,2]. Xromi® contains hydroxycarbamide, also known as hydroxyurea. In patients with SCD hydroxyurea significantly reduces the frequency of painful crises, acute chest syndrome, and the need for blood transfusions thereby improving overall morbidity and survival [3,4].

Although hydroxyurea has traditionally been marketed as capsules or tablets, solid oral dosage forms may be unsuitable for paediatric patients and adults with swallowing difficulties. Consequently, oral liquid formulations, including solutions and suspensions, have been

developed to enable accurate weight-based dose individualisation, facilitate dose titration to the maximum tolerated dose, and improve treatment adherence, particularly in children with SCD [5]. However, hydroxyurea is known to be chemically labile in aqueous environments with degradation influenced by formulation pH and storage conditions. Therefore, formulation development requires careful selection of excipients, pH optimisation, and appropriate packaging such as amber glass containers with refrigerated storage to ensure chemical stability throughout the product shelf life and during clinical evaluation [6,7].

The clinical efficacy of hydroxyurea in SCD is mainly attributed to its ability to increase foetal haemoglobin (HbF) levels which inhibits haemoglobin S polymerisation and reduces erythrocyte sickling. Additional benefits include improved RBC deformability, reduction in leucocyte and platelet counts, and decreased cellular adhesion to

vascular endothelium collectively resulting in improved microvascular blood flow [8,9].

Following oral administration, hydroxyurea is rapidly and extensively absorbed following oral administration with peak plasma concentrations typically achieved within 0.5-2.0 hours. Oral bioavailability is high and the apparent volume of distribution approximates total body water (0.5-0.9 L/kg in adults) indicating wide tissue distribution [10]. Elimination occurs through hepatic metabolism and renal excretion, with approximately 40-50% of the administered dose excreted unchanged in urine [10]. The terminal elimination half-life ranges from 1.5 to 3 hours in adults with considerable inter-individual variability in pharmacokinetic parameters such as maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) [11].

Bioequivalence studies are conducted to establish the therapeutic interchangeability of formulations containing the same active ingredient by demonstrating comparable rates and extents of absorption under identical study conditions [12,13]. Generic formulations provide cost-effective treatment options while maintaining therapeutic equivalence, and oral suspension formulations may further improve adherence in patients requiring liquid dosage forms. Therefore, the primary objective of the present study was to demonstrate the bioequivalence of hydroxyurea oral suspension 100 mg/mL (Test) and Xromi® (hydroxycarbamide oral solution 100 mg/mL, Reference) under fasting conditions in healthy adult subjects. The secondary objective was to evaluate the safety and tolerability of both formulations by monitoring Adverse Events (AEs) throughout the study.

MATERIALS AND METHODS

This was an open-label, randomised, balanced, two-treatment, two-sequence, two-period, single-dose, two-way crossover oral bioequivalence study conducted at Vivotech Research Lab Pvt., Ltd., Navi Mumbai, Maharashtra, India between 1st February 2024 to 6th February 2024 following prior written approval from the Ethics Committee (IEC approval no. EIEC/DEC/2023/030). The study was conducted in accordance with the Declaration of Helsinki [14], the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research Involving Human Participants [15], the International Council for Harmonisation Good Clinical Practice (ICH-GCP E6(R2)) [16] the New Drugs and Clinical Trials Rules [17,18], and the Central Drugs Standard Control Organisation (CDSCO) Guideline on the Investigation of Bioequivalence [19]. The study was not registered with CTRI; therefore, a CTRI registration number is not applicable. Written informed consent was obtained from all participants before initiation of any study-related procedures.

Inclusion criteria: Healthy adults aged 18-50 years with a Body Mass Index (BMI) of 18.5-30.0 kg/m² were screened within 21 days before dosing through demographic assessment, medical history, physical examination, vital signs, laboratory investigations, 12-lead Electrocardiography (ECG), and chest radiography where clinically indicated. Although both male and non-pregnant female subjects were eligible according to the protocol, only healthy male subjects were enrolled.

Exclusion criteria: Subjects with clinically significant medical conditions, hypersensitivity to hydroxyurea, substance abuse, infectious diseases, or any condition that could affect drug absorption, safety, or study outcomes were excluded from the study.

Study products: The Test (T) formulation was hydroxyurea oral suspension 100 mg/mL (Pure and Cure Healthcare Pvt., Ltd., India; Batch No. 0003791671; Expiry: March 2025). The Reference (R) formulation was hydroxycarbamide oral solution 100 mg/mL (XROMI®, Nova Laboratories Ltd.; Batch No. 1308PM147;

Expiry: July 2025), a globally approved oral liquid formulation authorised in the European Union in July 2019. The reference formulation contained hydroxycarbamide 100 mg/mL with excipients including xanthan gum, sucralose, strawberry flavour, methyl parahydroxybenzoate, sodium hydroxide, and purified water. The test product was formulated as an oral suspension and the reference as an oral solution. A single 500 mg/5 mL dose was administered under fasting conditions (≥ 10 h) with 240 $\pm$ 2 mL water followed by syringe rinsing to ensure complete dose delivery.

Study Procedure

The study was conducted under fasting conditions in healthy adult male subjects. The study compared hydroxyurea oral suspension 100 mg/mL (T) with hydroxycarbamide oral solution 100 mg/mL (R). Following an overnight fast of at least 10 hours, subjects received a single 500 mg/5 mL oral dose with 240 mL of water under supervision. Blood samples were collected pre-dose and up to 24 hours post-dose for pharmacokinetic assessment.

Subjects remained confined to the clinical facility during each period and followed standardised meal and water restrictions, including remaining seated for two hours post-dose. A 3-day washout period (>10 elimination half-lives of hydroxyurea) was maintained to minimise carryover effects. Subjects checked in on 01-Feb-2024 and 04-Feb-2024 for period I and II, respectively, with dosing performed on 02-Feb-2024 and 05-Feb-2024 according to the randomisation schedule. Subjects were randomly assigned to one of the two dosing sequences in balanced blocks according to a randomisation schedule generated using SAS® software, version 9.4 or higher, ensuring equal allocation between sequences. Balanced block randomisation was performed using the PROC PLAN procedure with specified randomisation.

During each period, 21 venous blood samples (5 mL each) were collected into K₂EDTA tubes, comprising one pre-dose sample and 20 post-dose samples collected at 0.17, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 15.00, 18.00, and 24.00 hours after dosing. Blood samples were collected through an indwelling forearm cannula whenever feasible, with venepuncture performed when required. Plasma was separated by centrifugation at 3800 rpm for 10 minutes at 10 $\pm$ 2°C and stored at -70°C (-60°C to -80°C) until analysis.

Disposition of subjects: The sample size was calculated for a two-treatment, two-period, two-sequence crossover bioequivalence study using the normal-approximation method described by Julious SA assuming a test-to-reference ratio of 90%, an intra-subject coefficient of variation of 22.12%, 80% statistical power, and a two-sided significance level of 5% [20]. The calculation was based on the log-transformed pharmacokinetic parameter and the anticipated intra-subject variability. A minimum of 24 evaluable subjects was specified in the study documentation; therefore, 30 subjects were enrolled to compensate for possible withdrawals.

All 30 enrolled subjects received the study medication during period I. Twenty-eight subjects completed both study periods and were included in the pharmacokinetic analysis. One subject withdrew consent during Period I, and one subject was discontinued before Period II because of a positive breath alcohol test. No replacement subjects were enrolled. Safety analyses included all dosed subjects.

Bioanalytical method: Plasma hydroxyurea concentrations were quantified using a validated LC-MS/MS method developed and validated in accordance with applicable regulatory guidelines. The analytical method was validated over a calibration range of 0.503-24.964 μ g/mL. Accuracy, precision, recovery, and matrix effect evaluations met predefined acceptance criteria, confirming reliable quantification of hydroxyurea throughout the study.

Pharmacokinetic and bioequivalence analysis: Pharmacokinetic analysis was performed using non-compartmental methods in Phoenix® WinNonlin® version 8.4. The primary bioequivalence endpoints were C_{max}, AUC_{0-t}, and AUC_{0-∞}, while supportive pharmacokinetic parameters included T_{max}, K_{el}, and t_{1/2}. C_{max} and T_{max} were obtained directly from observed data, and AUC values were calculated using the linear trapezoidal method, with extrapolation for AUC_{0-∞} based on the terminal elimination phase. T_{max} was summarised using median (range), while other parameters were presented as arithmetic and log-transformed geometric means. Bioequivalence was assessed using geometric mean ratios (T/R%) and corresponding 90% confidence intervals for C_{max}, AUC_{0-t}, and AUC_{0-∞}, with acceptance limits of 80.00-125.00%.

Safety evolution: It included monitoring of AEs along with clinical laboratory tests, vital signs, physical examination, and 12-lead ECG. The PI routinely questioned participants every hour regarding the occurrence of any AEs and instructed them to immediately report any untoward symptoms experienced during the study. When AE were reported, each was evaluated by the investigator for seriousness, severity (mild, moderate, or severe), and its causal relationship to the study drug.

STATISTICAL ANALYSIS

Statistical analysis was conducted using SAS® software version 9.4. Geometric means and coefficients of variation were calculated for C_{max}, AUC_{0-t}, and AUC_{0-∞}, while arithmetic means and standard deviations were determined for AUC% extrapolated, T_{max}, t_{1/2}, and K_{el}. ANOVA was performed using the PROC GLM procedure on natural log-transformed C_{max}, AUC_{0-t}, and AUC_{0-∞}. The model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The sequence effect was tested using subject nested within sequence as the error term. The 90% confidence intervals for the Test/Reference geometric mean ratios were obtained from the least-squares mean differences on the log scale and then back-transformed to obtain the corresponding geometric mean ratios and 90% confidence intervals. Intra-subject variability was estimated from the residual variance of the log-transformed pharmacokinetic parameters. Bioequivalence was concluded when the 90% confidence intervals for the test/reference geometric mean ratios for C_{max}, AUC_{0-t}, and AUC_{0-∞} were entirely contained within the predefined acceptance limits of 80.00–125.00%.

RESULTS

Study population: A total of 30 subjects (Subject Nos. 01-30) were enrolled and dosed in accordance with the Ethiwel Ethics Committee-approved protocol, of whom 28 completed both study periods. Subject No. 27 withdrew consent during Period I, and Subject No. 12 was discontinued prior to Period II due to a positive breath alcohol test; no subject replacement was performed. The safety population included all 30 subjects who received at least one dose of study medication. Plasma samples from all dosed subjects were analysed for hydroxyurea quantification; however, pharmacokinetic and statistical analyses were performed on the 28 subjects who completed both periods. Baseline demographic characteristics were comparable between the treatment sequence groups, indicating balanced randomisation.

Demographic and other baseline characteristics: A total of 30 healthy adult male subjects were enrolled and dosed, forming the safety population (N = 30). The mean (±SD) age, height, weight, and BMI were 35.53±4.47 years, 167.62±5.36 cm, 70.96±9.60 kg, and 25.16±3.04 kg/m², respectively. All participants were of Asian origin, non-smokers, and non-alcoholic and followed a non-vegetarian diet [Table/Fig-1].

The statistical (PK) population included 28 subjects, who completed both treatment periods without major protocol deviations. In this

Variables		Profile	N (%)
Race		Asian	30 (100.00)
		Others	0
Gender		Male	30 (100.00)
		Female	0
Diet		Non-vegetarian	30 (100.00)
		Vegetarian	0
Smoking habits		Non-smokers	30 (100.00)
		Smokers	0
Alcohol consumption		Non-alcoholics	30 (100.00)
		Alcoholics	0
Parameters	Mean±SD	Min	Max
Age years	35.53±4.47	21	43
Height (cm)	167.62±5.36	159.4	181.8
Weight (Kg)	70.96±9.60	52.28	89.04
BMI (Kg/m²)	25.16±3.04	18.62	29.92

[Table/Fig-1]: Overall demographic profile and safety population (N=30) .

set the mean (±SD) age, height, weight, and BMI were 35.35±4.45 years, 167.92±5.42 cm, 70.34±9.56 kg, and 24.95±3.04 kg/m², respectively. All subjects were Asian males, non-smokers, and non-alcoholic and followed a non-vegetarian diet [Table/Fig-2].

Variables		Profile	n (%)
Race		Asian	28 (100.00)
		Others	0
Gender		Male	28 (100.00)
		Female	0
Diet		Non-vegetarian	28 (100.00)
		Vegetarian	0
Smoking habits		Non-smokers	28 (100.00)
		Smokers	0
Alcohol consumption		Non alcoholics	28 (100.00)
		Alcoholics	0
Parameters	Mean±SD	Min	Max
Age (years)	35.35±4.45	21	43
Height (cm)	167.92±5.42	159.4	181.8
Weight (kg)	70.34±9.56	52.28	89.04
BMI (kg/m²)	24.95±3.04	18.62	29.92

[Table/Fig-2]: Overall demographic for statistical population (N=28).

Bioequivalence Analysis

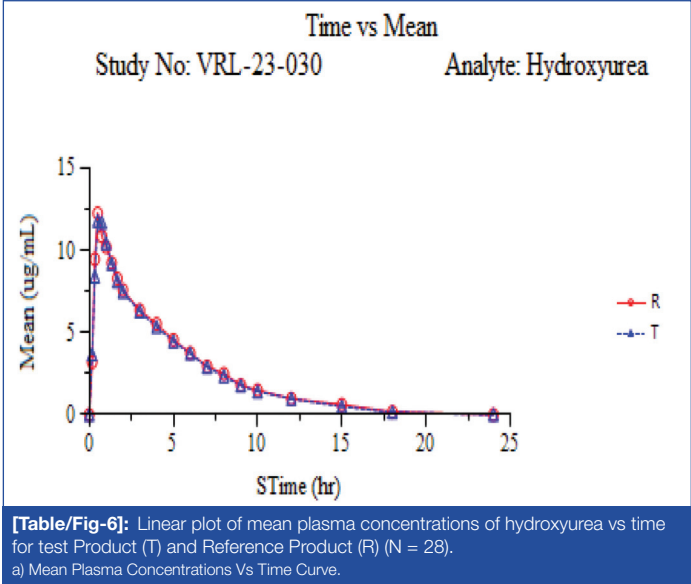
The mean±SD C_{max} values were 13.404±3.511 µg/ml for the test product (T) and 13.423±4.277 µg/mL for the Reference product (R). Mean±SD AUC_{0-t} values were 53.391±12.789 µg·h/mL and 54.543±13.467 µg·h/mL, while AUC_{0-∞} values were 57.075±13.194 µg·h/mL and 58.343±13.931 µg·h/mL for T and R, respectively. Median T_{max} (Min–Max) was 0.75 h (0.33–1.67) for T and 0.50 h (0.33–1.67) for Reference (R) product. Mean±SD extrapolated AUC percentages were 6.626±2.173% and 6.655±1.866% for T and R product, respectively [Table/Fig-3].

For ln-transformed pharmacokinetic parameters, the geometric mean T/R ratios were 100.57% for C_{max}, 97.87% for AUC_{0-t}, and 97.85% for AUC_{0-∞}. The corresponding 90% confidence intervals were 93.49–108.18%, 93.82–102.09%, and 93.84–102.02%, respectively, all within the predefined bioequivalence acceptance range of 80.00–125.00%. ISCV ranged from 9.2% to 16.1% [Table/Fig-4].

Safety evaluation: All 30 dosed subjects were included in the safety analysis. Exposure comprised 15 subjects receiving the Test (T) product and 15 receiving the Reference (R) product in Period I,

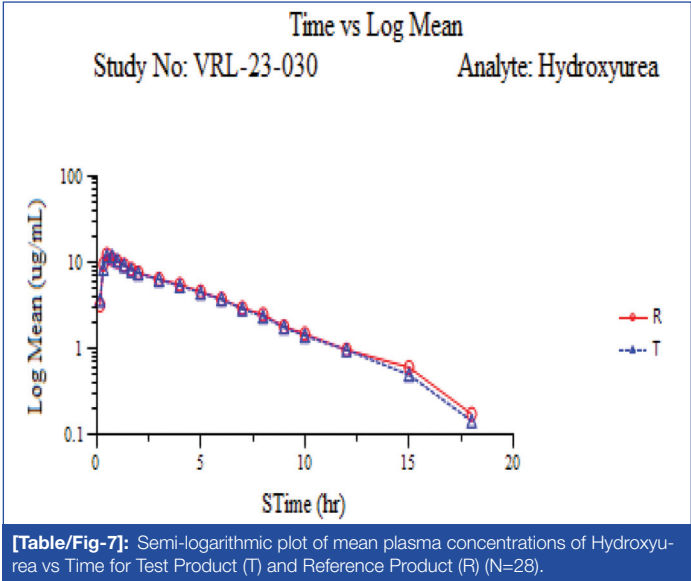
Pharmacokinetic parameters (Units)	Mean±SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
Cmax (µg/mL)	13.404±3.511	13.423±4.277
AUC0-t (µg.hr/mL)	53.391±12.789	54.543±13.467
AUC0-inf (µg.hr/mL)	57.075±13.194	58.343±13.931
Tmax (hr)	0.753±0.341	0.648±0.310
Kel (hr ⁻¹)	0.198±0.043	0.196±0.038
t1/2 (hr)	3.695±0.971	3.664±0.756
Extrapolated AUC (%)	6.626±2.173	6.655±1.866
	Median (Min-Max)	
Tmax (hr.)	0.750 (0.330-1.670)	0.500 (0.330-1.670)

[Table/Fig-3]: Descriptive statistics of pharmacokinetic parameters of Test product (T), and Reference product (R) for hydroxyurea (N=28).



Pharmacokinetics Parameter	Ln-transformed Geometric Least Squares Mean			p-value	90% CI	ISCV
	Test Product (T)	Reference Product (R)	T/R (%)			
Cmax (µg/mL)	13.0069	12.9331	100.57	0.6239	93.49-108.18	16.1%
AUC0-t (µg.hr/mL)	51.9972	53.1298	97.87	0.0173	93.82-102.09	9.3%
AUC0-∞ (µg*hr/mL)	55.7020	56.9288	97.85	0.0237	93.84-102.02	9.2%

[Table/Fig-4]: Geometric least squares mean, ratios, 90% confidence intervals, power and ISCV for pharmacokinetic parameters (Cmax, AUC0-t and AUC0-∞) of hydroxyurea (N=28).
*a statistically significant period effect (p-value <0.05)



followed by 14 subjects receiving each formulation in Period II after a 3-day washout period. AEs were monitored throughout the study and recorded irrespective of severity or suspected relationship to study treatment.

A total of three AEs were reported during the study. Two AEs occurred following administration of the Test (T) formulation: diarrhoea and constipation with abdominal pain, each reported in one subject (3.33%) during Period II. One additional event of sinus tachycardia was reported after completion of dosing and was monitored until resolution. All AEs were mild in intensity, transient in nature, resolved without intervention, and no events led to treatment discontinuation. No serious AEs, defined according to applicable clinical safety reporting criteria, were observed. Clinical laboratory assessments, vital signs, and physical examinations did not reveal clinically significant abnormalities during the study period. Given the single-dose administration and short study duration, no clinically meaningful haematological safety findings were identified [Table/Fig-5].

XROMI®(hydroxycarbamide oral solution 100 mg/mL, Reference) under fasting conditions in healthy adult male subjects. The geometric mean ratios for Cmax, AUC0–t, and AUC0–∞ were close to unity, and the corresponding 90% confidence intervals were entirely within the predefined bioequivalence acceptance limits of 80.00-125.00%. Both formulations were also well tolerated, with no unexpected safety findings observed during the study. The pharmacokinetic findings demonstrated rapid absorption of hydroxyurea following administration of both formulations, with median Tmax values of 0.50-0.75 hours, consistent with the known high oral bioavailability and rapid systemic uptake of hydroxyurea [21]. Comparable Cmax and AUC values, together with low intra-subject variability (9.2-16.1%), indicate similar rates and extents of absorption between the Test and Reference formulations. The observed variability was also comparable to that reported for other oral liquid hydroxyurea formulations, supporting the reproducibility of hydroxyurea pharmacokinetics in bioequivalence studies [12].

S. No.	Adverse Event (AE)	Treatment	Period	Severity	Causality	Status
1	Diarrhoea	Test	II	Mild	Probable	Resolved
2	Constipation with abdominal pain	Test	II	Mild	Probable	Resolved
3	Sinus tachycardia	NA	Post study	Mild	Probable	Resolved

[Table/Fig-5]: Adverse Events (AE) were reported during the entire course of study (N=30).

The present study findings are consistent with previously published investigations of oral hydroxyurea formulations. A paediatric pharmacokinetic and bioequivalence study of a ready-to-use liquid hydroxyurea formulation reported geometric mean ratios for Cmax and AUC within the accepted bioequivalence range and concluded therapeutic interchangeability with the reference formulation. Similarly, a population pharmacokinetic analysis demonstrated that liquid hydroxyurea formulations provide predictable systemic exposure with acceptable inter-individual variability when

Pharmacokinetics Evaluation

Mean plasma hydroxyurea concentration-time profiles following administration of the Test (T) and Reference (R) formulations are presented on linear and semi-logarithmic scales [Table/Fig-6,7].

DISCUSSION

This study successfully demonstrated the bioequivalence of hydroxyurea oral suspension 100 mg/mL (Test) and

administered on a body weight basis. The agreement between these published findings and the present study further supports the pharmacokinetic comparability of the Test formulation. From a regulatory perspective, bioequivalence is established when the 90% confidence intervals for the geometric mean ratios of the primary pharmacokinetic parameters fall within the predefined acceptance range of 80.00-125.00 [13]. The current investigation, the 90% confidence intervals for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ satisfied these criteria, confirming bioequivalence between the Test and Reference formulations. Although a statistically significant period effect was observed for the AUC parameters, no treatment or sequence effects were identified, and the predefined bioequivalence criteria were fulfilled. Period effects have been reported previously in crossover studies involving rapidly absorbed drugs with short elimination half-lives and are generally considered unrelated to formulation performance [13]. Both formulations exhibited a favourable safety profile following single-dose administration. All reported AEs were mild, transient, and resolved without intervention. No serious AEs, clinically significant laboratory abnormalities, or meaningful changes in vital signs, physical examination findings, or electrocardiograms were observed. These findings are consistent with the established short-term safety profile of hydroxyurea reported in previous clinical studies [22].

A major strength of the present study was the use of a randomised, crossover design, which minimised inter-subject variability and enabled direct comparison of the two formulations under controlled conditions. The validated LC-MS/MS bioanalytical method, intensive pharmacokinetic sampling schedule, and high study completion rate further enhanced the reliability of the pharmacokinetic and bioequivalence assessments. Overall, the present study demonstrated that hydroxyurea oral suspension 100 mg/mL is bioequivalent to Xromi® (hydroxycarbamide oral solution 100 mg/mL) and exhibits a comparable safety profile following single-dose administration. Overall, these findings support the interchangeability of hydroxyurea oral suspension 100 mg/mL with the reference product XROMI® and provide evidence for its use as an effective liquid formulation for accurate dose individualisation, particularly in paediatric patients and individuals with swallowing difficulties.

Limitation(s)

The study was conducted in healthy adult male subjects under fasting conditions following a single-dose administration; therefore, the findings may not be directly extrapolated to female subjects, fed-state conditions, or chronic clinical use.

CONCLUSION(S)

The Test product (T) hydroxyurea oral suspension 100 mg/mL manufactured by Pure and Cure Healthcare Pvt., Ltd., India, and Reference product (R) XROMI® (hydroxycarbamide oral solution 100 mg/mL) manufactured by Nova Laboratories Ltd., are bioequivalent with respect to rate and extent of absorption. Both formulations were safe and well tolerated, supporting the hydroxyurea oral suspension as an appropriate oral dosage form for clinical use in patients who require a liquid formulation.

Acknowledgements: The authors acknowledge the clinical and analytical teams involved in conducting the study and the participating volunteers.

Author's Contribution: AC and SJ contributed to study conceptualisation, design, and scientific review. MS coordinated the study, compiled data, drafted, and revised the manuscript. MR contributed to study conduct and data acquisition. BS contributed to pharmacokinetic and bioanalytical data review. KL performed statistical analysis and interpreted the bioequivalence results. All authors reviewed and approved the final manuscript.

Conflicts of interest: The authors declare that there are no conflicts of interest related to this study. Pure and Cure Healthcare Pvt., Ltd.,

India, supplied the investigational product; however, the company had no role in study design, data collection, data analysis, interpretation of results, manuscript preparation, or the decision to publish.

Editorial disclosure: Prospective trial registration was not completed before participant enrolment. The journal recognize the unique clinical value of this data. Henceforth publication is permitted as an exception with transparent disclosure.

REFERENCES

- [1] Yarbrow JW. Mechanism of action of hydroxyurea. *Semin Oncol*. 1992;19(3 Suppl 9):1-10.
- [2] Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. *Am J Hematol*. 2010;85:403-08. Doi: 10.1002/ajh.21699.
- [3] Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med*. 1995;332:1317-22. Doi: 10.1056/NEJM199505183322001.
- [4] Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: A multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377:1663-72. Doi: 10.1016/S0140-6736(11)60355-3.
- [5] Estep JH, Melloni C, Thornburg CD, Wiczling P, Rogers Z, Rothman JA, et al. Pharmacokinetics and bioequivalence of a liquid formulation of hydroxyurea in children with sickle cell anemia. *J Clin Pharmacol*. 2016;56:298-306. Doi: 10.1002/jcph.598.
- [6] Coache D, Friciu M, Marcellin RB, Bonnemain L, Viau A, Roullin VG, et al. Stability evaluation of compounded hydroxyurea 100 mg/mL oral liquids using a novel analytical method involving chemical derivatization. *PLoS One*. 2022;17. Doi: 10.1371/journal.pone.0270206.
- [7] European Medicines Agency. Xromi: EPAR - medicine overview [Internet]. Amsterdam: European Medicines Agency; 2019 [updated 2026 Apr 28; cited 2026 Aug 26]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/xromi>.
- [8] Green NS, Barral S. Emerging science of hydroxyurea therapy for pediatric sickle cell disease. *Pediatr Res*. 2014;75:196-204. Doi: 10.1038/pr.2013.227.
- [9] McGann PT, Ware RE. Hydroxyurea therapy for sickle cell anemia. *Expert Opin Drug Saf*. 2015;14:1749-58. Doi: 10.1517/14740338.2015.1088827.
- [10] Gwilt PR, Tracewell WG. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin Pharmacokinet*. 1998;34:347-58. Doi: 10.2165/00003088-199834050-00002.
- [11] Wiczling P, Liem RI, Panepinto JA, Garg U, Abdel-Rahman SM, Kearns GL, et al. Population pharmacokinetics of hydroxyurea for children and adolescents with sickle cell disease. *J Clin Pharmacol*. 2014;54:1016-22. Doi: 10.1002/jcph.303.
- [12] Rankine-Mullings A, Keenan R, Chakravorty S, Inusa B, Telfer P, Velangi M, et al. Efficacy, safety, and pharmacokinetics of a new, ready-to-use, liquid hydroxyurea in children with sickle cell anemia. *Blood Adv*. 2023;7:4319-22. Doi: 10.1182/bloodadvances.2023010099.
- [13] Marzo A, Fontana E. Critical considerations into the new EMA guideline on bioequivalence. *Arzneimittelforschung*. 2011;61:207-20. Doi: 10.1055/s-0031-1296190.
- [14] World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Participants [Internet]. 2024 [cited 2026 Aug 26]. Available from: <https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/>.
- [15] Mathur R, Swaminathan S. National ethical guidelines for biomedical & health research involving human participants, 2017: A commentary. *The Indian J Med Res*. 2018;148(3):279. Doi: 10.4103/0971-5916.245303.
- [16] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) [Internet]. Geneva: International Council for Harmonisation; 2016. Available from: <https://www.ich.org/page/efficacy-guidelines>.
- [17] Central Drugs Standard Control Organisation. Indian Good Clinical Practice Guidelines [Internet]. New Delhi: CDSCO; 2001 [cited 2026 Aug 26]. Available from: <https://cdsco.gov.in/opencms/opencms/en/Home/>.
- [18] Ministry of Health and Family Welfare. New Drugs and Clinical Trials Rules, 2019 [Internet]. New Delhi: Government of India; 2019 [cited 2026 Aug 26]. Available from: <https://cdsco.gov.in/opencms/opencms/en/Acts-and-rules/New-Drugs/>.
- [19] Central Drugs Standard Control Organization (CDSCO). Guidelines for Bioavailability and Bioequivalence Studies. Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, New Delhi; 2005
- [20] Julious SA. Tutorial in biostatistics: Sample sizes for clinical trials with normal data. *Stat Med*. 2004;23:1921-86. <https://doi.org/10.1002/sim.1783>.
- [21] Paule I, Sassi H, Habibi A, Pham KPD, Bachir D, Galactéros F, et al. Population pharmacokinetics and pharmacodynamics of hydroxyurea in sickle cell anemia patients, a basis for optimizing the dosing regimen. *Orphanet J Rare Dis*. 2011;6:30. Doi: 10.1186/1750-1172-6-30.
- [22] Ware RE, Aygun B. Advances in the use of hydroxyurea. *Hematology Am Soc Hematol Educ Program*. 2009;2009:62-69. Doi: 10.1182/asheducation-2009.1.62.

PARTICULARS OF CONTRIBUTORS:

1. Head, Department of Research and Development, Pure and Cure Healthcare Pvt. Ltd., Delhi, India.
2. Deputy General Manager, Department of Research and Development, Pure and Cure Healthcare Pvt. Ltd., Delhi, India.
3. Deputy General Manager, Department of Drug Regulatory Affairs, Pure and Cure Healthcare Pvt. Ltd., Delhi, India.
4. Director, Department of Bioanalytical, Vivotech Research Lab Pvt. Ltd., Navi Mumbai, Maharashtra, India.
5. Director, Department of Clinical, Vivotech Research Lab Pvt. Ltd., Navi Mumbai, Maharashtra, India.
6. Director, Department of Clinical, Vivotech Research Lab Pvt. Ltd., Navi Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Mamta Sharma,
Pure and Cure Healthcare Pvt. Ltd., Plot No.131 to 133, Block C, Mangolpuri
Industrial Area, Phase-I (Adjoining CBSE Office), Delhi-110083, India.
E-mail: mamta.sharma@akums.net

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Mar 04, 2026
- Manual Googling: Sep 05, 2026
- iThenticate Software: Sep 07, 2026 (3%)

ETYMOLOGY: Author Origin**EMENDATIONS:** 8**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: Funded by Pure and Cure Healthcare Pvt., Ltd., for the Test product.
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 07, 2026**Date of Peer Review: **May 12, 2026**Date of Acceptance: **Sep 09, 2026**Date of Publishing: **Nov 01, 2026**