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A bioequivalence study of oral Vonoprazan in healthy male subjects under fasting conditions

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ABSTRACT

Objectives: The aim of this study was to evaluate the bioequivalence (BE) of two oral tablet formulations of Vonoprazan (VNP) 20 mg in 30 healthy male subjects under fasting conditions.

Materials and Methods: This study was a randomized, open-label, balanced, two-period, two-sequence, single oral dose, and crossover study. Thirty (30) healthy subjects were assigned to one of two sequences protocol: INZELM® 20 mg, as reference product (R) sequence R-T or VNP 20 mg as test product (T) sequence T-R to period I and vice versa to period II, with a washout period between the two periods. Pharmacokinetic (PK) parameters in plasma concentrations were determined using a validated Liquid Chromatography-Mass Spectrometry (LC-MS/MS) method.

Results: The results showed that 90% confidence intervals for the test/reference geometric mean ratios (GMR) of C_{max} : 100.79% (94.55–107.44%), area under the curve ($AUC_{0-\infty}$): 97.42% (92.72–102.35%), and AUC_{0-inf} : 97.35% (92.52–102.43%) were within the BE (80–125%) acceptance range.

Conclusion: The PK profiles of INZELM® VNP 20 mg (Takeda Pharmaceutical Company Limited) as reference (R) product and VNP 20 mg (Laboratorios Leti, S.A.V) as test (T) product were bioequivalent. No adverse events were reported.

Keywords: Bioequivalence, Pharmacokinetic, Vonoprazan

INTRODUCTION

Vonoprazan (VNP) is a potassium-competitive acid blockers (P-CABs), a class of acid-suppressing agents like proton-pump inhibitor (PPI) drugs. The P-CABs inhibit gastric H^+ , K^+ -adenosine triphosphatase (ATPase), an enzyme that catalyzes the critical final step in gastric acid secretion.^[1] However, unlike PPIs, they inhibit the enzyme by reversible K^+ -competitive ionic binding (rather than irreversible covalent binding) and do not require acid activation within the parietal cell secretory canaliculus.^[2]

Following food consumption, parietal cell receptors actively transport hydrogen ions across the canalicular membrane, which is exchanged for luminal potassium ions. Hydrogen potassium-ATPase (HK-ATPase) transfers equal amounts of hydrogen and potassium along with passive movement of chloride ions to promote an acidic gastric environment as well as maintain electrochemical neutrality across the membrane. The final step in gastric acid production is through the HK-ATPase, referred to as a proton pump.^[2,3] VNP blocks this final step in acid production.

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VNP selectively and reversibly competes with luminal potassium ions required for hydrogen exchange.^[1-4] The positively charged side chain enables strong hydrogen bonding and charge interaction with the potassium-binding site. VNP competes with potassium's binding site to prevent potassium from binding and thereby inhibits gastric acid secretion.^[4]

VNP is rapidly absorbed with a peak plasma concentration (C_{max}) of 37.8 ng/mL being reached after 2 h with a single dose and an average of 3 h after reaching steady state with repeated dosing (T_{max}). The area under the curve (AUC) from administration to the end of the 12-h dosing interval is 273 ng*hr/mL.^[4] Both AUC and C_{max} increase dose proportionally with drug accumulation complete by the 3rd day of treatment and little to no accumulation in plasma after repeated doses. Meals high in fat have been shown to increase C_{max} by 5%, AUC by 15%, and T_{max} to 5 h; however, these differences are not considered clinically significant.^[4-6] Thus, VNP can be administered regardless of food intake. The half-life ($t_{1/2}$) is 7–9 h regardless of a meal. VNP displays time-independent pharmacokinetics (PKs) with steady state being reached by day 3 or 4.8. The volume of distribution is 782.7 L with plasma protein binding of 85–88% and unlikely to be saturated even at drug concentrations above therapeutic range. VNP is metabolized through cytochrome P450 (CYP) through CYP3A4/5, CYP2B6, CYP2C19, CYP2C9, and CYP2D6 with none of its metabolites being pharmacologically active. VNP is predominantly excreted through the urinary tract (67%), whereas 31% is excreted in feces. Dose adjustments are not needed for either renal dysfunction or mild hepatic impairment; however, the use should be avoided with an estimated glomerular filtration rate < 30 mL/min or in moderate-to-severe hepatic impairment (Child Pugh B or C).^[1,4-6] VNP binds reversibly to the receptor, is acid-stable, and is not affected by the presence of food.^[4]

Phase I studies conducted in healthy subjects with VNP in a dose range of 10mg to 40 mg once daily for 7 days produced rapid and sustained suppression of gastric acid secretion and was well tolerated.^[4-6] Others Phase 3 clinical trials have shown that VNP is non-inferior to PPIs as a component of *Helicobacter pylori* eradication regimens.^[4-6] VNP has also shown promise in duodenal ulcer-healing rates and in reducing symptoms of heartburn. Common adverse effects associated with VNP include nasopharyngitis, diarrhea, constipation, flatulence, dyspepsia, headache, and abdominal pain.^[4-6]

VNP is the first P-CAB approved in the United States for the treatment of *H. pylori* infection in adults in combination with amoxicillin (with or without clarithromycin).^[7] Current guidelines recommend several first-line treatments for eradicating *H. pylori*, in each of these regimens, a PPI and P-CAB are recommended as the anti-secretory agent of choice due to superior efficacy in reducing acid secretion.^[7]

The purpose of this bioequivalence (BE) study was to assess

and compare the PK profiles and safety of INZELM® VNP 20 mg, coated tablets (Takeda Pharmaceutical Company Limited) as reference (R) product to VNP 20 mg, coated tablets (Laboratorios Leti, S.A.V., República Bolivariana de Venezuela) as test (T) product in healthy adult subjects in randomized crossover study.

This study was conducted by ICBio Clinical Research Private Limited, in India.

MATERIALS AND METHODS

Ethical approval

This study was conducted in accordance with the Indian Council of Medical Research (ICMR) Guidelines (2017)^[8], the Central Drugs Standard Control Organization (CDSCO) New Drugs and Clinical Trials Rules (2019)^[9], the World Medical Association (WMA) Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects^[10], and the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guidelines.^[11] The study protocol and the corresponding informed consent form (ICF) were submitted to the Advisory Committee on Ethics (ACE) Independent Ethics Committee on May 14, 2024, and were certified by the CDSCO/Directorate General of Health Services (DGHS).

Study design

This was an open-label, randomized, two-treatment, two-period, two-sequence, single oral dose, and crossover BE study under fasting conditions comparing two VNP formulations. VNP 20 mg coated tablets were provided as the test formulation (T) by Laboratorios Leti S.A.V., República Bolivariana de Venezuela, batch N° EP-0623551-6R, date of expiry 03/2026, and the reference formulation (R) INZELM® 20mg coated tablets by Takeda Pharmaceutical Company, Hikari Yamaguchi Japan, batch N°551442, date of expiry 01/2026.

The 30 subjects were randomized to one of the two sequences (T-R) or (R-T). The randomization schedule was generated using the Statistical Analysis Software (SAS®) version 9.1.3 SAS Institute Inc., CARY, USA. One single dose was administered in each period. Subjects who received T product in period I were administered R product in period II and vice versa. The pre-screening period was 21 days. The study lasted for 7 days (October 17–24, 2024) with 5 days of washout period, considering the terminal half-life for VNP is 7–9 h.^[4,5]

Subjects

All volunteers underwent a screening procedure. Thirty healthy male volunteers who met the inclusion and exclusion

criteria were enrolled, had a mean age of 33.03 years, mean weight 70.03 Kg, mean height 1.66 cm, and body mass index of 25.23 kg/m² [Table 1].

A complete clinical history valid for 6 months before the start of the study; normal laboratory values as determined by medical history and physical examination at the time of screening; normal vital signs and physical examination; creatinine clearance of more than 50 mL/min; negative tests for hepatic transaminases, hepatitis B and C, human immunodeficiency virus, and venereal diseases research laboratory; and normal 12-lead electrocardiogram values, normal chest radiography, and negative result in urine drug tests. Urine for drugs of abuse and urine test for alcohol consumption were performed on the day of check-in of each period. Other key inclusion criterion was that subjects must be non-smokers or smokers who had not smoked for at least 10 h before the start of the study. They all signed the informed consent.

The exclusion criteria for this study were as follows: volunteers incapable of understanding the informed consent, history of diabetes, tuberculosis and systemic hypertension. Were also excluded subjects with a history of hypersensitivity to study medication, abnormalities cardiovascular, renal hepatic, metabolic, gastrointestinal, neurological, endocrine, hematopoietic, psychiatric. Subjects under medication that affect the hepatic metabolism of others drugs.

Drug administration

The subjects were admitted to the facility the night before the study. In each period, after an overnight fasting of 10 h, each subject received a single oral dose (1 × 20 mg) of either one T or R, following a randomization schedule and was administered with 240 mL ± 5 mL of drinking water at ambient temperature in a sitting position for 2 h after dosing. A total of 19 × 5 mL of venous blood samples were collected through cannula from each subject during each period,

withdrawn at pre-dose (00–00 h) and 00.50, 01.00, 01.33, 01.66, 02.00, 02.33, 02.66, 03.00, 03.33, 03.66, 04.00, 05.00, 06.00, 08.00, 10.00, 12.00, 24.00, and 36.00 h, post dose, the last sample was collected by direct venipuncture. The subjects received standardized meals (2500 Kcal), and drinking water was provided *ad libitum*.

Analytical methodology

Venous blood samples were collected in pre-labeled dipotassium ethylenediaminetetraacetic acid vacutainers and were centrifuged at 4000 rpm for 10 min at 2–8°C within 45 min of sample collection. Plasma was separated, labeled, and stored at –70°C ± 15°C before analysis. Subsequently, the plasma samples were processed, with the calibration curve (CC) of internal standard (ISTD).

VNP in human plasma was quantified using Validated LC-MS/MS method and was validated over the CC range of 0.404–1000.245 ng/mL for VNP fumarate, which was within the validated CC range as per method SOP N°MV-113-00 at the bioanalytical laboratory of ICBio Research Pvt. Ltd., Bangalore.

Liquid–Liquid extraction was carried out by adding 50 µL of ISTD dilution to all the samples. Aliquot 0.250 mL of the plasma samples and vortex to mix. Added 2.500 mL of extraction solvent and vortexed for 10 min in the vibramax at 2000 rpm. Then, the vials were transferred into a refrigerator centrifuge and centrifuged at 4000 rpm for 5 min at 4 ± 2°C. Finally, the supernatant was separated from the above samples by flash freeze and evaporated under nitrogen gas at 40°C, till the tubes are getting dried. The residues were reconstituted with 1 mL of reconstitution solution. An appropriate volume was transferred into a pre-labeled autosampler and the vials were arranged into autosampler at 10 ± 3°C, and injected using Liquid Chromatography - Electrospray Ionization - Mass Spectrometry (LC-ESI-MS/MS).

Controls samples were spiked with internal standard (IS) VNP fumarate D4, over the concentration range of 8.088–2005.880 ng/mL. Samples of plasma, IS, and quality control standard (QCS) were transferred to pre-labeled vials arranged into the autosampler at 10°C ± 2°C and injected into a liquid chromatography electrospray ionization tandem mass spectrometry instrument (LC-ESI-MS/MS) (Shimadzu BA LCMS/08050, Mumbai, India). The chromatographic separation was performed by BDS Hypersil C18, 4.6 × 50 mm, 5 µm high-performance liquid chromatography column (Shimadzu). The injection volume was 20 µL. The automatic sampler SIL-30ACMP was used, with the following specifications: pump LC-20AD, column oven CTO-20A, with a mobile phase of an organic mixture containing 0.1% formic acid solution: 80/20% with a retention time for the drug Vonoprazan of 2.0 min (±0.50) and Vonoprazan D4 IS: 2.8

Table 1: Demographic profile of subjects completing the bioequivalence study.

Age (years)	Mean±SD	33.03±6.79		
	Range	21–44		
	Gender	Male (M) 100%		
Age group		M	%	Total/%
	18–40	27	90	27/90
	41–64	3	10	3/10
Total	20–43	30	100	100
BMI (kg/m ²)	Mean±SD	25.23±2.73		
	Range	(21.36–29.27)		
Race	Asian	30	100	

BMI: Body mass index, SD: standard deviation, n = 30 subjects

min (± 0.50). The mass spectrometer was operated in positive electrospray mode. Identifications were based on multiple reactions monitoring transitions; m/z 315.10–345.00 for the VNP drug and m/z 316.00–349.00 for the IS-VNP D4. The inter-batch calibration standard was 1.21–9.71% with an accuracy of 96.84%–102.77%.

Statistical analysis

The sample size calculation for the study was based on the intra-subject coefficient of variation (CV%) for VNP obtained from published literature (C_{max} :14%, and AUC_{0-t} 15%),^[4,5] with the expected CV% not exceeding 20% and the ratio within 80 and 125%. The study required 25 evaluable subjects to demonstrate BE with a power of $\geq 80\%$ at 5% level of significance, 05 additional subjects were planned to be included in the study. Based on a sample size, 30 subjects were sufficient to demonstrate BE between the two VNP formulations. Statistical analysis was conducted on all of the subjects who complete both periods of the study as per protocol, using SAS® (software version 9.4, Institute, Inc., CARY, USA).

The primary PK parameters were evaluated and adhered to the Food and Drug Administration (FDA). Product specific guidance for generic development under fasting condition. The Pharmacokinetics (PK) parameters evaluated were: maximum peak concentration (C_{max}) and area under curve from time 0 to last measurable concentration (AUC_{0-t}). Others secondary PK parameters evaluated were as follows: Time to reach C_{max} (T_{max}), time required for plasma concentration to decrease by 50% ($T_{1/2}$), area under the plasma concentration–time curve from time 0 to infinity (AUC_{0-inf}), $AUC_{\%Extrap}$, constant of elimination (K_{el}), and the number of points of the terminal log-linear phase used to estimate the terminal rate constant. The natural log transformed (i.e., Ln-transformed) values for the PK parameters C_{max} and AUC_{0-t} were analyzed for statistical difference between test and reference formulations with analysis of variance (ANOVA) by a generalized linear model ANOVA using SAS®. Based on these parameters, the 90% confidence intervals (CIs) were constructed for the least square mean differences of log-transformed PK parameters C_{max} , AUC_{0-t} , and AUC_{0-inf} for VNP. The formulations were regarded as bioequivalent when the 90% CIs of the T and R ratio of C_{max} and AUC_{0-t} ranged from 80% to 125%.

Safety assessments

The safety of two formulations was evaluated through the assessment of adverse events (AEs) monitoring throughout the study. Vital signs were measured during baseline screening and at the conclusion of the study. Safety assessments were done based on clinical observation that

included laboratory data at the time of screening and at the end of the study. The ECG was recorded at the time of screening. Urine analysis for drugs of abuse was done before check-in in both periods.

RESULTS

All subjects (30) completed the study and were included in the PK and statistics evaluation. A non-compartmental analysis was applied for the estimation of PK parameters C_{max} , AUC_{0-t} , AUC_{0-inf} , T_{max} , K_{el} (h^{-1}), and $T_{1/2}$, of VNP in plasma concentration which are presented in Table 2, ANOVA analysis from Ln C_{max} , AUC_{0-t} , and AUC_{0-inf} . There were no statistically significant differences between the PK parameters of the two VNP formulations ($P > 0.05$).

The oral dosing of VNP 20 mg for 36 h post-dose is represented on arithmetic and logarithm scales, as shown in plasma concentration profile to test and reference formulations [Table 3, Figures 1 and 2].

The test/reference geometric mean ratios (GMRs) and 90% CIs for the logarithm of C_{max} , AUC_{0-t} , and AUC_{0-inf} , are presented in Table 4. The BE results were as follows: Ln C_{max} 100.79% (94.55–107.44%), AUC_{0-t} : 97.42% (92.72–102.35%), and AUC_{0-inf} : 97.35% (97.52–109.21%); these values are within the 90% CIs and acceptance criteria of 80–125% [Table 4]. There were no significant differences between the PK parameters of the two VNP formulations ($P > 0.05$).

Table 2: PK parameters for Vonoprazan 20 mg, oral dose after administration of Test (T) and Reference formulations (R) ($n=30$).

PK parameters	Mean \pm SD (Un-transformed data)	
Units	Test (T)	Reference (R)
C_{max} (ng/mL)	29.2897 \pm 7.98	29.2720 \pm 8.20
AUC_{0-t} (ng*h/mL)	326.8208 \pm 83.50	335.4210 \pm 85.01
$AUC_{0-\infty}$ (ng*h/mL)	352.8554 \pm 96.42	362.9999 \pm 101.44
T_{max} (h)	2.2336 \pm 0.94	2.1781 \pm 0.98
λ_z (h^{-1})	0.0783 \pm 0.01	0.0764 \pm 0.01
$T_{1/2}$ (h)	9.1340 \pm 1.70	9.3392 \pm 1.74
Extrapolated AUC (%)	6.9399 \pm 3.43775	7.0038 \pm 3.49
Median (Min, Max)		
T_{max} (h)*	2.000 (1.000–5.000)	2.000 (1.000–5.000)

*Note: For T_{max} Mean along with Min and Max value represented, Data presented as a mean \pm standard deviation. C_{max} : Maximum concentration, AUC_{0-t} : Area under the plasma concentration–time curve from time 0 to the last measurable concentration, $AUC_{0-\infty}$: Area under the plasma concentration–time curve from time 0 to infinity. The residual area in percentage is determined by the formula, $AUC_{\%Extrap}$: $([AUC_{0-inf} - AUC_{0-t}]/AUC_{0-inf}) \times 100$. K_{el} : Elimination rate constant, T_{max} : Time to reach C_{max} , $T_{1/2}$: Time required for plasma concentration to decrease by 50%, PK: Pharmacokinetic, h (hour)

Table 3: Vonoprazan 20 mg plasma concentration (ng/mL) versus time profile test and reference formulation in arithmetic and logarithmic scale.

Time (h)	Plasma concentration (ng/mL) Test (T)	Plasma concentration (ng/mL) Reference (R)	SD (T)	SD (R)	Log plasma (T)	Log plasma (R)	1/Ln SE (T)	1/Ln SE (R)
0	0.0000	0.0000	0.0000	0.0000	0	0	0	0
0.5	5.5976	5.5423	5.86	5.32	1.72	1.71	0.56	0.59
1	16.6705	17.9214	10.64	8.22	2.81	2.88	0.42	0.47
1.33	21.6923	23.9685	10.16	10.38	3.07	3.17	0.43	0.42
1.66	23.1153	24.9360	9.05	8.62	3.14	3.21	0.45	0.46
2	25.7049	26.2881	7.98	7.95	3.24	3.26	0.48	0.48
2.33	23.171	24.5931	6.07	6.35	3.14	3.2	0.55	0.54
2.66	23.2071	24.2804	5.79	5.99	3.14	3.18	0.48	0.55
3	22.686	23.1197	5.48	5.42	3.12	3.14	0.49	0.59
3.33	22.4951	22.5604	5.3	4.97	3.11	3.11	0.59	0.62
3.66	21.9591	22.4536	5.24	5.27	3.08	3.11	0.6	0.6
4	22.3328	22.6005	5.55	5.69	3.1	3.11	0.58	0.57
5	20.4577	20.2404	6.24	5.1	3.01	3	0.54	0.61
6	18.4076	19.4925	4.72	5.14	2.91	2.97	0.64	0.61
8	16.2655	16.2529	4.36	4.31	2.78	2.78	0.67	0.68
10	12.5488	13.0412	3.47	3.72	2.52	2.56	0.8	0.76
12	10.1575	10.4116	3.22	3.26	2.31	2.34	0.85	0.84
24	4.4433	4.4571	1.73	1.76	1.49	1.49	1.82	1.76
36	1.7868	1.8897	0.97	1.05	0.58	0.63	1.82	1.76

SD: Standard deviation, Ln: Natural logarithm, SE: Standard error

Table 4: Correlation of 90% CIs of Ln-transformed main PK variables for Vonoprazan after administration of two formulations (Test and Reference) $n=30$.

Parameters (units)	GMR mean ratio		Ratio (%) (T/R)	90% Confidence intervals (%)
	T	R		
Ln (C_{max}) (ng/mL)	28.27	28.04	100.79	94.55–107.44
Ln (AUC_{0-t}) (h*ng/mL)	316.36	324.75	97.42	92.72–102.35
Ln (AUC_{0-inf}) (h *ng/mL)	340.19	340.19	97.35	92.52–102.43

Data presented as a % mean Ln transformed. C_{max} : Maximum concentration, AUC_{0-t} : Area under the plasma concentration–time curve from time 0 to the last measurable concentration, BE acceptance criteria of 80–125%, GMR: Geometric mean ratios, CI: Confidence interval, PK: Pharmacokinetic

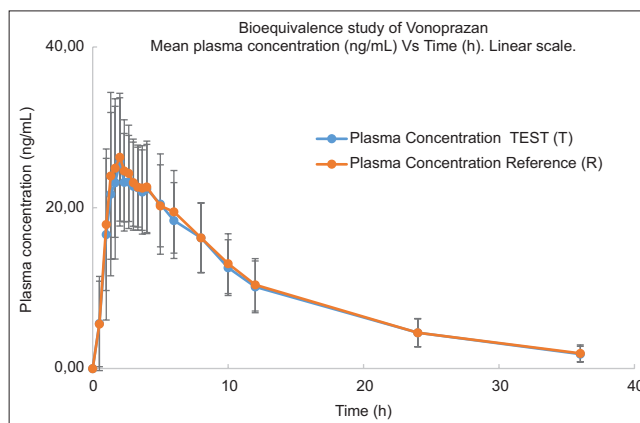


Figure 1: Linear plot of mean plasma concentrations of Vonoprazan 20 mg versus time for test formulation (T) and reference formulation (R) ($n = 30$).

These results meet the predefined BE requirements.

Tolerability and safety

The study safety was evaluated using AEs and laboratory tests. For the post-study safety analysis, before exit from the study, clinical biochemistry, and hematology tests were performed. There were no AEs reported in this study.

DISCUSSION

VNP is administered orally at 20 mg once daily for the treatment of gastroduodenal ulcer, at 20 and 10 mg once daily for the treatment and secondary prevention of reflux esophagitis, respectively, at 10 mg once daily for the

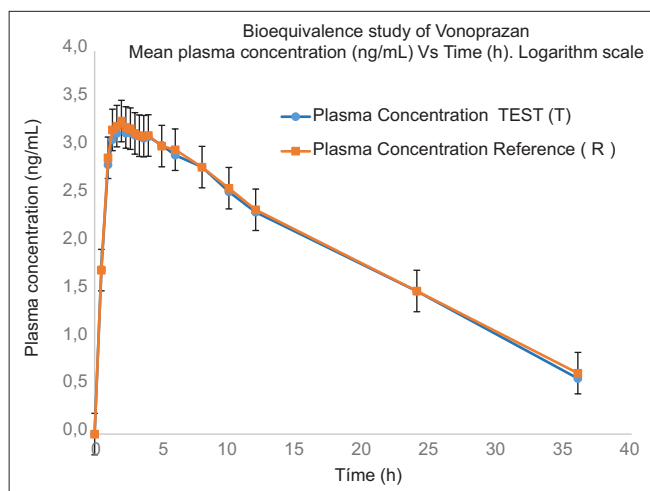


Figure 2: Ln-linear plot of mean plasma concentrations of Vonoprazan 20 mg versus time for test formulation (T) and reference formulation (R) ($n = 30$).

secondary prevention of low-dose aspirin- or non-steroidal anti-inflammatory drug-induced peptic ulcer, and at 20 mg twice daily in combination with clarithromycin and amoxicillin for the eradication of *H. pylori*. It inhibits H(+), K(+)-ATPase activities in a reversible and potassium-competitive manner with a potency of inhibition approximately 350 times higher than the PPI, lansoprazole.^[1,4-7] Guidelines for the treatment of *H. pylori* infection published by the American College of Gastroenterology in 2017 list several regimens as first-line therapy, all of which contain a P-CABs or PPI as the anti-secretory therapy.^[7]

This BE study assessed and compared the PK profiles and safety of INZELM[®] VNP 20 mg, coated tablets (Takeda Pharmaceutical Company Limited) as reference (R) product to VNP 20 mg, and coated tablets (Laboratorios Leti, S.A.V.), as test (T) product in healthy male adult subjects in randomized crossover, under fasting condition. The results of ln-transformed ratios of those parameters showed that the 90% CI were within the BE acceptance range of 80–125%, in accordance with international guidelines for BE studies.^[12,13]

This study was conducted only in a fasted condition following the FDA guideline because the data from clinical studies reported that VNP plasma concentration and drug exposure between both fed and fasting states were similar and, therefore, can be administered independent of food.^[12-14]

In Latin American countries, the importance of BE assessment is to approve generic medicines for marketing, ensuring their quality and standardized processes by confirming the quality in their manufacture. Thus, drugs that pass the BE assessment receive favorable consideration in approval by the local regulatory authorities, where the registration dossier will be submitted.^[15-18]

There is a need for generic drugs that are first-line treatments in their indications to ensure greater affordability of treatments.^[18-20] BE studies provide a framework for regulatory compliance and assurance of therapeutic equivalence in generic formulations with greater access to medicines to a larger number of the population.^[20-23]

Limitations

This study only included male subjects. Although the study was open to both males and females, only male participants were included as no female volunteers responded to the call for participation.

CONCLUSION

This study of a single oral dose of VNP 20 mg, coated tablets, demonstrated the BE of T product, and R product, in healthy subjects volunteers under fasting conditions. The PK profiles were similar and demonstrated that the 90% CIs for GMRs of C_{max} , AUC_{0-t} and AUC_{0-inf} were within the accepted BE range of 80–125%.

Ethical approval: The research/study approved by the Institutional Review Board at ACE Independent Ethics Committee, number ICBio/009/0224, dated May 14, 2024.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient informed consent.

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Conflicts of interest: There are no conflicts of interest

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