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Pharmacokinetic Comparison and Bioequivalence Evaluation of Two 20-mg Vonoprazan Fumarate Tablets in Bangladeshi Healthy Male Subjects

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Abstract

Background: Vonoprazan fumarate, a novel potassium-competitive acid blocker, outperforms traditional proton pump inhibitors in acid suppression and can be effectively combined with antibiotics to eradicate Helicobacter pylori. **Objective:** The study aimed to determine if two Vonoprazan formulations—Vonoprazan Fumarate 20 mg Tablet of Beximco Pharmaceuticals Limited, Bangladesh (test product) and Takecab 20 mg Tablet of Takeda Pharmaceutical Company Limited, Japan (reference product)—met FDA's bioequivalence requirements by comparing their pharmacokinetic characteristics in healthy Bangladeshi adults. **Methods:** This was a single-center, randomized, open-label, two-period, two-sequence, laboratory-blind, double-crossover experiment. After 10 hours of fasting, 18 subjects were randomly assigned to receive a single oral dose of either formulation. During each treatment period, blood samples were collected at specific times (pre-dose and up to 48 hours post-dose) to measure plasma Vonoprazan levels using liquid chromatography-tandem mass spectrometry. A non-compartmental model was used to calculate pharmacokinetic parameters using the plasma drug concentration-time profile. A statistical comparison of the pharmacokinetic parameters of the two formulations of the test and reference product was conducted using SAS® statistical software to assess the bioequivalence. Primary pharmacokinetic parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) and secondary parameters (T_{max}, $T_{1/2}$, K_{el}, and AUC extrapolation) were calculated for both drug formulations. If the confidence intervals for the natural log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ val-

ues fell between 80% and 125%, the drug products would be considered bioequivalent. **Result:** The geometric mean ratio of Vonoprazan between the test and reference groups was found to be 109.04% (99.47% - 119.53%), 101.37% (95.58% - 107.50%), and 101.24% (95.43% - 107.41%), with 90% confidence intervals (CIs) for the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, and these outcomes met the regulatory requirements for assuming bioequivalence. **Conclusion:** The results demonstrated that the generic formulation of Vonoprazan 20 mg Tablet of Beximco Pharmaceuticals Limited is bioequivalent to the reference product.

Keywords

Bioequivalence, Vonoprazan, Pharmacokinetics

1. Introduction

The healthcare system is significantly impacted by acid-related disorders (ARDs), and overexposure to acid is thought to be one potential mechanism of injury in ARDs [1]. Because of this, drugs referred to as acid inhibitors were developed to treat gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) by stopping the stomach from producing an excessive quantity of acid [2]. As the final stage of the acid secretion pathway, the gastric proton pump enzyme H^+, K^+-ATPase, is the main target in the pharmacological therapy of acid-related disorders [3]. The two major categories of drugs that inhibit this enzyme are proton-pump inhibitors (PPIs) and potassium-competitive acid blockers [P-CABs] [3].

Proton pump inhibitors (PPIs) have been widely utilized since 1991 to treat a wide range of upper gastrointestinal (GI) tract diseases, generally referred to as acid-related disorders [4]. Proton pump inhibitors (PPIs) have significantly enhanced the treatment of illnesses associated with acidity, yet certain medical needs persist and may require additional care. For example, about one-third of individuals with GERD fail to respond symptomatically, either partially or entirely, to PPI treatment and may require further medical care [5]. For greater control of 24-hour intragastric acidity, approaches other than PPI medication have been considered, mainly using potassium-competitive acid blockers (P-CABs) [6] [7].

Several candidate compounds acting as P-CABs have been invented to identify an efficient medication for the treatment of acid-related disorders. However, most have been rejected during the clinical phase of experiments due to their inadequate efficacy and safety challenges (e.g., hepatotoxicity) [8]-[10]. To overcome the limitations of earlier medications in the class, Takeda Pharmaceutical Company Limited (Japan) developed the potent and novel P-CAB (Vonoprazan) with a distinct chemical structure and pharmacological profile [11]. It offers advantages over the conventional proton-pump inhibitors (PPIs),

including fast onset of action [12], high accumulation and slow clearance [13], improved control over acid secretion at night [14], acid stability, and the ability to bind to the proton pump without the need for enteric coating or acid activation [15]-[17]. Furthermore, TAK-438 F has minimal CYP polymorphism, making it less susceptible to the effects of CYP inducers or inhibitors [18].

Vonoprazan has gained clinical interest for the treatment of disorders associated with acid reflux because of its potential benefits over proton pump inhibitors [19]. It has shown potential as a treatment option for acid-related conditions such as reflux oesophagitis, erosive oesophagitis, gastric ulcer, duodenal ulcer, peptic ulcer, gastro-oesophageal reflux, and Helicobacter pylori eradication [20] [21]. This innovative acid suppressant successfully lowers stomach acid and was recently licensed in Japan to treat acid reflux-related conditions [22]-[25].

Vonoprazan's chemical name is 1-(5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl)-N methylmethanamine fumarate. Vonoprazan fumarate is slightly soluble in water [26]. It ionically and reversibly binds the stomach proton pump [27] [28]. Compared to conventional PPIs, which have much shorter half-lives ($t_{1/2}$ = 1 - 2 hours), Vonoprazan has a much longer plasma half-life ($t_{1/2}$ = about 7 hours when taken in a fasting state), allowing for a once-daily dose for clinical use. It is rapidly absorbed and reaches the maximum plasma level (C_{max}) within two hours [29].

The demand for generic versions of Vonoprazan is increasing since it offers a more cost-effective option for most patients, improving treatment adherence. To correlate the generic medication with the biopharmaceutical quality, therapeutic efficacy, and safety of the reference product, generic drugs must demonstrate their bioequivalence with their reference (innovator) medicine [30]. Bioequivalence is shown when two drugs are pharmaceutically equivalent, and their bioavailability after administration is within the allowed specified limits [31].

This study aims to provide a comprehensive bioequivalence analysis of the two formulations of Vonoprazan Fumarate 20 mg tablets from Beximco Pharmaceuticals Limited, Bangladesh, and Takecab 20 mg tablets from Takeda Pharmaceutical Company Limited, Japan. The research confirms the bioequivalence of these formulations and focuses on key pharmacokinetic parameters and their potential clinical relevance. The findings will enhance clinicians' and formulators' existing knowledge of Vonoprazan's pharmacokinetic profile, ensuring interchangeable use without compromising efficacy.

2. Methods

2.1. Study Design

This was a single-site, open-label, randomized, balanced, laboratory-blind, single-dose, two-treatment, two-sequence, two-period, two-way crossover oral bioequivalence study of Vonoprazan Fumarate 20 mg tablet manufactured by Beximco Pharmaceuticals Limited, Bangladesh (T) and Takecab 20 mg (Vonoprazan Fumarate 20 mg) tablet of Takeda Pharmaceutical Company Limited, Japan,

in healthy adult male human subjects under fasting conditions. SAS was used for randomization and treatment allocation. All the study personnel, as well as the participants, were unblinded to the treatment assigned in each period. Nevertheless, during the analytical procedures, the analyst remains blinded to the sequence of treatment allocation. The clinical investigation was completed over 15 days. Based on Vonoprazan's reported plasma half-life, which ranges from 7 to 9 hours [32] [33], a seven-day washout time was considered appropriate for this clinical study since it exceeds the seven half-lives recommended by the FDA [34].

2.2. Study Center and Study Duration

The study was conducted at one of Bangladesh's earliest DGDA-approved Contract Research Organizations (CRO). The clinical part of the study was carried out at Novus Clinical Research Services Limited from January 25 to February 04, 2024, while the analytical stage was carried out from February 15 to March 04, 2024.

2.3. Ethical Standards/Compliance with Ethics Guidelines

The study adhered to the most recent versions of the Declaration of Helsinki and the International Council for Harmonization's current guidelines for good clinical practice [35] [36]. The study documents, including the protocol and consent form, were reviewed and approved by the Bangladesh Medical Research Council (BMRC) of the National Research Ethics Committee (NREC) on November 2023 (Reference No.: BMRC/NREC/2022-2025/272). The study was also approved by the Directorate General of Drug Administration (DGDA) on January 2024 (Reference No.: DGDA/CTP-04/2016/1303).

2.4. Study Products

Table 1 shows the Identification of both Investigational Products.

Table 1. Identification of the investigational product(s).

IMP details	Test product (T)	Reference product (R)
Trade Name	-	Takecab®
Generic Name	Vonoprazan Fumarate	Vonoprazan Fumarate
Specification	20 mg/tablet	20 mg/tablet
Batch/Lot No.	49322501	546244
Expiry Date	10/2025	01/2026
Manufacturer	Beximco Pharmaceuticals Ltd., Bangladesh	Takeda Pharmaceutical Company Limited, Japan

2.5. Study Population

The participants had to go through a pre-study screening process. Randomly, 48

Bangladeshi volunteers were chosen from Novus's registered volunteer database if they could participate, communicate well with the researchers, be available during the study period, and give written informed consent. Following a pre-study medical evaluation, 18 healthy participants were enrolled in the study as subjects. Volunteers aged 18 - 55 with a Body Mass Index (BMI) between 18 and 30 kg/m^2 were recruited for the study [37]. All participants underwent a thorough health assessment, including measurements of blood pressure (BP), pulse rate, temperature, and respiration rate during a physical examination and interview. Additionally, they underwent a 12-lead ECG, chest radiography, hematology and blood chemistry tests, urinalysis, tests for alcohol and drug abuse, and a COVID antigen test. Furthermore, serological examinations included testing for antibodies to HIV, hepatitis B, and hepatitis C. All tests were conducted at the diagnostic center of Novus Clinical Research Services Limited. Selected participants were required to be free of any significant disease or clinically significant abnormal laboratory values upon evaluation of medical history, physical examination, and laboratory tests.

Individuals with known allergies or hypersensitive intolerances to Vonoprazan, chronic illnesses, bleeding disorders, or abnormal health conditions assessed by baseline medication, medical history, and vital signs were excluded from the study. Subjects with difficult vein accessibility were also excluded. Participants were advised to avoid medications impacting liver drug-metabolizing enzymes for at least one month before and during the trial. They were also instructed not to use any prescribed medications for 14 days or over-the-counter (OTC) products for seven days before and during the trial. Participants were asked to abstain from consuming alcohol, beverages, or food containing xanthines for 48 hours before the study and until the final blood sample was collected. Moreover, individuals who had experienced blood loss or donated more than 350 milliliters of blood in the three months before the experiment were ineligible to participate.

2.6. Drug Administration

On the day before medication administration, eligible participants checked into the clinical pharmacology unit and fasted for 10 hours (except for water) to establish baseline plasma measurements. Randomization was done using SAS (Version 9.4; SAS Institute Ind., USA) by a statistician to allocate individuals to dosing-order subgroups, T/R and R/T. Each participant received a test or reference formulation tablet with 240 milliliters of water. Participants were prohibited from drinking water for one hour before and after drug administration. Following dosing, participants were closely monitored while seated for four hours.

2.7. Blood Sampling

A pre-dose (0.00 hour) pharmacokinetic blood sample was taken on the dosing day, one hour before the study drug's administration, to establish the baseline plasma level. Blood samples (5 mL) were collected in K_2EDTA tubes from the

forearm vein at specific intervals ranging from 0.25 to 48.00 hours after drug administration. The collected samples were subjected to centrifugation (3500 RPM for 10 minutes at 5˚C ± 3˚C) to separate plasma, which was then transferred to polypropylene tubes and stored at −70˚C until liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis was performed.

2.8. Safety Evaluation

Clinical laboratory testing (hematology, clinical biochemistry, serology, and urine analysis), physical examinations, vital signs, ECGs, and subject-reported adverse events (AEs) monitoring were all included in the safety assessments. Following administering the medication, vital signs (blood pressure, pulse rate, respiration rate, and body temperature) were recorded at 1.00, 3.00, 5.00, 7.00, 9.00, 11.00, 13.00, 24.00, and 48.00 hours. Throughout the trials, spontaneous reports of adverse events were collected and assessed for severity and correlation with the study medication. Upon completion of the study, clinical laboratory determinations were performed and evaluated to monitor adverse events.

2.9. Bioanalytical Method

The concentration of Vonoprazan in plasma was measured using protein precipitation and a validated LC-MS/MS method, with Linagliptin as the internal standard. Chromatographic separation utilized an ACE 3 C18-AR column with a size of 4.6 × 50 mm and a 3.0 μm particle size at a column temperature of 30˚C and a flow rate of 0.600 mL/min. The lower limit of quantitation (LLOQ) for Vonoprazan was 0.500 ng/mL, with a dynamic range of 0.500 to 75 ng/mL. The method was found to be linear across this concentration range, with a correlation coefficient greater than 0.99. Quality control (QC) samples at concentrations of 0.500, 2.00, 15.00, 25.00, and 50.00 ng/mL were analyzed and distributed equally among the volunteers' plasma samples to evaluate method accuracy and precision. Vonoprazan's within-run precision and accuracy ranged from 2.23% to 9.27% and 96.4% to 120.7%, respectively, whereas its between-run precision and accuracy ranged from 4.16% to 9.57% and 102.4% to 111.8%, respectively.

After completing both study periods, pharmacokinetic analysis was conducted for each participant. Key pharmacokinetic parameters including the maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from administration to the last observed quantifiable concentration at time t ($AUC_{0\text{-}t}$), area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$), time to reach maximum observed plasma concentration (T_{max}), and plasma half-life ($t_{½}$) were calculated based on the plasma concentrations of Vonoprazan.

2.10. Statistical Analysis

Statistical analysis was conducted using the SAS® statistical software, Version 9.4 of SAS Institute Ind., USA. ANOVA was used to evaluate the log (Ln) trans-

formed pharmacokinetic parameters (AUC_{0-t} and $AUC_{0-\infty}$) at a significance level of 5% ($\alpha = 0.05$). The terms sequence, period, and formulation were used in the ANOVA model. When the 90% confidence intervals (CIs) for the geometric mean ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for both analytes fall between 80% and 125% for the Ln-transformed data, bioequivalence will be declared [38] [39].

3. Results

3.1. Subject Disposition and Demographics

Each of the eighteen enrolled participants who received the Vonoprazan test or reference therapy completed the trial. Table 2 summarizes the baseline demographics of all subjects who completed the study.

Table 2. Demographic details of subjects who completed the study (N = 18).

Characteristic	Values
Total number of male subjects	18
Age, mean (SD), range, years	25 (2.7344), 20 - 33
Weight, mean (SD), range, kg	66.64 (9.4126), 51.15 - 87.00
Height, mean (SD), range, cm	166.20 (5.4939), 156 - 174
BMI, mean (SD), range, kg/m^2	24.13 (2.6193), 19.30 - 29.80

3.2. Pharmacokinetic Properties

Table 3 summarizes the major pharmacokinetic parameters of Vonoprazan under fasting conditions.

Table 3. Summary results of pharmacokinetic parameters.

Takecab 20 mg tablet *i.e.* Vonoprazan Fumarate 20 mg (Reference Product)							
Variable	**N**	**Arithmetic Mean**	**SD**	**CV%**	**Min**	**Median**	**Max**
T_{max} (hr)	18	1.531	0.4012	26.2	0.75	1.65	2.00
C_{max} (ng/mL)	18	35.0669	5.30023	15.1	27.072	35.140	47.149
AUC_{0-t} (hr * ng/mL)	18	322.4877	84.19805	26.1	167.221	339.739	467.481
$AUC_{0-\infty}$ (hr * ng/mL)	18	340.2188	83.07971	24.4	181.085	358.885	482.675
AUC_% Extrap_obs (%)	18	5.5785	3.71879	66.7	1.850	3.613	13.367
$T_{½}$ (hr)	18	8.2283	1.38669	16.9	6.135	8.646	10.676
K_{el} (hr^{-1})	18	0.0867	0.01543	17.8	0.065	0.080	0.113
Vonoprazan Fumarate 20 mg tablet (Test Product)							
	N	**Arithmetic Mean**	**SD**	**CV%**	**Min**	**Median**	**Max**
T_{max} (hr)	18	1.629	0.5967	36.6	0.75	1.50	3.00

Continued

C_{max} (ng/mL)	18	39.0124	9.58088	24.6	21.845	38.350	55.525
AUC_{0-t} (hr * ng/mL)	18	326.1952	84.98408	26.1	185.947	323.019	456.491
$AUC_{0-\infty}$ (hr * ng/mL)	18	343.9048	84.14690	24.5	199.389	343.720	470.143
AUC_% Extrap_obs (%)	18	5.4578	3.76077	68.9	1.425	3.541	12.520
$T_{½}$ (hr)	18	8.0532	1.81257	22.5	4.208	7.960	11.444
K_{el} (hr^{-1})	18	0.0910	0.02432	26.7	0.061	0.087	0.165

Overall, plasma concentrations (Figure 1 and Figure 2) and exposure to Vonoprazan were similar between the two treatments.

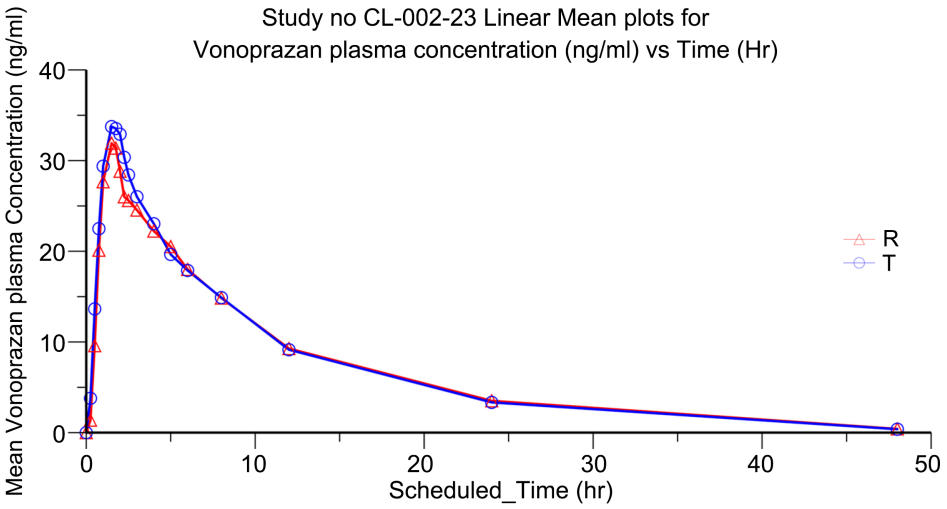

Figure 1. Linear mean plots for Vonoprazan plasma concentration (ng/ml) vs Time (Hr).

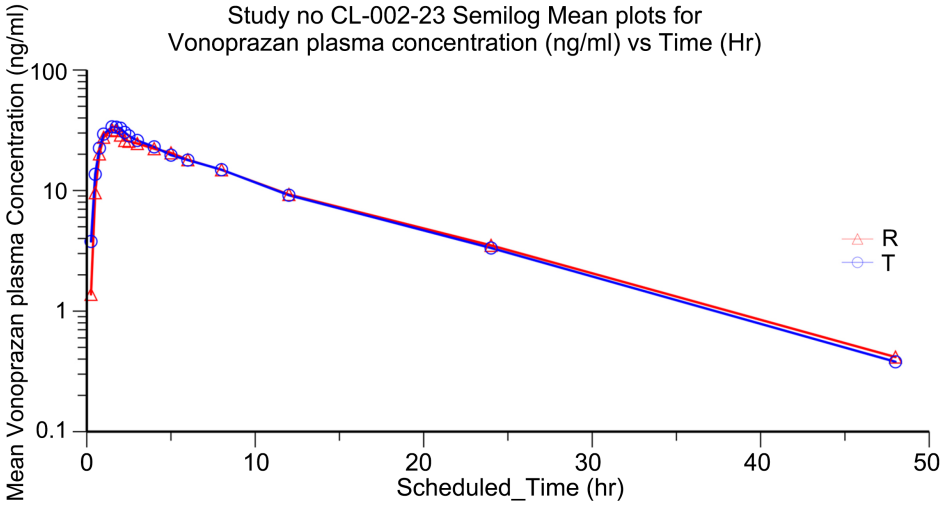

Figure 2. Semilog mean plots for Vonoprazan plasma concentration (ng/ml) vs Time (Hr).

Table 4 shows the geometric means, geometric mean ratios (test/reference), 90% confidence interval, and intra-subject percentage CV of the bioequivalence statistics derived from the log-transformed data for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The 90% confidence intervals for Vonoprazan C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 99.47% - 119.53%, 95.58% - 107.50%, and 95.43% - 107.41%, respectively. The 90% confidence intervals of the geometric mean ratios for the three parameters all fell within the predetermined range of 80% to 125%. Therefore, these findings suggest that the bioequivalence requirements were met.

Table 4. Statistical results of Ln-transformed test product (T) vs reference product (R) Vonoprazan.

Parameter	Geometric Least Squares Means (GEOLSM)		T/R Ratio (%)	90% Confidence Interval		Intra Subject CV (%)	Power (%)
	Test Product	Reference Product		Lower Limit (%)	Upper Limit (%)		
C_{max} (ng/mL)	37.836	34.699	109.04	99.47	119.53	15.89	97.50
AUC_{0-t} (hr * ng/mL)	314.963	310.710	101.37	95.58	107.50	10.12	99.98
$AUC_{0-\infty}$ (hr * ng/mL)	333.399	329.312	101.24	95.43	107.41	10.19	99.98

C_{max} = Maximum plasma drug concentration, AUC_{0-t} = AUC from time 0 (baseline) to the last measurable concentration, $AUC_{0-\infty}$ = AUC from baseline extrapolated to infinity.

The ANOVA results (Table 5) show that using logarithmic-transformed data, no sequence, period, or formulation effects were observed ($p \geq 0.5$) for any PK parameters.

Table 5. p-values for sources of variations obtained from the analysis of variance (ANOVA).

	ANOVA p-values		
Parameters	LCmax	$LAUC_{0-t}$	$LAUC_{0-\infty}$
Sequence	0.1235	0.5760	0.5072
Period	0.3063	0.2314	0.1993
Formulation	0.1196	0.6916	0.7205

3.3. Safety Analysis

During the trial, Vonoprazan demonstrated good tolerability. Only two subjects reported adverse events of diarrhea and vertigo, both of which were moderate and not considered possibly or probably related to the study treatment by the investigator. These events did not lead to any premature discontinuation of the trial by participants, nor were any deaths or serious adverse events reported. The laboratory safety tests, 12-lead ECGs, and vital signs showed no clinically significant abnormalities. Additionally, the general health status of all participants was

deemed clinically fit after the study's clinical phase.

4. Discussion

The study compared the pharmacokinetics of a generic formulation of Vonoprazan 20 mg film-coated tablet to those of the reference drug. Determining the bioequivalence of a generic medication with its reference drug is crucial as it confirms the similarity in pharmacokinetic parameters, which is essential for ensuring that the absorption rates and extent of both formulations are identical. The increasing use of generic products has amplified the significance of bioequivalence research.

Our findings demonstrated that the pharmacokinetic profiles of the reference and test drugs were highly similar, with the geometric mean ratio (GMR) and its 90% confidence interval (CI) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ falling within the 80% to 125% bioequivalence acceptability range in terms of absorption rate and extent when administered as a single dose under fasting conditions.

In this study, the insignificant variations in T_{max} and C_{max} reported between the Vonoprazan formulations, while statistically within the acceptable bioequivalence range, are unlikely to have a significant clinical impact. These slight differences may have a minor impact on the time-to-peak therapeutic effect (T_{max}) and may barely influence the extent of the drug's effects (C_{max}). However, since every parameter meets the bioequivalence criteria, these slight variations are unlikely to have a significant impact on the drug's effectiveness.

Although pharmacokinetic similarity is indicated through bioequivalence, therapeutic efficacy can also be influenced by additional factors such as formulation variations, patient variability, and clinical aspects. Therefore, while the generic formulation may act as a cost-effective alternative to the reference drug, further studies may be needed to ensure that therapeutic outcomes remain consistent across different patient populations and clinical situations.

5. Limitations

The study aimed to offer valuable insights into Vonoprazan's bioequivalence. Still, there are a few limitations, such as a small sample size, a single-dose design, and a lack of specific evaluation of concomitant medications' influence on Vonoprazan pharmacokinetics. Future research could benefit from larger sample sizes and multiple dosing regimens to better understand the variability in Vonoprazan pharmacokinetics over time and under different dosing regimens. It's also crucial to consider potential drug-drug interactions and examine the impact of co-administered medications on Vonoprazan's bioavailability and metabolism.

6. Conclusion

This bioequivalence study's findings offer valuable insights into the pharmacokinetic profile of Vonoprazan. By conducting a thorough analysis and compari-

son of pharmacokinetic parameters between the test and reference formulations, we have substantiated that the test formulation of Vonoprazan is bioequivalent to the reference formulation. The absence of significant differences in the rate and extent of absorption supports this. These results indicate that healthcare providers can confidently prescribe or dispense Vonoprazan, as the test and reference formulations are interchangeable and produce similar therapeutic effects in patients due to their comparable systemic exposure and pharmacokinetic properties.

Conflicts of Interest

There are no conflicts of interest.

References

[1] Yang, X., Li, Y., Sun, Y., Zhang, M., Guo, C., Mirza, I.A., *et al.* (2017) Vonoprazan: A Novel and Potent Alternative in the Treatment of Acid-Related Diseases. *Digestive Diseases and Sciences*, **63**, 302-311. https://doi.org/10.1007/s10620-017-4866-6

[2] Ganser, A.L. and Forte, J.G. (1973) K^+-Stimulated ATPase in Purified Microsomes of Bullfrog Oxyntic Cells. *Biochimica et Biophysica Acta* (*BBA*)-*Biomembranes*, **307**, 169-180. https://doi.org/10.1016/0005-2736(73)90035-7

[3] Sachs, G., Shin, J.M. and Hunt, R. (2010) Novel Approaches to Inhibition of Gastric Acid Secretion. *Current Gastroenterology Reports*, **12**, 437-447. https://doi.org/10.1007/s11894-010-0149-5

[4] Khan, M.A., Howden, C.W. (2018) The Role of Proton Pump Inhibitors in the Management of Upper Gastrointestinal Disorders. *Gastroenterology & Hepatology*, **14**, 169-175.

[5] Fass, R. and Sifrim, D. (2009) Management of Heartburn Not Responding to Proton Pump Inhibitors. *Gut*, **58**, 295-309. https://doi.org/10.1136/gut.2007.145581

[6] Mulford, D.J., Leifke, E., Hibberd, M. and Howden, C.W. (2021) The Effect of Food on the Pharmacokinetics of the Potassium-Competitive Acid Blocker Vonoprazan. *Clinical Pharmacology in Drug Development*, **11**, 278-284. https://doi.org/10.1002/cpdd.1009

[7] Akiyama, J., Hosaka, H., Kuribayashi, S., Moriyasu, S., Hisada, Y., Okubo, H., *et al.* (2019) Efficacy of Vonoprazan, a Novel Potassium-Competitive Acid Blocker, in Patients with Proton Pump Inhibitor-Refractory Acid Reflux. *Digestion*, **101**, 174-183. https://doi.org/10.1159/000497775

[8] Ene, M.D., Khan-Daneshmend, T. and Roberts, C.J.C. (1982) A Study of the Inhibitory Effects of SCH 28080 on Gastric Secretion in Man. *British Journal of Pharmacology*, **76**, 389-391. https://doi.org/10.1111/j.1476-5381.1982.tb09232.x

[9] Rawla, P., Sunkara, T., Ofosu, A. and Gaduputi, V. (2018) Potassium-Competitive Acid Blockers—Are They the Next Generation of Proton Pump Inhibitors? *World Journal of Gastrointestinal Pharmacology and Therapeutics*, **9**, 63-68. https://doi.org/10.4292/wjgpt.v9.i7.63

[10] Kim, H., Park, S., Cheung, D., Cho, Y., Kim, J., Kim, S., *et al.* (2010) Clinical Trial: Inhibitory Effect of Revaprazan on Gastric Acid Secretion in Healthy Male Subjects. *Journal of Gastroenterology and Hepatology*, **25**, 1618-1625. https://doi.org/10.1111/j.1440-1746.2010.06408.x

[11] Martinucci, I., Blandizzi, C., Bodini, G., Marabotto, E., Savarino, V., Marchi, S., *et*

al. (2017) Vonoprazan Fumarate for the Management of Acid-Related Diseases. *Expert Opinion on Pharmacotherapy*, **18**, 1145-1152. https://doi.org/10.1080/14656566.2017.1346087

[12] Luo, H., Deng, W. and Zou, K. (2014) Protonated Form: The Potent Form of Potassium-Competitive Acid Blockers. *PLOS ONE*, **9**, e97688. https://doi.org/10.1371/journal.pone.0097688

[13] Hou, X., Meng, F., Wang, J., Sha, W., Chiu, C., Chung, W.C., *et al.* (2022) Vonoprazan Non-Inferior to Lansoprazole in Treating Duodenal Ulcer and Eradicating *Helicobacter pylori* in Asian Patients. *Journal of Gastroenterology and Hepatology*, **37**, 1275-1283. https://doi.org/10.1111/jgh.15837

[14] Scott, D.R., Munson, K.B., Marcus, E.A., Lambrecht, N.W.G. and Sachs, G. (2015) The Binding Selectivity of Vonoprazan (TAK-438) to the Gastric H^+, K^+-ATPase. *Alimentary Pharmacology & Therapeutics*, **42**, 1315-1326. https://doi.org/10.1111/apt.13414

[15] Sachs, G., Shin, J.M., Vagin, O., Lambrecht, N., Yakubov, I. and Munson, K. (2007) The Gastric H,K ATPase as a Drug Target: Past, Present, and Future. *Journal of Clinical Gastroenterology*, **41**, S226-S242. https://doi.org/10.1097/mcg.0b013e31803233b7

[16] Shin, J.M. and Sachs, G. (2009) Long-Lasting Inhibitors of the Gastric H,K-ATPase. Expert *Review of Clinical Pharmacology*, **2**, 461-468. https://doi.org/10.1586/ecp.09.33

[17] Savarino, E., Martinucci, I., Furnari, M., Romana, C., Pellegatta, G., Moscatelli, A., *et al.* (2016) Vonoprazan for Treatment of Gastroesophageal Reflux: Pharmacodynamic and Pharmacokinetic Considerations. *Expert Opinion on Drug Metabolism & Toxicology*, **12**, 1333-1341. https://doi.org/10.1080/17425255.2016.1214714

[18] Qiao, Y., Zhao, J., Yue, X., Zhang, Y., Zhang, R., Xu, Y., *et al.* (2017) Study on Pharmacokinetics and Bioequivalence of Vonoprazan Pyroglutamate in Rats by Liquid Chromatography with Tandem Mass Spectrometry. *Journal of Chromatography B*, **1059**, 56-65. https://doi.org/10.1016/j.jchromb.2017.05.013

[19] Akazawa, Y., Fukuda, D. and Fukuda, Y. (2016) Vonoprazan-Based Therapy for *Helicobacter pylori* Eradication: Experience and Clinical Evidence. *Therapeutic Advances in Gastroenterology*, **9**, 845-852. https://doi.org/10.1177/1756283x16668093

[20] Abbasi, A., Siddiqui, S.A., Ram, B., Khan, J.U.A., Sheikh, K., Ali, A., *et al.* (2023) Real-World Evidence to Evaluate the Efficacy and Safety of Vonoprazan in Gastrointestinal Disorders in the Pakistani Population. *Cureus*, **15**, c147. https://doi.org/10.7759/cureus.48994

[21] Garnock-Jones, K.P. (2015) Vonoprazan: First Global Approval. *Drugs*, **75**, 439-443. https://doi.org/10.1007/s40265-015-0368-z

[22] Shin, J.M., Inatomi, N., Munson, K., Strugatsky, D., Tokhtaeva, E., Vagin, O., *et al.* (2011) Characterization of a Novel Potassium-Competitive Acid Blocker of the Gastric H,K-ATPase, 1-[5-(2-Fluorophenyl)-1-(pyridin-3-Ylsulfonyl)-1*H*-Pyrrol-3-Yl]-*N*-Methylmethanamine Monofumarate (TAK-438). *Journal of Pharmacology and Experimental Therapeutics*, **339**, 412-420. https://doi.org/10.1124/jpet.111.185314

[23] Ashida, K., Sakurai, Y., Hori, T., Kudou, K., Nishimura, A., Hiramatsu, N., *et al.* (2015) Randomised Clinical Trial: Vonoprazan, a Novel Potassium-Competitive Acid Blocker, vs. Lansoprazole for the Healing of Erosive Oesophagitis. *Alimentary Pharmacology & Therapeutics*, **43**, 240-251. https://doi.org/10.1111/apt.13461

[24] Murakami, K., Sakurai, Y., Shiino, M., Funao, N., Nishimura, A. and Asaka, M. (2016) Vonoprazan, a Novel Potassium-Competitive Acid Blocker, as a Component of First-Line and Second-Line Triple Therapy for *Helicobacter pylori* Eradication: A Phase III, Randomised, Double-Blind Study. *Gut*, **65**, 1439-1446. https://doi.org/10.1136/gutjnl-2015-311304

[25] Takeda Pharmaceutical Company Limited, Takecab (Vonoprazan Tablets) Package Insert. http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400256_23290 30F1020_1_04

[26] Mo, Q.L., Zhao, B.W. and Huang, F.F. (2017) Vonoprazan Fumarate Composition and Preparation Method Thereof. Google Patents WO2018133009A1. https://patents.google.com/patent/WO2018133009A1/en

[27] Hori, Y., Imanishi, A., Matsukawa, J., Tsukimi, Y., Nishida, H., Arikawa, Y., *et al.* (2010) 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-Methylmethana mine Monofumarate (TAK-438), a Novel and Potent Potassium-Competitive Acid Blocker for the Treatment of Acid-Related Diseases. *Journal of Pharmacology and Experimental Therapeutics*, **335**, 231-238. https://doi.org/10.1124/jpet.110.170274

[28] Oshima, T. and Miwa, H. (2018) Potent Potassium-Competitive Acid Blockers: A New Era for the Treatment of Acid-Related Diseases. *Journal of Neurogastroenterology and Motility*, **24**, 334-344. https://doi.org/10.5056/jnm18029

[29] Sugano, K. (2018) Vonoprazan Fumarate, a Novel Potassium-Competitive Acid Blocker, in the Management of Gastroesophageal Reflux Disease: Safety and Clinical Evidence to Date. *Therapeutic Advances in Gastroenterology*, **11**. https://doi.org/10.1177/1756283x17745776

[30] Tjandrawinata, R.R. *et al.* (2024) Bioequivalence Study of Dapagliflozin 10 mg Film Coated Tablets in Healthy Indonesian Subjects under Fasting. *Journal of Bioequivalence & Bioavailability*, **16**, 1-7.

[31] European Medicines Agency (2010) Guideline on the investigation of bioequivalence. Committee for Medicinal Products for Human Use (CHMP).

[32] Jenkins, H., Sakurai, Y., Nishimura, A., Okamoto, H., Hibberd, M., Jenkins, R., *et al.* (2015) Randomised Clinical Trial: Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Repeated Doses of TAK-438 (Vonoprazan), a Novel Potassium-Competitive Acid Blocker, in Healthy Male Subjects. *Alimentary Pharmacology & Therapeutics*, **41**, 636-648. https://doi.org/10.1111/apt.13121

[33] Echizen, H. (2015) The First-in-Class Potassium-Competitive Acid Blocker, Vonoprazan Fumarate: Pharmacokinetic and Pharmacodynamic Considerations. *Clinical Pharmacokinetics*, **55**, 409-418. https://doi.org/10.1007/s40262-015-0326-7

[34] Food and Drug Administration (2014) Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs-General Considerations-Draft Guidance. Food and Drug Administration, Center for Drug Evaluation and Research.

[35] The World Medical Association, INC (2013) Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects.

[36] European Medicines Agency, Committee for Human Medicinal Products (2016) International Council for Harmonization Guideline for Good Clinical Practice E6 (R2).

[37] ASEAN Guideline for the Conduct of Bioavailability and Bioequivalence Study. https://www.fda.gov.ph/wp-content/uploads/2021/03/ASEAN-Guideline-for-the-C

onduct-of-Bioavailability-and-Bioequivalence-Studies-July-2004.pdf

[38] FDA (1992) Guidance on Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design. Division of Bioequivalence. Office of Generic Drugs, Center for Drug Evaluation Research, Food and Drug Administration, Rockville.

[39] Chen, M., Patnaik, R., Hauck, W.W., Schuirmann, D.J., Hyslop, T. and Williams, R. (2000) An Individual Bioequivalence Criterion: Regulatory Considerations. *Statistics in Medicine*, **19**, 2821-2842. https://doi.org/10.1002/1097-0258(20001030)19:20<2821::aid-sim548>3.3.co;2-c