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Bioequivalence Report

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Pharmacokinetic comparison of two bazedoxifene acetate 20 mg tablet formulations in healthy Korean male volunteers

Ji-Sun Yeun [1], Hye-Su Kan [2], Minyu Lee [3], Namsick Kim [3], Tae-Young Oh [3], Seung-Kwan Nam [3], Yoon Seok Choi [3], In Sun Kwon [1], and Jang Hee Hong [1,4,5,*]

[1]Clinical Trials Center, Chungnam National University Hospital, Daejeon 34134, Korea
[2]Center for Infectious Diseases Control, Korea Centers for Disease Control and Prevention, Cheongju 28159, Korea
[3]Huons Co., Ltd, Seongnam 13486, Korea
[4]Department of Pharmacology, College of Medicine, Chungnam National University, Daejeon 34134, Korea
[5]Department of Medical Science, College of Medicine, Chungnam National University, Daejeon 34134, Korea

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***Correspondence to**
Jang Hee Hong
Departments of Medical Science and Pharmacology, Clinical Trials Center, College of Medicine, Chungnam National University, 99 Daehak-ro, Yuseong-gu, Daejeon 34134, Korea.
E-mail: boniii@cnu.ac.kr

ORCID iDs
Ji-Sun Yeun
https://orcid.org/0000-0003-2902-8368
Hye-Su Kan
https://orcid.org/0000-0003-3583-7049
Minyu Lee
https://orcid.org/0000-0002-4603-8608
Namsick Kim
https://orcid.org/0000-0002-4691-6722
Tae-Young Oh
https://orcid.org/0000-0002-8263-5805
Seung-Kwan Nam
https://orcid.org/0000-0002-8207-5051
Yoon Seok Choi
https://orcid.org/0000-0002-5332-6368
In Sun Kwon
https://orcid.org/0000-0002-1723-436X
Jang Hee Hong
https://orcid.org/0000-0002-0623-5455

ABSTRACT

Bazedoxifene, used as bazedoxifene acetate, is a selective estrogen receptor modulator that selectively affects the uterus, breast tissue, bone metabolism, and lipid metabolism by antagonizing or enhancing estrogens in the estrogen receptor in the tissue. This study was conducted as an open, randomized, two-period, two-treatment, crossover design to compare the pharmacokinetic (PK) characteristics and tolerability of two bazedoxifene tablets when administered to 50 healthy Korean male volunteers. Enrolled subjects were randomly allocated to 2 sequences of a single oral administration of a test drug and a reference drug, or vice versa with a 14-day washout period between the two doses. Serial blood samples were collected over 96 h for PK analysis. Plasma concentration of bazedoxifene was assayed using liquid chromatography-tandem spectrometry mass. Forty-five participants completed the study with no clinically relevant safety issues. The peak concentrations (C_{max}, mean ± strandard deviation) of reference drug and test drug were 3.191 ± 1.080 and 3.231 ± 1.346 ng/mL, respectively, and the areas under the plasma concentration-time curve from 0 to the last measurable concentration (AUC_{last}) were 44.697 ± 21.168 ng•h/mL and 45.902 ± 23.130 ng•h/mL, respectively. The geometric mean ratios of test drug to reference drug and their 90% confidence intervals for C_{max} and AUC_{last} were 0.9913 (0.8828–1.1132) and 1.0106 (0.9345–1.0929), respectively. The incidence of adverse events between the two formulations was similar. The present study showed that PK and tolerability of two bazedoxifene tablet formulations were comparable when administered to healthy Korean male volunteers.

Trial Registration: Clinical Research Information Service Identifier: KCT0003978

Keywords: Bazedoxifene; Bioequivalence; Pharmacokinetics

INTRODUCTION

Bazedoxifene is a third generation selective estrogen receptor modulator that affects uterine and breast tissue, bone metabolism and lipid metabolism by selectively antagonizing or

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Conflict of interest
- Authors: Minyu Lee, Namsick Kim, Tae-Young Oh, Seung-Kwan Nam, and Yoon Seok Choi are employees of HUONS Co., Ltd. The authors have no other potential conflicts of interest to disclose regarding the content of this article.
- Reviewers: Nothing to declare
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enhancing estrogen at the estrogen receptor in the tissue [1-4]. Bazedoxifene has been reported to increase bone density as well as reduce the risk of breast cancer through preclinical and clinical trials [5-7]. Therefore, it is one of the alternative drugs that is attracting attention in terms of patient safety because it can significantly alleviate the side effects of bisphosphonates which are the most frequently prescribed treatments for osteoporosis. Bazedoxifene acetate has four types of crystalline polymorphs including amorphous forms, which are classified by synthesis methods. Reference drugs were prepared using a crystalline form A that has better solubility and bioavailability than other forms. Therefore, the crystalline form A has been the first choice on the market. Avoiding patent issues, test drugs were designed using a crystalline form D that has relatively insufficient properties [8].

However, an innovative and stabilized pharmaceutical composition was expected to show comparable pharmacokinetic (PK) profiles with reference drugs.

In the present study, we aimed to evaluate and compare the PK characteristics and tolerability of two bazedoxifene tablet formations after single-dose in healthy Korean male volunteers under fasting state.

METHODS

Participants

All the volunteers gave their informed consent agreeing to participate before the screening procedure. Healthy Korean male volunteers aged 19–35 years with body mass index of 18.0–30.0 kg/m^2 and weight > 50 kg were screened for enrollment based on medical history, physical examination, vital signs, laboratory tests, and 12-lead electrocardiogram. Volunteers with a history of drug or alcohol abuse and potential users were excluded. Additionally, volunteers with a history of genetic disorders, such as galactose intolerance or Lapp lactase deficiency, were excluded. No one participated in any other clinical trials within 3 months before the first dose of investigational products (IPs) in this trial. Based on previous PK studies of bazedoxifene, the intra-subject variability (ISV) is estimated for $AUC_{0\text{-}t}$ and the peak concentrations (C_{max}) was 27.3% and 34.5%, respectively, when 22.6 mg of Bazedoxifene acetate (20 mg as Bazedoxifene) is administered orally to an adult. Therefore, this study calculates the sample size based on the ISV 34.5%, which is the highest value of the ISV [9,12]. As results, at least 42 subjects were required to detect 80% to 125% equivalence margin between each treatment group with 80% statistical power. Finally, the sample size was determined to 52 subjects with consideration rate of drop-out. The protocol of this study was reviewed and approved by Chungnam National University Hospital Institutional Review Board on September 28, 2017, and all procedures were performed in accordance with the Korean Good Clinical Practice guidelines and the recommendations of the Declaration of Helsinki on biomedical research involving human subjects. The study was also registered at the Clinical Research Information Service (KCT0003978), one of the primary registries of the World Health Organization International Clinical Trials Registry Platform.

Study design

The present study was conducted as a randomized, open-label, single-dose, two-treatment, two-period, two-way crossover study at Clinical Trials Center, Chungnam National University Hospital (Daejeon, Korea). The IPs were reference formulation (VIVIANT(R) tablet 20 mg, Pfizer Ltd., Seoul, Korea), and test formulation (VIVIANT(T) tablet 20 mg, Huons

Ltd., Seongnam, Korea). All subjects were randomly assigned to one of the following two sequences: A (R-T), B (T-R) with a 14-day washout period between dosing periods. The test product or the reference product was orally administered once at a period with 150 mL of water following an overnight fast of at least 10 hours. Blood samples were collected predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours postdose. Concomitant medications were prohibited except for the treatment of adverse events (AEs). For safety, AEs, vital signs, laboratory tests, and physical examinations were performed throughout the study.

Determination of plasma concentration

Blood was collected into EDTA K2 tubes and allowed to stand for 30 min. Each blood sample was then centrifuged for 10 min at 1,910 ×*g* at 4°C, and two aliquots of 1.5 mL plasma were transferred into Eppendorf tubes, frozen, and stored at –70°C until quantification.

Plasma bazedoxifene concentrations were determined using validated ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS, Waters Corp., Milford, MA, USA). An aliquot of the upper organic layer was injected into the UPLC-MS/MS system (MS/MS system, Water XevoTM TQ-S MS, Waters Corp., Manchester, UK). The column used was the Waters ACQUITY UPLC®BEH C18, 1.7 μm (2.1 mm [ID] × 50 mm [L]), and the mobile phase consisted of 0.1% (v/v) formic acid in distilled water, Acetonitrile mixture maintained at 0.4 mL/min. The targets were detected using a multiple reaction monitoring method with positive electrospray ionization, and the MS transitions were 471.15 to 126.00.

The calibration curve for bazedoxifene was linear over the range of 0.05–25 ng/mL ($r^2 > 0.99$) with intraday accuracy: 96.9–111.8%; precision: 3.0–4.5%; interday accuracy: 102.2–112.7%; and precision: 5.7–8.2% [9].

PKs evaluation

The individual plasma concentration-time curves were constructed using Prism 6 for Windows (GraphPad Software, La Jolla, CA, USA). The area under the plasma concentration-time curve from 0 to the last measurable concentration sampling time (AUC_{last}) was calculated by noncompartmental methods using Phoenix WinNonlin version 6.3 (Pharsight Co., Mountain View, CA, USA). The C_{max} and the time to peak plasma concentration after administration (T_{max}) values were directly obtained from the plasma concentration-time curves. AUC_{last} was calculated using a linear trapezoidal method when concentrations are increasing, and a log-linear trapezoidal summation when concentrations are decreasing. From the terminal slope, linear regression was used to estimate the elimination rate constants and to obtain the area under the plasma concentration versus time curve from time 0 to infinity (AUC_{inf}), and the terminal elimination half-life ($t_{1/2}$) was obtained by calculating the ln(2)/terminal elimination constant (λ_z) at the terminal phase of the log-linear plot of the concentration-time curve. To compare the PK profiles of reference drug and test drug, the log-transformed individual C_{max} and AUC_{last} values were analyzed using a mixed-effects analysis of variance. The treatment effects are shown as the geometric mean ratio (GMR; test drug/reference drug) and 90% confidence intervals (90% CIs) [10].

Safety evaluation

Throughout the study, safety was assessed based on AEs, concomitant medications, physical examination, vital signs, clinical laboratory evaluation, and electrocardiograms. AEs were coded with system organ classes and preferred terms. The frequency and severity of AEs in the reference drug and test drug groups were compared using a chi-square or Fisher exact test.

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Statistical analysis

The statistical analysis was performed by using SAS (version 9.3, SAS Institute Inc., Cary, NC, USA). The plasma concentrations below the lower limit of quantification after drug administration were assigned values of zero if collected before C_{max} and were treated as missing values if collected after C_{max}. Descriptive statistics, including mean ± standard deviation (SD), were used to summarize the PK data for the two formulations. To compare the PK profiles of reference drug and test drug, the log-transformed individual C_{max} and AUC_{last} values were analyzed using a mixed-effects analysis of variance. Formulation, sequence, and period were used as fixed effects, and a participant nested within the sequence was used as a random effect. The frequency and severity of AEs in the reference drug and test drug groups were compared using a chi-square or Fisher exact test. T_{max} was compared between the formulations using a signed-rank test, and a distribution-free 90% CI for the median difference was estimated using a Hodges-Lehmann estimator. The two tablet formulations would be considered bioequivalent if the 90% CIs for GMRs were within the range of 0.8 to 1.25.

RESULTS

Subjects

A total of 60 volunteers underwent screening tests, and the 52 volunteers were eligible to enroll in the study. However, 50 volunteers were randomized except for two who withdrew their consent before randomization. Therefore, 50 participants were randomized and included in the safety and PK evaluations. Subsequently, 4 subjects withdrew consent, and 1 subject was eliminated due to the judgment of a clinical researcher. Therefore 45 participants of them administered the study drug during the two periods and completed the study (**Fig. 1**).

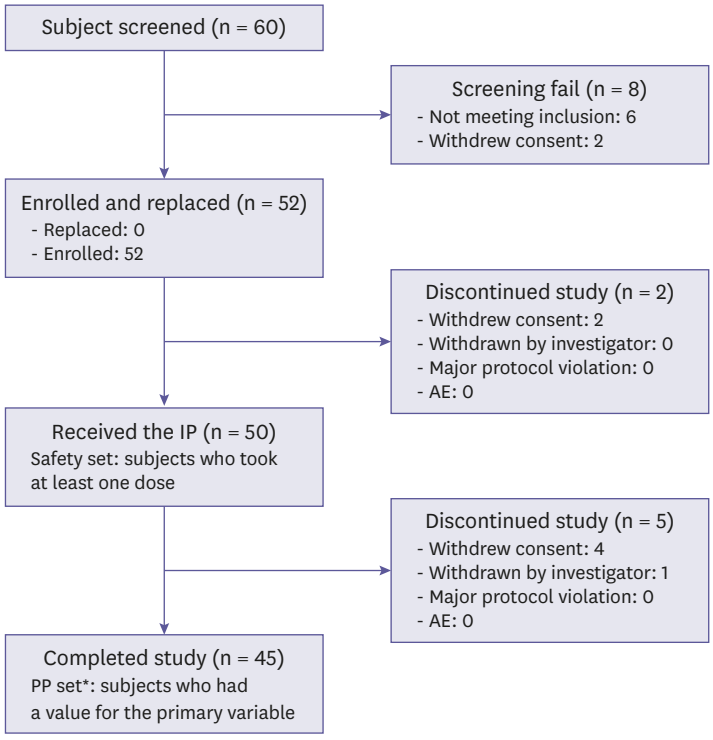

Figure 1. Disposition of the study participants.
IP = investigational products; AE = adverse events; PP = per protocol.
*Per-protocol analysis: analysis of subjects who faithfully adhered to the clinical trial protocol.

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Table 1. Demographic characteristics of the study participants

Characteristics	Group A (n = 25)	Group B (n = 25)	Total (n = 50)	*P* value
Age (yr)	26.0 ± 4.3	25.3 ± 5.4	25.6 ± 4.9	0.233*
Weight (kg)	72.6 ± 7.0	69.9 ± 10.2	72.3 ± 8.8	0.564*
Height (cm)	172.7 ± 4.5	172.9 ± 5.2	172.8 ± 4.8	0.464*
Drinking†				0.684§
Yes	16	14	30	
No	10	10	20	
Smoking†				0.059§
Yes	6	12	18	
No	20	12	32	
Caffeine†				0.139§
Yes	4	9	13	
No	11	6	17	

Values are presented as mean ± standard deviation.
*Mann-Whitney *U* test; †*t* test; §Chi-square test.

Participant demographics including age, height, and weight, and alcohol, nicotine, and caffeine consumption are presented in **Table 1** and were not significantly different between the two groups.

PK analysis

The mean plasma concentration-time profiles for bazedoxifene was shown in **Fig. 2**. The C_{max} (mean ± SD) values for the reference drug and the test drug were 3.191 ± 1.080 ng/mL and 3.231 ± 1.346 ng/mL, respectively, and the corresponding values for AUC_{last} were 44.697 ± 21.168 ng•h/mL and 45.902 ± 23.130 ng•h/mL, respectively (**Table 2**). In the comparison of bazedoxifene PKs, the GMR (test drug/reference drug) of the C_{max} and AUC_{last} were 0.9913, 1.0106, and the 90% CIs were 0.8828–1.1132 and 0.9345–1.0929, respectively. All the confidence intervals of GMRs for C_{max} and AUC_{last} were within the range of 0.8 to 1.25, which is the criterion for bioequivalence (**Table 3**).

Safety evaluation

No serious AEs occurred in this study, and no unexpected AEs that could have influenced the outcome of the study were observed. A total of 8 AEs were reported in 7 subjects after oral administration of any investigational drugs. Severities of the AEs were mild and they are

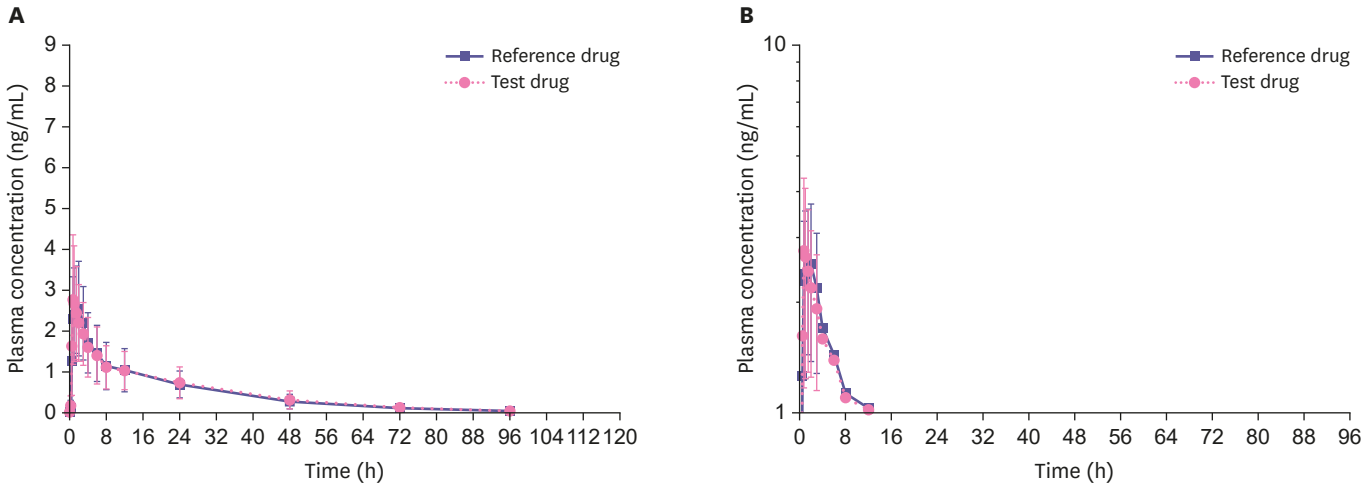

Figure 2. Mean plasma concentration-time profiles of bazedoxifene using (A) linear and (B) log-linear scales.
Reference drug, VIVIANT® tablet, Pfizer Corp., Ltd; test drug, VIVANT tablet, Huons Corp., Ltd.

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Table 2. Summary of PK parameters after a single oral administration of the two formulations of bazedoxifene

PK parameters	Test drug (n = 45)	Reference drug (n = 45)
C_{max} (ng/mL)	3.231 ± 1.346 (33.9)	3.191 ± 1.080 (33.9)
AUC_{last} (ng·h/mL)	45.902 ± 23.130 (50.4)	44.697 ± 21.168 (47.4)
AUC_{inf} (ng·h/mL)	48.910 ± 23.658 (48.4)	46.938 ± 21.809 (46.5)
T_{max}* (h)	1.00 [0.50 to 4.02]	1.50 [0.50 to 6.00]
$t_{1/2}$ (h)	18.6 (43.6)	17.7 (23.3)

Values are presented as the mean (CV%).
PK, pharmacokinetic; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration-time curve to the last sampling time; AUC_{inf}, area under the plasma concentration-time curve to infinity; T_{max}, time to C_{max}; $t_{1/2}$, terminal half-life.
*Median, [min to max].

Table 3. Bioequivalence assessment of PK parameters

PK parameters	Geometric mean ratio (test drug/reference drug)	
	Point estimate	90% confidence interval
C_{max} (ng/mL)	0.9913	0.8828 to 1.1132
AUC_{last} (ng·h/mL)	1.0106	0.9345 to 1.0929

PK, pharmacokinetic; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration-time curve to the last sampling time; AUC_{inf}, area under the plasma concentration-time curve to infinity.

resolved without complication. Any intervention was not required. There were no significant AEs, and there were no differences between the treatment groups according to the test drug and the reference drug. There were no clinically significant changes in the clinical laboratory parameters of the test drug across the two groups. No significant changes were observed in the combination medications, vital signs, ECG, and physical examination findings.

DISCUSSION

The object of the study was to compare the PK parameters and assess the bioequivalence of two formulations of bazedoxifene. A new formulation has been developed and manufactured for different crystal form type D compared to the conventional crystal form type A of bazedoxifene acetate.

In the present study, after single dosing of test drug (a crystal form type D of bazedoxifene acetate), the 90% CIs for GMRs of C_{max} and AUC_{last} satisfied commonly accepted bioequivalence criteria, compared with reference drug (a crystal form type A of bazedoxifene acetate). we showed that the PK characteristics of bazedoxifene were similar between the two drug formulations. The similarity of the drug PK provided evidence of the bioequivalence of the two drug formulations. Our PK results and the safety findings are consistent with those of previous clinical studies. The PK parameters calculated in this study were similar to those of the previous study [11,12].

The blood samples were obtained up to 96h after single dosing. With regard to the percentage of extrapolated AUC (AUC_{extra} %), which is the marker of sufficient duration of evaluation, the AUC_{extra} % of the test and reference drug were 6.05 and 6.17%, respectively. These results imply that the sampling time points were appropriately selected to characterize the absorption and elimination phase of bazedoxifene.

In conclusion, this study found that the PK values for two formulations were within the commonly accepted bioequivalence range of 0.8 to 1.25. reference drugs and test drugs of bazedoxifene acetate were safe and well tolerated. Therefore, it has been proved that test drugs can be used as a treatment and prevention agent for osteoporosis like reference drugs.

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