



Bioequivalence Study of 100-mg Cilostazol Tablets in Healthy Thai Adult Volunteers

Somruedee Chatsiricharoenkul, MD^{1,2}, Yanisorn Nanchaipruek, MD¹,
Patcharaporn Manopinives, MSc (Pharm)², Suparat Atakulreka, MPharm²,
Suvimol Niyomnaitham, MD, PhD^{1,2,*}

¹ Department of Pharmacology, Siriraj Hospital, Mahidol University, Bangkok, Thailand

² Siriraj Clinical Research Center, Siriraj Hospital, Mahidol University, Bangkok, Thailand

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ABSTRACT

Background: Cilostazol is a vasodilator with anticoagulant effect for treatment of peripheral vascular disease. Cilostazol 100-mg tablet was shown to increase walking distance in this patient population.

Objective: The aim of this study was to investigate and compare the pharmacokinetic profiles and safety of Bestazol 100-mg tablet (Berlin Pharmaceutical Industry Co Ltd, Bangkok, Thailand), which is a generic formulation of cilostazol, with the original brand Pletaal 100-mg tablet (Korea Otsuka Pharmaceutical Co Ltd, Seoul, South Korea) in healthy Thai adult volunteers.

Methods: The pharmacokinetic profiles of Bestazol (test) and Pletaal (reference) 100-mg tablets were compared in a single-dose, open-label, 2-treatment, 2-period, 2-sequence, randomized crossover study in healthy Thai adult volunteers. This study was conducted at the Siriraj Clinical Research Center, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Each volunteer was initially treated according to either the test–reference or the reference–test sequence, after which each volunteer was switched to the other study sequence after a 2-week washout period. Pharmacokinetic analysis was performed using log-transformed ratios for C_{max} , AUC_{0-12h} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, and λ_z for both cilostazol and 3,4-dehydro-cilostazol (its active metabolite) with 90% CI. Physical examination, clinical laboratory data, vital signs, and adverse events were assessed in all participants.

Findings: A total of 28 volunteers were included in the final analysis. The ratios of the geometric mean and the 90% CI compared test to reference of cilostazol formulations and were 101.86% (90% CI, 91.88%–112.92%), 107.78% (90% CI, 99.67%–116.56%), and 110.46% (90% CI, 102.68%–118.82%) for C_{max} , AUC_{0-12h} , and $AUC_{0-\infty}$, respectively. The ratios of the geometric mean and the 90% CI compared test to reference of 3,4-dehydro-cilostazol and were 106.72% (95% CI, 95.31%–119.50%), 110.54% (95% CI, 101.92%–119.89%), and 107.37% (95% CI, 96.74%–119.16%) for C_{max} , AUC_{0-12h} , and $AUC_{0-\infty}$, respectively. No significant difference was observed between formulations for T_{max} . The most common adverse event was headache (51.85%), with no significant difference in incidence between the test and reference groups. No serious adverse events related to the studied drugs were reported. The findings of this study indicate these 2 cilostazol tablet formulations to be bioequivalent.

Conclusions: Bestazol 100-mg tablet was bioequivalent to Pletaal 100-mg tablet. Thus, the formulations can be used interchangeably in clinical practice.

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Introduction

Cilostazol, which is a quinolinone derivative, is a cyclic nucleotide phosphodiesterase III inhibitor with the molecular formula $C_{20}H_{27}N_5O_2$. The active compound cilostazol is generally known as 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone.¹ It is a vasodilator with antiplatelet-antithrombotic effects.^{2,3} It was first approved in Japan in 1988, and 50-mg and

* Address correspondence to: Suvimol Niyomnaitham, MD, PhD, Siriraj Hospital Department of Pharmacology, Mahidol University, 2 Wanglang Rd, Srisavarinthira Building 12th Floor, Bangkoknoi, Bangkok 10700, Thailand.

E-mail address: suvimol.niy@mahidol.edu (S. Niyomnaitham).

100-mg tablets have been approved by the US Food and Drug Administration since January 1999 for reduction of intermittent claudication symptoms in patients with peripheral vascular disease.^{1,4–7}

Regarding its pharmacokinetic profile, cilostazol is well absorbed, with C_{max} occurring approximately 3 hours after oral administration. It is strongly protein bound and detectable in plasma for at least 36 hours after administration.^{1,8} Two of its metabolites, 3,4-dehydro-cilostazol (OPC-13015) and 4'-trans-hydroxy-cilostazol (OPC-13213), are identifiable and considered pharmacologically active. Following oral administration of parent drug, 56% of total analytes in plasma were cilostazol and 15% were 3,4-dehydro-cilostazol (4 to 7 times as active as cilostazol). Four percent of total analytes in plasma were 4'-trans-hydroxy-cilostazol only one-fifth as active as cilostazol.¹ Cilostazol has a half-life of approximately 11 hours and its steady state is reached within 4 days. After cilostazol was metabolized, the unchanged form of cilostazol could not be detected in urine.^{8,9} Approximately 30% of the dose is excreted as 4'-trans-hydroxy-cilostazol (OPC-13213) in urine, and <2% is excreted as 3,4-dehydro-cilostazol (OPC-13015).¹

Cilostazol is commonly used in clinical practice for prevention of stent thrombosis, stent restenosis, recurrence of cerebral infarction, and reduction of intermittent claudication symptoms.^{10,11} The Inter-Society Consensus for the Management of Peripheral Arterial Disease II recommends cilostazol as a first-line therapy for symptoms of claudication.¹² Several studies report association between cilostazol and improvement in walking distance in patients with peripheral vascular disease.^{1,5,7} According to the American Heart Association/American College of Cardiology guideline for management of peripheral arterial disease, cilostazol is strongly recommended (level IA recommendation) as an effective therapy to improve claudication symptoms.¹³

Cilostazol is extensively metabolized by liver iso-enzymes (primarily by cytochrome P450 3A4 (CYP3A4), and to some degree by cytochrome P450 2C19 (CYP2C19)) to active metabolite.^{14–16} Significant drug interactions between cilostazol and agents that inhibit cytochrome P450 were observed in a previous study. Accordingly, the dose of cilostazol should be reduced during periods of coadministration with CYP3A4 or CYP2C19 inhibitors.^{15–17} A few side effects of cilostazol administration have been reported, but they are treatable and mainly mild to moderate in intensity. Some commonly reported adverse reactions include headache, diarrhea or abnormal stools, palpitation, tachycardia, arrhythmia, peripheral vascular disorder, dizziness, and eye disorder.^{1,3,7} Among those reported adverse effects, headache is the most common.^{18–20}

Cilostazol has become widely prescribed due to its proven benefits. The aim of this study was to investigate and compare the pharmacokinetic profiles and safety of test¹ versus reference² formulations of cilostazol 100 mg tablets and its main metabolite in healthy Thai adult volunteers.

An original brand name version of cilostazol is Pletaal, and this was used as the reference formulation. A more affordable generic version of the drug would yield greater accessibility to a wider range of patients. Bestazol is a generic version of cilostazol that was used as the test formulation.

Subjects and Methods

Healthy adult volunteers

The healthy Thai adult volunteers who were enrolled in this study were orally administered 100-mg cilostazol at the Siriraj

Clinical Research Center, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Volunteers were aged 18 to 45 years, and all had a body mass index (BMI) within the range of 18.00 to 25.00. All volunteers were in good health as indicated by medical history, comprehensive physical examination, and normal or acceptable results for all performed laboratory screening tests. All female volunteers had a negative urine pregnancy test. All volunteers were evaluated for drugs or supplements that they had taken that could interact with cilostazol or its active metabolite, 3,4-dehydro-cilostazol. Those suspected of taking or of having recently taken any drug that could adversely influence or interact with cilostazol, recent smokers, regular alcohol drinkers, and recent blood donors were excluded. All volunteers provided written informed consent to participate. The study protocol and related material were approved by Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University, Thailand (COA No. Si532/2012). The study was carried out in accordance with the current revision of the Declaration of Helsinki (2008) concerning medical research in humans.

Study design

This was a single-dose, open-label, 2-treatment, 2-period, 2-sequence, randomized crossover bioequivalence study to compare the safety and pharmacokinetic profiles of cilostazol Bestazol 100, a generic tablet formulation of cilostazol, with the original Pletaal 100 tablets. Volunteers were randomly equally divided into 2 groups. Each volunteer was treated initially according to either the test-reference (TR) or the reference-test (RT) sequence, after which each participant was switched to the other study sequence after a 2-week washout period. A single dose of either test or reference product was administered to each volunteer with 240 mL water after fasting for at least 10 hours. A total of 15 blood samples were collected within 1 hour before dosing, and then 0.75, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 24, and 48 hours after dosing. At the screening visit, complete blood count, blood urea nitrogen, creatinine, total bilirubin, aspartate transaminase, alanine aminotransferase, alkaline phosphatase, fasting blood glucose, hepatitis B viral profile, and urinalysis were the laboratory investigations performed in all volunteers. Pregnancy testing was performed in female volunteers at the screening visit and before every drug administration. Vital signs (eg, temperature, respiratory rate, blood pressure, and heart rate) and physical examination were measured before drug administration, at 24 hours and 48 hours after drug administration, and when any adverse events occurred. Standard meals were prepared and served at 4, 8, and 12 hours after drug administration. A 250-mL glass of drinking water was served at 1 and 3 hours after dosing. At 4 hours after dosing, volunteers were allowed to drink regularly. Adverse events were closely monitored and assessed throughout the participation period. Concomitant medications were assessed throughout the study.

Sample size was calculated to yield a power of 80% with an alpha level of 0.05. Assuming the %intrasubject CV for C_{max} and AUC was 25%.^{6,8,18} The 90% CI indicated that a total of 28 participants would be sufficient for the study. To account for possible dropouts, 32 subjects were included in the study.

Given that 3,4-dehydro-cilostazol (OPC-13015) is 4 to 7 times more potent than cilostazol, whereas 4'-trans-hydroxy-cilostazol (OPC-13213) is only 0.2 times as potent as cilostazol. Therefore 4'-trans-hydroxy-cilostazol was not included in the analysis.^{7,8} Plasma concentrations of cilostazol and 3,4-dehydro-cilostazol were determined using a validated LC-MS/MS method at International Bio Service Co Ltd (Nakhon Pathom, Thailand) under the Good Laboratory Practice standard.^{21,22} Validation of this method was performed as recommended by the US Food and Drug Administration.²³ Repaglinide was used as an internal standard in the analysis. The assays of cilostazol and 3,4-dehydro-cilostazol were

¹ Trademark: Bestazol® (Berlin Pharmaceutical Industry Co Ltd, Bangkok, Thailand).

² Trademark: Pletaal® (Korea Otsuka Pharmaceutical Co Ltd, Seoul, South Korea).

Table 1

Precision and accuracy for the analysis of cilostazol and 3,4-dehydro-cilostazol in human plasma.

QC samples	Batch	Intrabatch (n = 6)			Interbatch (n = 3)		
		Mean ng/mL (SD)	Accuracy (%)	Precision (%)	Mean ng/mL (SD)	Accuracy (%)	Precision (%)
Cilostazol LLOQ (5 ng/mL)	1	5.01 (0.11)	100.28	2.12	5.04 (0.15)	100.71	2.91
	2	4.90 (0.16)	98.01	3.29			
	3	5.19 (0.14)	103.83	2.72			
LQC (15 ng/mL)	1	15.62 (0.37)	104.16	2.38	15.51 (0.74)	103.38	4.77
	2	14.72 (0.38)	98.11	2.59			
	3	16.18 (0.48)	107.88	2.95			
MQC (850 ng/mL)	1	909.68 (11.55)	107.02	1.27	905.86 (44.36)	106.57	4.90
	2	859.72 (18.42)	101.14	2.14			
	3	948.20 (18.85)	111.55	1.99			
HQC (1500 ng/mL)	1	1390.74 (60.36)	92.72	4.34	1405.03 (85.49)	93.67	6.08
	2	1327.58 (50.34)	88.51	3.79			
	3	1496.76 (40.69)	99.78	2.72			
3,4-dehydro-cilostazol LLOQ (1 ng/mL)	1	0.96 (0.03)	95.92	3.31	1.00 (0.05)	99.80	4.81
	2	0.98 (0.03)	98.31	2.64			
	3	1.05 (0.02)	105.17	2.36			
LQC (3 ng/mL)	1	3.03 (0.06)	101.05	1.87	3.03 (0.10)	100.88	3.17
	2	2.93 (0.11)	97.61	3.70			
	3	3.12 (0.08)	104.00	2.57			
MQC (175 ng/mL)	1	193.90 (2.48)	110.80	1.28	190.85 (5.21)	109.06	2.73
	2	184.83 (3.70)	105.62	2.00			
	3	193.83 (4.00)	110.76	2.07			
HQC (275 ng/mL)	1	269.06 (10.90)	97.84	4.05	269.30 (8.18)	97.93	3.04
	2	261.24 (8.78)	95.00	3.36			
	3	277.59 (7.44)	100.94	2.68			

HQC = highest quality control; LLOQ, lower limit of quantification; LQC = lowest quality control; MQC = median quality control; QC = quality control.

linear over a range of concentrations of 5 to 1700 ng/mL and 1 to 350 ng/mL, respectively. The coefficient of determination (r^2) was >0.99. Precision was expressed as %CV, whereas accuracy was measured as percent of the nominal value. Both precision and accuracy were acceptable for intrabatch and interbatch assessments in the lower limit of quantification, lowest quality control, median quality control, and highest quality control samples, and the data are presented in Table 1.

If any serious or nonserious adverse events occurred, appropriate standard treatment was given and further investigation was performed, as deemed necessary. Subject withdrawal from the study for his or her own safety was left to the discretion of the investigators.

Analysis

WinNonlin software version 3.1 (Certara LP, Princeton, New Jersey) was used to calculate all pharmacokinetic parameters by non-compartmental methods. The parameters for evaluating bioequivalence were the log-transformed C_{max} and AUC. Other important parameters included in the analysis were λ_z and $t_{1/2}$.

Statistics

Subjects were orally administered 100 mg cilostazol. All safety data were listed and summarized. The 90% CI for the ratios of geometric mean were calculated based on the difference in the log-transformed $AUC_{0-\infty}$, AUC_{0-last} , and C_{max} between the test and reference formulations. The 90% CI of the ratio (Bestazol:Pletaal formulation) of least squares means from ANOVA of the log-transformed $AUC_{0-\infty}$, AUC_{0-last} , and C_{max} for cilostazol and 3,4-dehydro-cilostazol should be between 0.80 and 1.25 (80%–125%).²⁴ This study evaluated each formulation, and 90% CIs were calculated for the geometric mean ratio of Bestazol to Pletaal for $AUC_{0-\infty}$, AUC_{0-last} , and C_{max} using WinNonlin software. Nonparametric Friedman test was performed on T_{max} using Kinetics 2000

Table 2

Demographic characteristics of healthy Thai adult volunteers.

Characteristic	TR group (n = 16)	RT group (n = 16)
Gender*		
Male	10	6
Female	6	10
Age (y) [†]	27.5 (5.9)	32.0 (6.1)
Weight (kg) [†]	60.5 (9.9)	59.2 (12.3)
Height (cm) [†]	166.5 (6.6)	164.5 (10.5)
Body mass index [†]	21.73 (2.19)	21.64 (2.30)

TR = test-reference; RT = reference-test.

* Values are presented as number of healthy adult volunteers.

† Values are presented as mean (SD).

software (Lawrence Livermore National Laboratory, Livermore, California).^{25,26}

Results

Healthy adult volunteers

A total of 32 subjects (16 men and 16 women) were initially enrolled. Volunteers were equally randomized to the TR and RT groups. Four subjects (3 in TR, and 1 in RT) withdrew from the study for personal reasons. There were no significant differences in demographic characteristics between the 2 groups (Table 2). In the TR group (10 men and 6 women), volunteers had a mean age of 27.5 years (range = 19–42 years), and a mean BMI of 21.73 (range = 18.33–25.00) at the time of screening. In the RT group (6 men and 10 women), mean age was 32 years (range = 23–41 years), and mean BMI was 21.64 (range = 18.42–24.98).

Pharmacokinetic parameters

Based on the protocol, only 28 out of 32 subjects whose blood samplings were completed were included for bioequivalence sta-

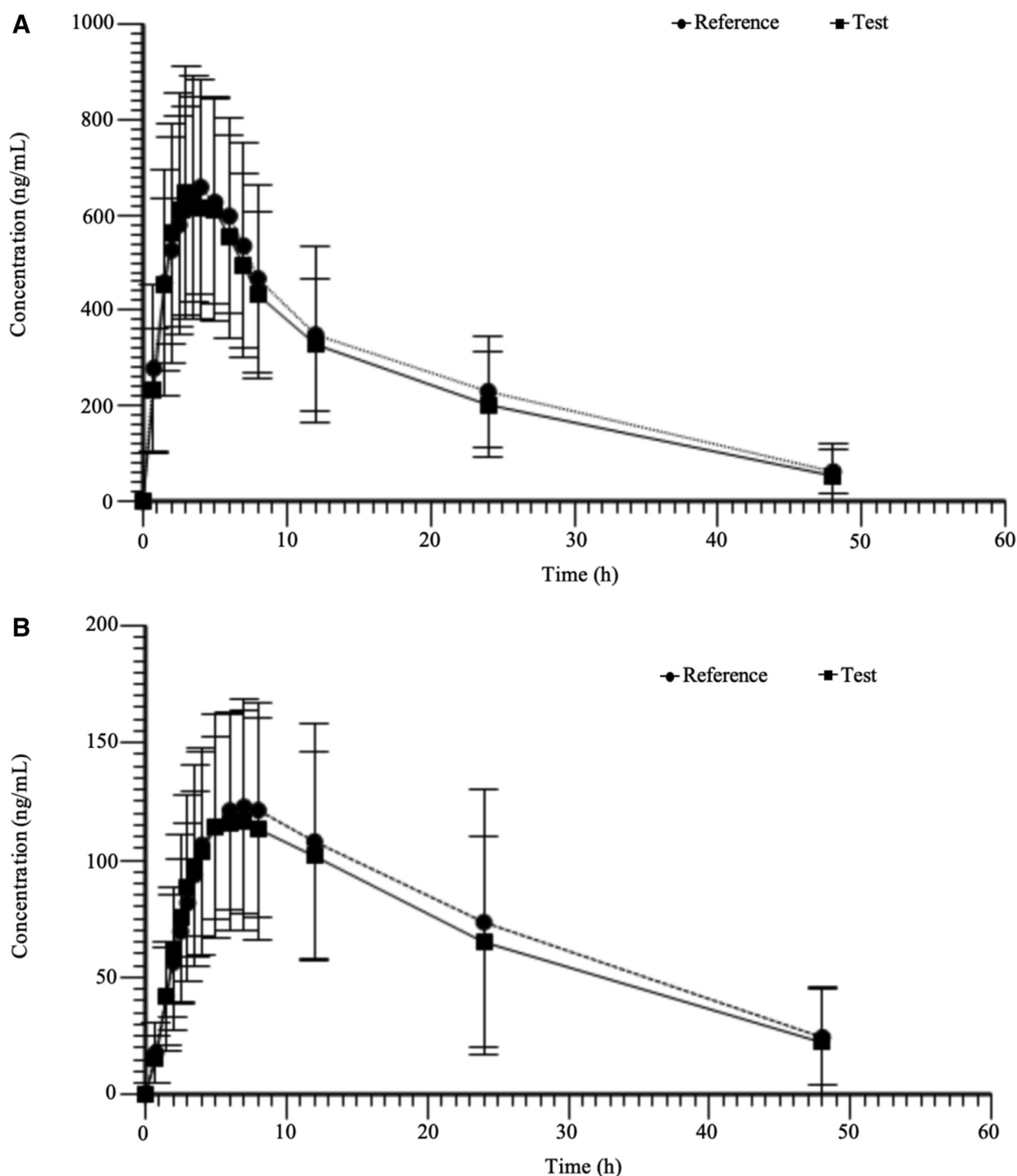


Figure 1. Mean (SD) plasma concentration-time profiles of (A) cilostazol, (B), 3,4-dehydro-cilostazol after single-dose administration of test and reference formulations.

tistical analysis. The mean plasma concentration-time profiles of cilostazol and 3,4-dehydro-cilostazol are shown in Figure 1.

The geometric mean (%) of the 2 formulations of cilostazol were 701 (31.4%) ng/mL and 690 (34.3%) ng/mL for C_{max} ; 11,700 (36.0%) ng/h/mL and 10,900 (38.5%) ng/h/mL for AUC_{0-last} ; 13,724 (38.1%) ng/h/mL and 12,458 (40.0%) ng/h/mL for $AUC_{0-\infty}$ (Bestazol and Pletaal, respectively). Median T_{max} was 4.00 hours for Bestazol formulation, and 3.25 hours for the Pletaal tablet. $t_{1/2}$ was 13.5 hours for Bestazol formulation, and 11.8 hours for Pletaal tablet (Table 3). There are no statistically significant differences of the ratio of

parameters for the C_{max} (90% CI, 0.9188–1.1292), AUC_{0-last} (90% CI, 0.9967–1.1656), and $AUC_{0-\infty}$ (90% CI, 1.0268–1.1882) between products.

The geometric means (%CV) of the 2 formulations of 3,4-dehydro-cilostazol were 131 (37.8%) ng/mL and 124 (42.2%) ng/mL for C_{max} ; 3108 (44.9%) ng/h/mL and 2824 (52.0%) ng/h/mL for AUC_{0-last} ; 3407 (44.9%) ng/h/mL and 3335 (60.8%) ng/h/mL for $AUC_{0-\infty}$ (Bestazol and Pletaal, respectively). Median T_{max} was 7.50 hours for Bestazol formulation, and 6.00 hours for the Pletaal tablet. $t_{1/2}$ was 14.3 hours for Bestazol formulation, and 14.1 hours

Table 3

Comparison of pharmacokinetic parameters duplication for the test* and reference† formulations cilostazol (N = 28).

Parameter	Test	Reference
C _{max} (ng/mL)‡	701 (31.4)	690 (34.3)
AUC _{0–last} (ng/h/mL)‡	11,700 (36.0)	10,900 (38.5)
AUC _{0–∞} (ng/h/mL)‡	13,724 (38.1)	12,458 (40.0)
T _{max} (h)§	4.00 (1.50–7.00)	3.25 (1.50–6.00)
t _{1/2} (h)‡	13.5 (56.9)	11.8 (52.0)
λ _Z (h ^{–1})‡	0.0515 (56.9)	0.0586 (52.0)

λ_Z = terminal rate constant or the slope of the regression line.

* Trademark: Bestazol® (Berlin Pharmaceutical Industry Co Ltd, Bangkok, Thailand).

† Trademark: Pletaal® (Korea Otsuka Pharmaceutical Co Ltd, Seoul, South Korea).

‡ Values presented as mean (%CV).

§ Values are presented as median (range).

Table 4

Comparison of pharmacokinetic parameters for the test* and reference† formulations of 3,4-dehydro-cilostazol (N = 28).

Parameter	Test	Reference
C _{max} (ng/mL)‡	131 (37.8)	124 (42.2)
AUC _{0–last} (ng/h/mL)‡	3108 (44.9)	2824 (52.0)
AUC _{0–∞} (ng/h/mL)‡	3407 (44.9)	3335 (60.8)
T _{max} (h)§	7.50 (3.50–24.0)	6.00 (2.50–24.0)
t _{1/2} (h)‡	14.3 (47.3)	14.1 (59.1)
λ _Z (h ^{–1})‡	0.0486 (47.3)	0.0492 (59.1)

λ_Z = terminal rate constant or the slope of the regression line.

* Trademark: Bestazol® (Berlin Pharmaceutical Industry Co Ltd, Bangkok, Thailand).

† Trademark: Pletaal® Korea Otsuka Pharmaceutical Co Ltd, Seoul, South Korea).

‡ Values presented as mean (%CV).

§ Values are presented as median (range).

Table 5

Point estimates (90% CI) of the log-transformed test/reference ratios of cilostazol (N = 28).

Parameter	Point estimate (90% CI)	Power
C _{max} (ng/mL)	101.86 (91.88–112.92)	97.12
AUC _{0–last} (ng/h/mL)	107.78 (99.67–116.56)	99.80
AUC _{0–∞} (ng/h/mL)	110.46 (102.68–118.82)	99.92

Table 6

Point estimates (90% CI) of the log-transformed test/reference ratios of 3,4-dehydro-cilostazol (N = 28).

Parameter	Point estimate (90% CI)	Power
C _{max} (ng/mL)	106.72 (95.3–119.50)	94.55
AUC _{0–last} (ng/h/mL)	110.54 (101.9–119.89)	99.69
AUC _{0–∞} (ng/h/mL)	107.37 (96.74–119.16)	96.87

for Pletaal tablet (Table 4). There were no statistically significant differences of the ratio of parameters for C_{max} (90% CI, 0.9531–1.1950), AUC_{0–last} (90% CI, 1.0192–1.1989), and AUC_{0–∞} (90% CI, 0.9674–1.1916) between products.

Point estimates and 90% CIs of the log-transformed test/reference ratios of cilostazol and 3,4-dehydro-cilostazol are shown in Tables 5 and 6, respectively.

Safety

Throughout the course of this study, all adverse events were closely observed and monitored. A total of 27 episodes of adverse events were reported by 16 of 32 volunteers (50%). Adverse events that occurred in this study are presented in Table 7. No subject was withdrawn due to adverse events. Headache was the most frequently noted adverse event, followed by dizziness. All of the reported adverse events were mild in intensity.

Table 7

Incidence of adverse events (AEs) for the test* and reference† formulations of cilostazol.

Body system	Reported AE incidence		Total
	Test	Reference	
Central nervous system			
Headache	7	7	14
Dizziness	2	2	4
Drowsiness	1	–	–
Insomnia	–	1	1
Gastrointestinal system			
Nausea	1	1	2
Diarrhea	–	1	1
Abdominal pain with loose stool	1	–	1
Cardiovascular system			
Palpitation	1	–	1
Other organ system			
Dysmenorrhea	–	1	1
Fatigue	–	1	1
Total	13	14	27

* Trademark: Bestazol® (Berlin Pharmaceutical Industry Co Ltd, Bangkok, Thailand).

† Trademark: Pletaal® (Korea Otsuka Pharmaceutical Co Ltd, Seoul, South Korea).

Discussion

Cilostazol, a cyclic nucleotide phosphodiesterase III inhibitor, has been effectively used for treatment of central and peripheral vascular diseases that burden quality of life of patients.^{10–13}

A single-dose, open-label, 2-treatment, 2-period, 2-sequence, randomized crossover bioequivalence study was conducted in 2 groups of Thai healthy adult volunteers, in which there were no significant differences in baseline characteristics between the groups. Although 4 subjects withdrew from the study, a total 28 participants was sufficient for the study at power of 80%. A crossover design was used to reduce confounding covariates and the number of subjects needed. The C_{max}, AUC, and T_{max} of this study showed concordance with previous Asian population studies.^{6,27,28} Based on previously published pharmacokinetic data, the half-life of cilostazol is approximately 11 hours and T_{max} is 3.3 hours.^{2,8} The washout period in this study was 2 weeks, which covered longer than 5 times the half-life of cilostazol. The T_{max} of test and reference drugs was 4 hours and 3.25 hours, respectively, which was not significantly different.

The safety results showed that both formulations were well tolerated. The most common adverse event was headache, similar to previous reports.^{18–20} The analytical method (ie, LC-MS/MS) analyzing the concentrations of both cilostazol and 3,4-dehydro-cilostazol demonstrated good precision and accuracy.

The ratios of C_{max}, AUC_{0–last}, and AUC_{0–∞} for cilostazol and its main metabolite, 3,4-dehydro-cilostazol between test and reference were bioequivalent within the guideline range indicated by the US Food and Drug Administration (0.80–1.25).²⁴ Therefore, the same therapeutic responses are expected from both formulations.

Conclusions

The generic Bestazol 100-mg tablet was bioequivalent to the original Pletaal 100-mg tablet. Thus, the formulations can be used interchangeably in clinical practice.

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Dr Chatsirichaoenkul was responsible for conceptualization, methodology, supervision, project administration, investigation,

formal analysis, and writing the original draft of the manuscript. Dr Nanchaipruek was responsible for investigation, formal analysis, visualization, and review and editing of the manuscript. Drs Manopinives and Atakulreka were responsible for conceptualization, investigation, formal analysis, visualization, and review and editing of the manuscript. Dr Niyomnaitham was responsible for conceptualization, methodology, project administration, formal analysis, review and editing of the manuscript, and funding acquisition.

Conflicts of Interest

Drs Chatsiricharoenkul, Nanchaipruek, Manopinives, Atakulreka, and Niyomnaitham report the receipt of grants from Berlin Pharmaceutical Industry Co Ltd during the conduct of the study. An investigator fee in the amount of \$670 was paid to the team led by Dr Chatsiricharoenkul, but the authors were not compensated to publish.

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The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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