# Bioequivalence Study of Two Formulations of Simvastatin 20 mg Tablet in Healthy Filipino Participants under Fasting Conditions: A Randomized, Open-label, Two-way Crossover Study

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## ABSTRACT

**Objectives.** Bioequivalence studies provide evidence that generic drugs can produce the same blood levels as the innovator, suggesting similar efficacy and safety and indicating interchangeability without the need to titrate dosing. This study aimed to compare the rate and extent of absorption of two simvastatin 20 mg tablets of Pascual Laboratories, Inc. with two Zocor 20 mg tablets of Merck Sharp & Dohme (I.A.) Corp. in healthy Filipinos. The study also monitored the safety and tolerability of the medications, under the same conditions. Proof of bioequivalence is required by FDA Philippines to establish the interchangeability of generic products and their innovators.

**Methods.** Twenty-four healthy participants were administered with a single oral dose of two 20 mg simvastatin tablets under fasting conditions, in a randomized, open-label, blind-endpoint analysis, two-way crossover study, with a washout period of one week. Pharmacokinetic blood sampling was done up to 24 h post-dose. Simvastatin was measured using Liquid Chromatography-Tandem Mass Spectrometry with a validated method. The geometric mean ratios for maximum plasma concentration ($C_{max}$) and area under the plasma-concentration-time curve from time zero to the last observed concentration at time 24 h ($AUC_{0-24}$) were used for bioequivalence.

**Results.** All 24 participants, 12 males and 12 females, completed the study. Mean age was 24.21 years, mean weight was 58.81 kg, and mean BMI was 23.16 kg/m$^2$. The ratios of $C_{max}$ and $AUC_{0-24}$ were 102.17% (90% CI: 89.19-117.03), and 101.29% (90% CI: 86.87-118.10), respectively, and were both within the bioequivalence limits of 80% to 125%. No adverse event was reported and both formulations were well-tolerated.

**Conclusion.** Simvastatin 20 mg tablet of Pascual Laboratories, Inc. and the innovator Zocor 20 mg tablet are bioequivalent. Single two-tablet doses of both products are safe and well tolerated.

*Keywords: bioequivalence study, Simvastatin, HMG-CoA reductase inhibitor*



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## INTRODUCTION

Cardiovascular disease (CVD) remains one of the top causes of mortality in the Philippines,[1] and statin use may help its prevention. While the national health insurance has a benefit package with this intervention, it is relatively new in implementation and members still have to register to avail of this outpatient health service.[2] The high prices of medicines especially innovator brands is still a challenge to statin access.

Government efforts to improve access to medicine include the Universal Health Care Act, Generics Act, Cheaper Medicines Act, and other legislations and programs. Generic medicines are cheaper than innovator drugs but

patients sometimes hesitate to use generics thinking they do not compare to branded drugs.[3] The growing number of generic products made available to consumers has highlighted the need for bioequivalence studies, which provides evidence that generic drugs can produce the same blood levels as the innovator, which in turn suggests similar efficacy and safety. This would show that they are therapeutically equivalent and are interchangeable without the need to titrate dosing.

One of the commonly prescribed statins in the Philippines is simvastatin. It is an oral hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor indicated to help lower cholesterol production and reduce dyslipidemia-associated complications.[4] The drug inhibits the first and rate-limiting step in cholesterol biosynthesis.[4,5] It is available in 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg tablets. The maximum recommended dose is 40 mg/day.[4,6] It is well-absorbed from the gastrointestinal tract (maximum concentration at 1.3-2.4 h) with low bioavailability (5%) due to first-pass metabolism. It is excreted via the feces (60%) and urine (13%).[7] Common adverse effects include headache, myalgia, abdominal pain, constipation, nausea, and upper respiratory infections.[4,6]

Locally, simvastatin products are of different brands and prices, with the generics costing around 23 – 43% of the innovator,[8] illustrating that bioequivalent generics could yield significant savings for patients.

This study was conducted in the Philippines to determine if two 20 mg tablets of the generic simvastatin of Pascual Laboratories, Inc. is bioequivalent to two 20 mg tablets of the reference Zocor of Merck Sharp and Dohme (I.A.) Corp. It also determined and compared the safety and tolerability of single two-tablet doses of both products. Proof of bioequivalence is required by FDA Philippines to establish the interchangeability of generic products and their innovators.

## MATERIALS AND METHODS

### Materials

Test Drug – Simvastatin 20 mg tablet (manufactured by Pascual Laboratories, Inc., Bulacan, Philippines) purchased by Pascual Laboratories, Inc. from Mercury Drug Corporation and supplied to Pharmalytics Corporation, the Contract Research Organization (CRO).

Reference Drug – Zocor 20 mg tablet (manufactured by Merck Sharp & Dohme Ltd. Cramlington, U.K.) purchased by Pascual Laboratories, Inc. from Mercury Drug Corporation and supplied to the CRO.

Other materials are mentioned within the procedure where they were used.

### Study design

This bioequivalence study was a randomized, open-label, blind-endpoint analysis, two-way crossover, single-dose study in healthy Filipino participants under fasting conditions conducted in compliance to the International Conference on Harmonization – Good Clinical Practice (ICH-GCP) Guidelines and the Declaration of Helsinki. The Protocol and Informed Consent Form were reviewed and approved by the Ethics Review Board of the University of the East Ramon Magsaysay Memorial Medical Center, Inc. Research Institute for Health Sciences (UERMMMCI-RIHS) prior to implementation.

The primary objective was to compare the rate and extent of absorption of two 20 mg tablets of the generic simvastatin (Pascual Laboratories, Inc.) and two 20 mg tablets of innovator Zocor (Merck Sharp & Dohme [I.A.] Corp.) as test and reference products, respectively. The secondary objective was to evaluate the safety and tolerability of single two-tablet doses of both products.

Potential recruits from referrals and a pool of healthy volunteers were called or sent a message for screening that was conducted 28 days to 2 days before the first dose of the study drug. Enrolled participants were admitted and confined in the clinical facility of the CRO the day before dosing and were discharged after the last pharmacokinetic (pK) sampling in each treatment period. Participants returned to the facility after seven days for the second treatment period, where the other study drug was administered, and the same procedures were followed as in the first treatment period. Physical examination, hematology and blood chemistry tests, and clinical interview for documentation of adverse events were done for participant safety assessment. Final safety assessments were conducted seven days after the last pK sampling. This study was conducted in July to August 2019.

### Study participants

Twenty-four healthy Filipino participants, 12 males and 12 females, aged 18 to 45 years were enrolled in the study after duly consenting and signing the Informed Consent Form. The following were excluded: potential participants with a history of allergy and/or sensitivity to simvastatin or any HMG-CoA reductase inhibitor; blood pressure of less than 90/60 mm Hg; pulse rate less than 50 bpm; clinically significant cardiovascular, renal, hepatic, endocrine, metabolic, psychiatric, hematological or other abnormalities; current or a history of gastric diseases in the past six months; gastro-intestinal disorders which may impair drug absorption; clinically significant deviation in clinical chemistry and hematology, urinalysis, chest x-ray, and electrocardiogram (ECG); positive pre-study urine drug screen, Hepatitis B, Human Immunodeficiency Virus (HIV), and pregnancy test; use of any drug 10 days prior to and during the study; those who cannot abstain from grapefruit, citrus fruits and food and/or beverages containing caffeine or other xanthines; those who are current smokers or smoking within 10 days prior to the study or alcoholics; and those who participated in a clinical study four weeks prior to the first study visit or with significant illness four weeks before study screening. Sample size was based on a previous published bioequivalence study with two additional participants in case of dropouts.[9]

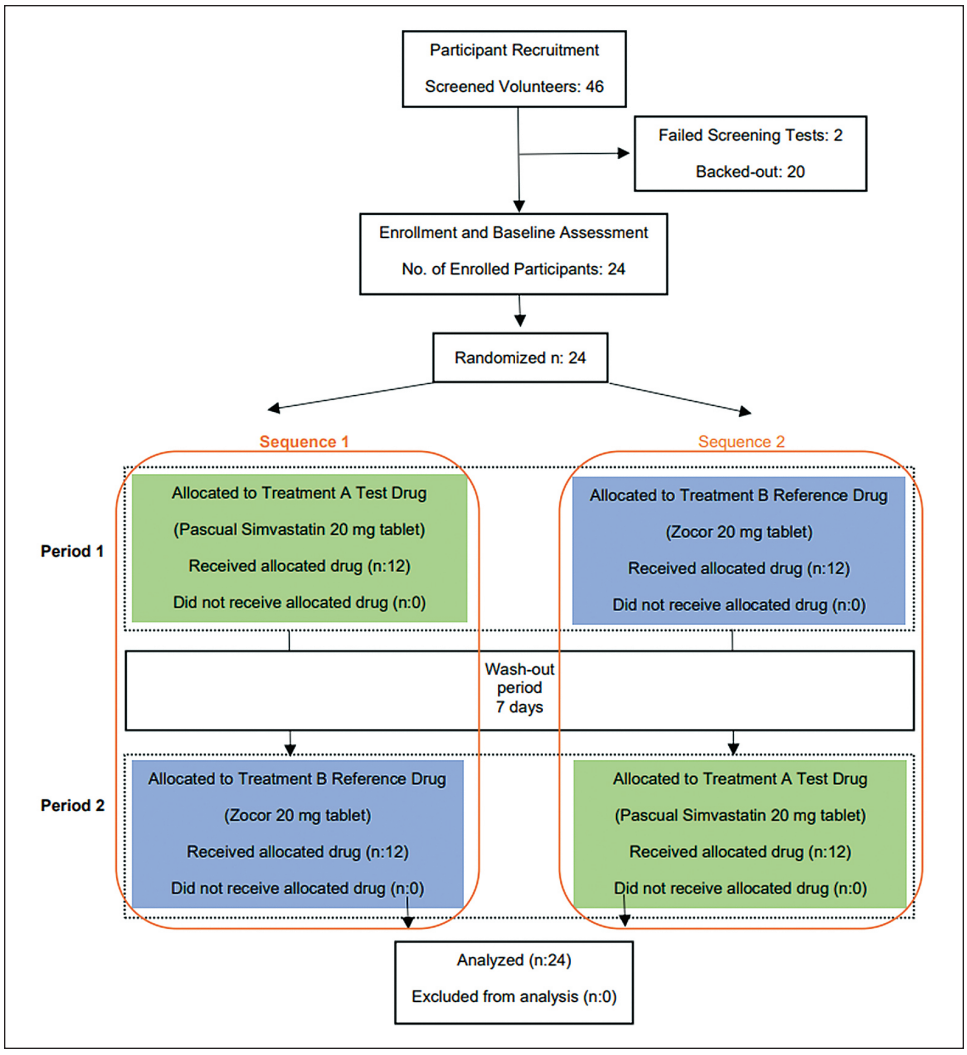


**Figure 1.** Participant flow.

## Randomization and Interventions

Participants under fasted conditions were randomly allocated to two-treatment sequences to receive two 20 mg tablets of either test (n=12) or reference product (n=12) with 240 mL water. Randomization procedure utilized a balanced block design using the program in "Randomization.com". In the first treatment period, Sequence 1 participants were given the Test Drug while Sequence 2 received the Reference Drug. In the second treatment period, they were crossed-over to the other drug, with Sequence 2 participants given the Test Drug and Sequence 1 the Reference Drug (Figure 1). Dosing was two 20 mg tablets per approved Protocol because the validated method for analysis was for 40 mg.

As an open-label study, investigators and participants knew what drugs were given in both treatment groups, which was not expected to bias drug blood levels. However, the pK analysts were blinded to the drug assignment of the samples analyzed to prevent confirmation bias.

## Outcome Measurement

In each treatment period, blood samples were extracted at the following time-points: pre-dose; 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 9.00, 12.00, and 24.00 hours post-dose. Samples were centrifuged within 15 min of collection at approximately 3,000 rpm for 10 minutes at 4°C, then plasma were divided in two aliquots and transferred into identically labelled microcentrifuge tubes and stored upright at -70°C until assayed.

The primary pK parameters were AUC from time zero to the last observed concentration at time 24 h ($AUC_{0-24}$) and maximum plasma concentration ($C_{max}$). Secondary pK parameters were time to maximum plasma concentration ($T_{max}$), AUC from time zero to infinite time ($AUC_{0-inf}$), half-life ($t_{1/2}$), and terminal elimination rate constant ($K_{el}$).

Axis Clinicals Limited (Hyderabad, India) performed the pK analysis using a fully validated Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS; Agilent) technology. Plasma samples were dispensed in tubes and the

internal standard solution was added. The analytical column used was Agilent Eclipse XDB C18, 4.6 X 150 mm, 5 µm. Mobile phase used 0.5 mM Ammonium Acetate Buffer (pH 4.0±0.3): Acetonitrile (20:80), and run time was 6.0 minutes.

The validation conformed to the FDA guideline on "Bioanalytical Method for Human Studies" and EMA's "Guidance on Bioanalytical Method Validation", International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025 requirements.

### Statistical analyses

The pharmacokinetic parameters were statistically analyzed using the Statistical Analysis System (SAS®) software 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive analysis included arithmetic means, geometric means, maximum values, minimum values, standard deviations, and coefficients of variation. Analysis of Variance (ANOVA) was performed on all major pK parameters. The 90% Confidence Intervals (CI) were calculated for $C_{max}$ and $AUC_{0-24}$. The Test/Reference ratios were calculated using the Least Square Means for Ln-transformed $C_{max}$ and $AUC_{0-24}$. Drugs were considered bioequivalent if the 90% CI of ratios for $C_{max}$ and $AUC_{0-24}$ fall within the 80%-125% range.

## RESULTS

### Study Population

Twenty-four healthy Filipino participants, 12 males and 12 females, were enrolled and randomized in the study. All 24 participants completed the study and received two 20 mg tablets of the two simvastatin formulations separated by a 7-day washout period. Mean age was 24.21 years, mean weight was 58.81 kg, and mean BMI was 23.16 kg/m$^2$ (Table 1).

### Pharmacokinetics

AUC of the test and reference formulations were 66.3458 h.ng/mL and 65.5036 h.ng/mL, respectively. $C_{max}$ of test and reference formulations were 15.0180 ng/mL and 14.6996 ng/mL, respectively. Other pharmacokinetic parameters are shown in Table 2. Comparing both formulations, the ratios of log-transformed geometric means for $C_{max}$ (102.17% [90% CI: 89.19-117.03]) and $AUC_{0-24}$ (101.29% [90% CI: 86.87-118.10]) are shown in Table 3. For both $AUC_{0-24}$ and $C_{max}$ the limits of 90% Confidence Interval were within 80% to 125%. The similarity of both formulations is further illustrated by the overlap of their plasma simvastatin concentration-time curves (Figure 2).

### Safety and Tolerability

No clinically relevant or drug-related adverse event or tolerability concern was observed in both treatment periods. There were no clinically significant deviations in vital signs throughout the whole study period. Blood pressure, pulse

**Table 1.** Demographic Characteristics of the Study Participants

| Characteristic | Frequency (Percent) or Value |
|---|---|
| ***Gender*** | |
| Male | 12 (50%) |
| Female | 12 (50%) |
| ***Age (years)*** | |
| Mean ± SD | 24.21±6.04 |
| Range | 18-45 |
| ***Height (cm)*** | |
| Mean ± SD | 159.14±8.58 |
| Range | 145.00-175.30 |
| ***Weight (kg)*** | |
| Mean ± SD | 58.81±9.06 |
| Range | 40.00-79.50 |
| ***BMI (kg/m$^2$)*** | |
| Mean ± SD | 23.16±2.62 |
| Range | 18.50-27.00 |

**Table 2.** Summary of Pharmacokinetic Parameters of Plasma Simvastatin following Two-tablet Oral Doses of Pascual Simvastatin 20 mg Tablet and Zocor 20 mg Tablet

| Parameter (Units) | Pascual Simvastatin 20 mg Tablet (Test) n=24 | Zocor 20 mg Tablet (Reference) n=24 |
|---|---|---|
| $AUC_{0-24}$ *(h.ng/mL)** | 66.3458 | 65.5036 |
| $C_{max}$ *(ng/mL)** | 15.0180 | 14.6996 |
| $T_{max}$ *(h)†* | 2.438 ± 1.6373 | 1.733 ± 1.3120 |
| $T_{1/2}$ *(h)†* | 5.513 ± 2.1354 | 6.723 ± 4.3660 |
| $K_{el}$ *(h)†* | 0.14625 ± 0.060288 | 0.13838 ± 0.071043 |

**Geometric mean – these parameters are analyzed as geometric means in a BE study; †arithmetic mean*

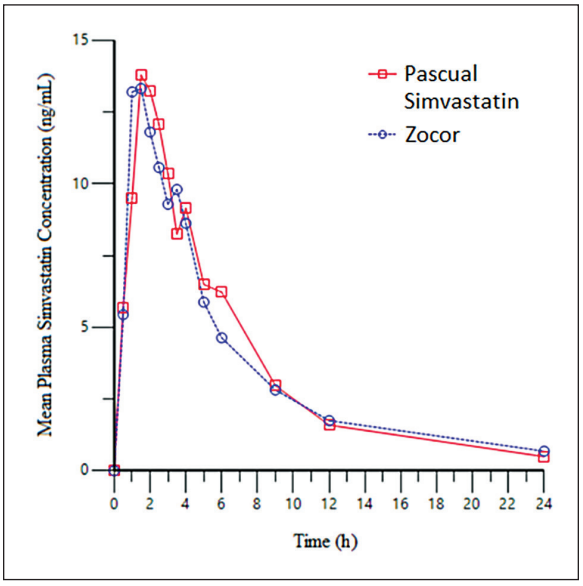


**Figure 2.** Mean plasma concentration vs. time profile of Simvastatin.

**Table 3.** Ratio of the Adjusted Geometric Means and Corresponding 90% Confidence Intervals for Simvastatin Plasma Pharmacokinetic Parameters following Two-tablet Oral Doses of Pascual Simvastatin 20 mg Tablet and Zocor 20 mg Tablet

| Parameters | $L_n$ transformed Data | | | | | |
|---|---|---|---|---|---|---|
| | Geometric Mean | | Ratio% | 90% Confidence Interval | Intra Subject Coefficient of Variation (%) | Power (%) |
| | Pascual Simvastatin | Zocor | | | | |
| ***Ln $C_{max}$*** | 15.0180 | 14.6996 | 102.17 | 89.19-117.03 | 27.9 | 86 |
| ***Ln $AUC_{0-24}$*** | 66.3458 | 65.5036 | 101.29 | 86.87-118.10 | 31.7 | 78 |

rate, respiratory rate, and axillary body temperature remained within normal limits.

## DISCUSSION

Simvastatin is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet and exercise to reduce elevated TC, LDL-C, Apolipoprotein B, TG, and increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia. This could lead to lowering the risk of total mortality by reducing coronary heart disease (CHD) deaths, non-fatal myocardial infarction and stroke, and the need for revascularization procedures in patients at high risk of coronary events.[4, 6,7]

### Pharmacokinetics

#### *Maximum Concentration and Area Under the Curve*

After oral drug administration, the peak plasma drug concentration or $C_{max}$ in this study was 15.0180 ng/mL for the test product and 14.6996 ng/mL for the reference product. These were higher than those reported from studies in Korean volunteers (5.37 ng/mL and 6.21 ng/mL)[9,10], Malaysians (2.61 ng/mL)[11], and Jordanians (3.24 ng/mL)[12]. These studies utilized either two tablets of 20 mg simvastatin or one simvastatin 40 mg tablet. Studies showed increased simvastatin concentration with genetic polymorphism among whites, African Americans, Europeans, and Koreans from as low as 14%-20% elevation to as high as 162%-200% elevation.[13-16]

The total amount of drug that reaches systemic circulation, represented by $AUC_{0-24}$, in this study was 66.3458 h.ng/mL and 65.5036 h.ng/mL for the test and reference products, respectively. This was also higher than that observed in Korean volunteers (28.52 h.ng/mL)[10], Malaysian subjects (10.90 h.ng/mL)[11], and Jordanians (10.18 h.ng/mL and 11.67 h.ng/mL)[12]. Studies also showed increased AUC with genetic polymorphism among Finnish, Chinese, Japanese, and Koreans by as low as 12% elevation to as high as 273% elevation.[13,16-20]

Compared to available studies in normal subjects, $C_{max}$ values obtained in this study were higher by around 3 to 7 times, and $AUC_{0-24}$ was higher by around 3 to 6 times. Although higher simvastatin $C_{max}$ and $AUC_{0-24}$ were also observed with genetic polymorphisms compared to normal subjects in various other nationalities, the elevations observed here were even higher. This may point to the possibility of a genetic polymorphism or a combination of polymorphisms among Filipinos that cause an even slower metabolism of simvastatin compared to other identified polymorphisms. In the absence of genetic polymorphism studies among Filipinos, this hypothesis would be interesting to investigate.

#### *Time to Peak Plasma Concentration*

The time to reach the maximum drug concentration obtained in this study (2.438±1.6373 h and 1.733±1.3120 for test and reference products, respectively) was close to that of prior studies among Koreans (2.23±1.70 h[9] and 1.67 h [median][10]), but higher than in Malaysians (1.33±0.71 h).[11] Normal peak plasma concentrations of both active and total HMG-CoA reductase inhibitors were reported to be attained within 1.3 to 2.4 hours post-dose.[6,7] The $T_{max}$ obtained in this study and in the other cited studies can be reasonably considered within or close to the normal range.

#### *Half-life*

The time wherein the drug concentration is reduced to one half of its original concentration in the plasma in this study was 5.513±2.1354 h for the test product and 6.723±4.3660 h for the reference. It is fairly close to the result of one Korean study at 6.42±5.29 h.[10] However, it is higher than another study on Korean volunteers (2.81±2.80 h)[9], among Malaysian subjects (3.16±1.68 h)[11], and among Jordanians (2.80±0.99 h)[12]. The elimination half-life of simvastatin has been reported as 2 hours.[9] However, some references indicate that half-life can reach up to 5 hours.[21-23] The half-lives obtained for test and reference products in this study tend to be higher than what is usually obtained in other studies, but close to one study. These comparisons suggest that the values obtained here may still actually be in the normal range, although in the upper normal.

#### *Comparison of Test and Reference Products*

This study showed that the 90% confidence interval for ratios of geometric means for primary endpoints, $AUC_{0-24}$ (101.29%) and $C_{max}$ (102.17%) were within the accepted bioequivalence limits of 80 to 125%. The pharmacokinetic parameters for the two formulations showed similarity

in rate and extent of absorption and can be considered therapeutic equivalents, meaning they can be used interchangeably without need for dose titration.

Single two-tablet doses of both simvastatin 20 mg formulations were safe and well tolerated in all participants. It should be noted, however, that adverse effects may be observed in the normal course of maintenance medication which may not be detected with single doses of the drug.

This study illustrates how availability of bioequivalent products could help provide therapeutically equivalent options to consumers which are more affordable. At the time of the study, the Test Drug costs around ₱13 per tablet while the Reference Drug costs more than double at around ₱32. In 2019, a survey studied the availability, prices, and affordability of prescribed medicines in the Philippines, including simvastatin. It showed that lower priced generics of simvastatin are highly available to consumers and more affordable, with the lowest-priced generic costing less than a third of the Innovator and needing less than a day's wage for a month's treatment.[24] Ultimately, this contributes to treatment sustainability which is important in preventing cardiovascular disease morbidity and mortality.

### Limitations of the Study

Being a standard 2x2 crossover design, this study does not provide independent estimates of intra-subject variabilities for the Test Product and Reference Product as each subject received the Test or Reference Product only once. The study could not actually evaluate the efficacy of the Test Drug vs. the Reference Drug but the similar blood levels produced only suggests that they could exert similar effects on patients. Only safety and tolerability of single two-tablet doses of the drugs were observed and the study could not conclude on safety and tolerability of prolonged or maintenance use, which is how this drug is taken by patients.

## CONCLUSIONS

Based on the results of this study, two 20 mg tablets of simvastatin of Pascual Laboratories, Inc. is bioequivalent to two 20 mg tablets of the reference Zocor of Merck Sharp & Dohme (I.A) Corp. The two may be considered therapeutically equivalent and may be used interchangeably without need for dose titration. Single two-tablet doses of both products are safe and well tolerated.

The higher $C_{max}$ and $AUC_{0-24}$ observed in this study compared with other studies may suggest the presence of genetic polymorphisms which is recommended for further investigation.

### Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

### Author Disclosure

Dr. Balaccua and Ms. Aquino are both employees of Pascual Laboratories, Inc.

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