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# Bioequivalence of Omeprazole Delayed-Release Capsules in Healthy Filipino Subjects

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## Abstract

**Study background:** Omeprazole is indicated for the treatment of various acid-related gastrointestinal disorders. It is acid labile and therefore administered orally as enteric-coated granules in capsules.

**Methods:** This randomized, open-label, single dose, two-way cross-over clinical pharmacology study in healthy adult Filipino subjects evaluated the bioequivalence of a new 40 mg delayed-release (enteric-film coated) capsule formulation of omeprazole (Pfizer Inc., US) relative to the reference marketed Losec® capsule (2 x 20 mg; AstraZeneca, Sweden; enteric-coated granules in capsule) under fasted conditions. Pharmacokinetic blood sampling was carried out at various time points for 12 h post-dose and plasma samples were analysed using a fully validated ultra performance liquid chromatography with tandem Mass Spectrometry technology. The primary endpoints were area under plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_{last}$) and maximum plasma concentration ($C_{max}$) for omeprazole.

**Results:** Twenty five subjects (12 females and 13 males; mean age 26 years; mean body mass index 24 kg/m²) completed the study. When administered as one omeprazole 40 mg delayed-release capsule, the ratios of the adjusted geometric means of the primary endpoints, $AUC_{last}$ and $C_{max}$, were contained within the established bioequivalence limits of 80 to 125% compared with two Losec® 20 mg capsules: 100.4% (90% confidence interval: 90.8–110.9%) and 90.4% (90% confidence interval: 81.2–100.6%), respectively. The two omeprazole formulations were well tolerated and no serious adverse event or other significant adverse event was noted.

**Conclusion:** Based on the results of this study in healthy adult Filipino subjects, the new omeprazole 40 mg delayed-release capsule and the established marketed Losec® capsule (2x20 mg) are bioequivalent. Omeprazole 40 mg delayed-release capsule was safe and well tolerated.

**Keywords:** Bioequivalence; Capsule; Losec; Omeprazole; Pharmacokinetics

**Abbreviations:** AE: adverse event; AUC: area under plasma concentration-time curve; $AUC_{extrapolated}$%: area under plasma concentration-time curve extrapolated from time of last quantifiable concentration to infinity as percentage of the total area under concentration-time curve; $AUC_{inf}$: area under plasma concentration-time curve from time zero extrapolated to infinite time; $AUC_{last}$: area under plasma concentration-time curve from time zero to the time of the last quantifiable concentration; $AUC_{last}/AUC_{inf}$: ratio of area under plasma concentration-time curve from time zero to the time of the last quantifiable concentration and area under concentration-time curve from time zero extrapolated to infinite time; BAU: bioavailability Unit; BE: bioequivalence; BMI: body mass index; CI: confidence interval; $C_{max}$: maximum plasma concentration; CV: coefficient of variation; CYP450: cytochrome P450; ECG: electrocardiogram; LLOQ: lower limit of quantification; MRT: mean residence time; PK: pharmacokinetic; $t_{1/2}$: half-life; $T_{max}$: time to maximum plasma concentration; UPLC-MS/MS: ultra performance liquid chromatography with tandem Mass Spectrometry; λz: terminal elimination rate constant

## Introduction

Omeprazole is a lipophilic weak base that is converted to its active protonated form in the highly acidic environment of the intracellular canaliculi within the parietal cells of the stomach [1,2]. It blocks the final step in gastric acid production through specific irreversible inhibition of the gastric proton pump (H+/K+-ATPase) in the parietal cells [1,2]. This provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion.

Omeprazole is indicated for the treatment of gastroesophageal reflux and peptic ulcer disease, as well as for acid aspiration prophylaxis [1-3]. Omeprazole is acid labile and therefore administered orally as enteric-coated granules in capsules [1,2]. Absorption in the small intestine is rapid, with peak plasma concentrations achieved approximately 1–2 h after dosing [4,5]. Bioavailability from a single oral dose of omeprazole is approximately 40%, increasing to 60% after repeated once-daily administration [4,5]. Omeprazole is 97% plasma protein bound and completely metabolized by the hepatic microsomal oxidative system cytochrome P450 (CYP450) enzymes [4,5]. The elimination half-life in plasma is usually <1 h with no omeprazole accumulation

during once-daily administration; almost 80% is excreted as metabolites in the urine with the remainder in the faeces [4,5]. The most common side effects associated with omeprazole treatment are headache, abdominal pain, constipation, diarrhea, flatulence and nausea/vomiting which occur in 1–10% of individuals [4-6].

This article reports the data from a bioequivalence (BE) study conducted in the Philippines to evaluate the bioequivalence of a new delayed-release (enteric-film coated) capsule formulation of omeprazole (Pfizer Inc., US) relative to the reference marketed Losec® capsule (enteric-coated granules in capsule; AstraZeneca, Sweden) [7] at 40 mg under fasting conditions for potential registration application. In consultation with the local regulatory agency, it was deemed acceptable to conduct the study without testing BE of the formulations under fed conditions. The chosen doses of omeprazole (40 mg delayed release capsule as Test treatment and 2x 20 mg Losec® as Reference treatment) are within the prescribed limits used in the treatment of peptic ulcer disease and were approved for use in our study by the local regulatory agency (only 20 mg Losec capsule was available in the local country market).

## Methods

### Study design

This BE study was a randomized, open-label, two-way cross-over, single dose clinical pharmacology study in healthy adult Filipino subjects conducted in a single site in the Philippines (Bioavailability Unit, De La Salle Health Sciences Institute, Dasmariñas, Cavite, Philippines). The primary objective was to determine BE of a 40 mg omeprazole delayed-release capsule formulation (Pfizer Inc., US) to a reference marketed capsule formulation (Losec®; AstraZeneca, Sweden) [7]; a secondary objective was to evaluate the safety and tolerability of omeprazole capsules. Enrolled subjects received either one omeprazole 40 mg delayed-release capsule (Test treatment) with 240 mL water under fasted conditions or two Losec® 20 mg capsules (Reference treatment) administered with 240 mL water under fasted conditions. A wash-out period of at least 7-days separated the two treatment periods.

Screening assessments occurred within 28 days prior to the first dose of study medication. Enrolled subjects were admitted and confined in the Bioavailability Unit (BAU) the day before the first dosing day of each treatment period until the final pharmacokinetic (PK) sampling at the end of each treatment period. Subjects were not confined at the BAU during the wash-out period. All subjects were required to return to the BAU for follow-up at least 7 days after the final PK sampling at the end of the second treatment period. In order to standardize the conditions on PK sampling days, in addition to fasting overnight (i.e., for at least 10 h pre-dose), all subjects were required to refrain from lying down (except when required for blood pressure, pulse rate, and electrocardiogram [ECG] measurements), eating, and drinking beverages other than water during the first 4 h post-dosing. Water was permitted until 1 h prior to study medication administration and 2 h after dosing. Between 2-4 h after dosing, subjects could drink water up to a maximum of 200 mL; water could be consumed without restriction beginning 4 h post-dosing.

Subject safety was monitored throughout by physical examination, recording of vital signs, laboratory test results, and clinical interview for documentation of adverse events (AEs).

The final protocol and informed consent documentation were reviewed and approved by the Independent Ethics Committee at the investigational center participating in the study (De La Salle Health Sciences Institute, Dasmariñas, Cavite, Philippines). The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines.

### Study participants

Healthy Filipino female and male subjects aged 18 to 55 years with a body mass index (BMI) of 17.5 to 30.5 kg/m² and a total body weight >50 kg (110 lbs), who provided informed consent and were willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures, were eligible for enrolment into the study. Subjects were deemed healthy if there were no clinically-relevant abnormalities identified by a detailed medical history, full physical examination (including blood pressure and pulse rate measurement), chest x-ray, 12-lead ECG, and clinical laboratory tests. In addition, pregnancy testing and urine testing for drug abuse was conducted at screening and prior to each treatment period.

Exclusion criteria included: any evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease; history of regular alcohol consumption exceeding 7 drinks per week for females or 14 drinks per week for males (1 drink= 150 mL of wine, or 360 mL of beer, or 45 mL of hard liquor) within 6 months of screening; any condition possibly affecting drug absorption; a positive urine drug screen; use of oral antibiotics within 2 weeks or intravenous antibiotics within 2–3 months of study start; treatment with an investigational drug within 30 days or five half-lives (whichever was longer) prior to the first dose of study medication; use of prescription or non-prescription drugs and dietary supplements within 7 days or 5 half-lives (whichever was longer) prior to the first dose of study medication; intake of herbal supplements, hormonal methods of contraception, and hormone replacement therapy within 28 days prior to the first dose of study medication; intake of Depo-Provera® within 6 months prior to the first dose of study medication; pregnancy/breastfeeding; unwillingness or inability to use acceptable methods of non-hormonal contraception within 14 days prior to the first dose of study medication and for 28 days after the last dose of study medication (if female of childbearing potential); blood donation of approximately 500 mL or more within 56 days prior to dosing; history of sensitivity to the study medications or related substances, or to any of the ingredients used in the study drug formulation; investigational site staff members, relatives of site staff members, or Pfizer employees directly involved in the conduct of the trial.

Restrictions included: no consumption of grapefruit or grapefruit-related citrus fruits (e.g., Seville oranges, pomelos) from 7 days prior to first dose of study treatment and until collection of the final (PK) blood sample; no consumption of any alcohol or caffeine-containing products, or use of tobacco or nicotine-containing products, for 24 h prior to dosing until collection of final PK sample of each study period; no use of oral, transdermal, intrauterine, injected or implanted hormonal methods of contraception for female subjects; male subjects had to use an acceptable method of contraception starting from the first dose of study medication and for at least 28 days after the last dose of the study medication; no strenuous activity was allowed during the study.

### Pharmacokinetic evaluation

In each treatment period, blood samples (10 mL) were collected

via catheter into lithium heparin-containing tubes at the following specified time-points: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h post-dose. After sample collection, plasma specimens were separated from whole blood by centrifugation at approximately 3000 revolutions per min for about 10 min at 4ºC, transferred to polypropylene tubes, and stored frozen within 1 h of collection at –70ºC until assayed. Plasma samples were analysed for omeprazole concentration.

The primary PK parameters were AUC from time zero to the time of the last quantifiable concentration ($AUC_{last}$) and maximum plasma concentration ($C_{max}$) for omeprazole. Secondary PK parameters were time to maximum plasma concentration ($T_{max}$), AUC from time zero extrapolated to infinite time ($AUC_{inf}$), half-life ($t_{1/2}$), terminal elimination rate constant ($\lambda z$), mean residence time (MRT), ratio of $AUC_{last}$ and $AUC_{inf}$ ($AUC_{last}/AUC_{inf}$), and AUC extrapolated from time of last quantifiable concentration to infinity as percentage of the total AUC ($AUC_{extrapolated}$%).

### Analytical methods

PT Equilab International (Jakarta, Indonesia) analyzed plasma samples for omeprazole concentrations using a fully validated ultra performance liquid chromatography with tandem Mass Spectrometry (UPLC-MS/MS; TQD, Waters) technology. Plasma samples were dispensed in appropriate tubes, and then internal standard (rabeprazole, 5 ppm, 20 µL) and methanol organic solvent (99.9%, 500 µL) was added. Following manual shaking, the tubes were centrifuged at 4500 rpm for approximately 10 minutes at room temperature. The supernatants (organic phase) were transferred to microtubes which were centrifuged at 14000 rpm for approximately 5 minutes at room temperature; The 3 µL of this solution was injected into the UPLC-MS/MS system set up with an Acquity C18 column (2.1 x 50 mm, 1.7 µm); 99.9% acetonitrile and 10 mM ammonium acetate pH 6 (60:40 volume/volume) was used as the mobile phase. The mass spectrometer was operated in the positive ionization mode and monitored the transition ions m/z 346.2→198.1 and 360.3 →242.2 for omeprazole and rabeprazole, respectively. The concentration range for the plasma assay ranged from 2.01 to 5000 ng/mL, the lower limit of quantification (LLOQ) was 2.01 ng/mL. Intra-assay coefficients of variation were 7.25%, 3.68% and 3.23% at low (6.03 ng/mL), medium (804 ng/mL) and high (4019 ng/mL) concentrations, while inter-assay coefficient of variation (CV) were 5.43%, 5.86% and 4.68% at low, medium and high concentrations, respectively.

### Statistical analyses

A sample size of 24 completers (12 subjects per sequence) was required to provide at least 99% power that the 90% confidence interval (CI) for the ratio of Test treatment to Reference treatment for $AUC_{last}$ would lie within the acceptance region of 80 to 125%, and 92.6% power that 90% CI for the ratio of Test treatment to Reference treatment for $C_{max}$ would lie within the acceptance region of 80 to 125%. Consequently, this study had at least 90% power overall to demonstrate bioequivalence of the Test treatment to the Reference treatment (i.e., equivalence in both $AUC_{last}$ and $C_{max}$); this estimate was based on the assumption that the true ratio between Test treatment and Reference treatment for both $AUC_{last}$ and $C_{max}$ was 1.02 and within-subject standard deviations of 0.165 and 0.215 for $log_e AUC_{last}$ and $log_e C_{max}$, respectively, based on the average ratio and average within-subject standard deviations from five published studies [8-12].

Natural log transformed $AUC_{inf}$, $AUC_{last}$ and $C_{max}$ of omeprazole were analyzed using a mixed-effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test treatment minus

Reference treatment) and corresponding 90% CIs were exponentiated to provide estimates of the ratio of adjusted geometric means (Test treatment/Reference treatment) and 90% CIs. Bioequivalence was concluded if the 90% CIs for the ratio of adjusted geometric means for both $AUC_{last}$ and $C_{max}$ were completely within the boundaries of 80 to 125%. Descriptive statistics were used to summarize all PK parameters ($AUC_{inf}$, $AUC_{last}$, $C_{max}$, $T_{max}$, $t_{1/2}$, $\lambda z$, MRT, $AUC_{last}/AUC_{inf}$, and $AUC_{extrapolated}$%).

## Results

### Study population

Twenty six Filipino subjects were enrolled and randomized to receive study treatment. All 26 subjects received a 40 mg dose of each of the two omeprazole formulations and were included in the safety analyses. Twenty five subjects completed the study and were included in the PK analyses; one subject was withdrawn after dosing with Losec˚ (Reference) treatment during the second treatment period due to an AE (vomiting). Completed Filipino subjects included 12 females and 13 males, mean age were 26 years (range 18–44 years) and mean BMI was 24 kg/m² (range 18–29 kg/m²).

### Pharmacokinetics

The mean plasma omeprazole concentration–time profiles for both treatment groups are displayed in Figure1a and 1b. Total exposures ($AUC_{last}$ and $AUC_{inf}$) of omeprazole were similar for both formulations: single-dose administration of the 40 mg delayed-release capsule and 40 mg (2 x 20 mg) Losec˚ (Table 1). The mean $C_{max}$ value of omeprazole was slightly higher following administration of the Losec˚ capsule than after the omeprazole delayed-release capsule; absorption of Losec˚ was slightly faster than that of the omeprazole delayed-release capsule with the median time to reach maximal concentrations occurring at 2.5 h and 3.0 h, respectively (Table 1). The mean $t_{1/2}$ values were similar between the two capsule formulations (Test treatment: 1.62 h; Reference treatment: 1.74 h).

Following attainment of $C_{max}$, mean omeprazole plasma concentrations declined in parallel for both formulations. Variability estimates for $AUC_{last}$ and $AUC_{inf}$ were slightly higher for the Losec˚ capsule (CV = 81% and 83%, respectively) than for the delayed-release capsule (CV = 67% and 71%, respectively), but estimates for $C_{max}$ (CV = 45% and 44%, respectively) were similar between both formulations (Table 1). Intra-subject variability estimates for AUClast, AUCinf, and Cmax were 2.49%, 2.54%, and 3.08%, respectively. When administered as one omeprazole 40 mg delayed-release capsule, the ratios of the adjusted geometric means of the primary endpoints, $AUC_{last}$ and $C_{max}$, were 100.4% (90% CI: 90.8-110.9%) and 90.4% (90% CI: 81.2-100.6%), respectively, compared with two 20 mg Losec˚ capsules (Table 2).

The bounds of the 90% CI for the ratios of omeprazole delayed-release capsule/Losec˚ for both exposure estimates ($AUC_{last}$ and $C_{max}$) were within the 80 to 125% range, indicating that the 40 mg omeprazole delayed-release capsule formulation was bioequivalent with the Losec˚ capsule (2x20 mg).

### Adverse events

One subject experienced vomiting 30 min after dosing with Losec˚ in the second treatment period. Since vomiting affects drug absorption and PK profile, the subject was permanently discontinued from the study due to this treatment-emergent AE, which was considered treatment-related by the investigator. The subject remained in the BAU for observation, where blood pressure, pulse rate, respiratory rate
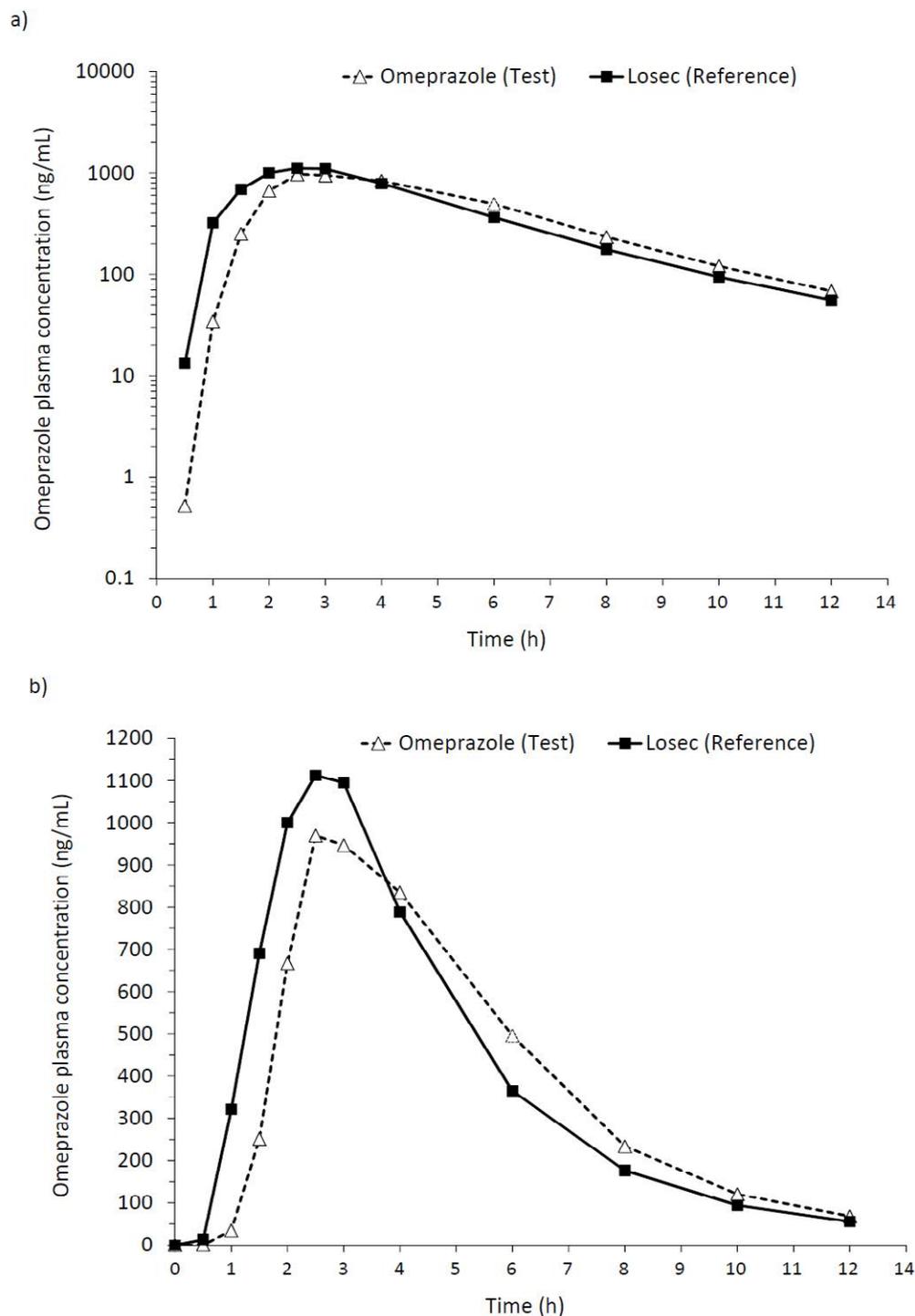
**Figure 1:** Mean plasma omeprazole concentration–time profiles following single oral doses of omeprazole delayed-release capsule formulation (1x40 mg) and Losec® capsule (2x20 mg), a) semi-log plot and b) linear plot.

and oral body temperature were noted to remain within normal limits throughout the observation period. There were no deaths, serious AEs, or dose reductions or temporary discontinuations due to AEs, nor were there any clinically significant abnormalities in laboratory test data, vital signs, or physical examinations. The two omeprazole formulations were safe and well tolerated in this study.

## Discussion

Omeprazole is a widely prescribed proton pump inhibitor used for treating various acid-related gastrointestinal disorders. It is available in an increasing number of formulations and therefore BE information is required to ensure therapeutic equivalence of a new formulation compared with a reference formulation, and is considered one aspect

| Parameter (Units) | Losec® (2 x 20 mg) (Reference treatment) n=25 | Omeprazole 40 mg delayed-release capsule (Test treatment) n=25 |
|---|---|---|
| $AUC_{last}$ (ng*h/mL)[a] | 3866.1 (81) | 3905.0 (67) |
| $AUC_{inf}$ (ng*h/mL)[a] | 3944.2 (83) | 3983.8 (71) |
| $C_{max}$ (ng/mL)[a] | 1339.4 (45) | 1212.0 (44) |
| $T_{max}$ (h)[b] | 2.5 [1.5–4.0] | 3.0 [2.0–6.0] |
| $t_{1/2}$ (h)[c] | 1.74 ± 0.69 (40) | 1.62 ± 0.67 (41) |
| $\lambda z$[c] (1/h) | 0.45 ± 0.15 (34) | 0.49 ± 0.17 (35) |
| MRT[c] | 3.72 ± 0.76 (20) | 4.26 ± 1.01 (24) |
| $AUC_{last}/AUC_{inf}$[c] | 0.98 ± 0.03 (3.5) | 0.97 ± 0.04 (4.2) |
| $AUC_{extrapolated}$%[d] | 2.25 [0.21–14.64] (151) | 2.68 [0.19–15.99] (153) |

[a]Geometric mean (percent coefficient of variation [%CV]); [b]median [range]; [c]arithmetic mean ± standard deviation (%CV); [d]median [range] (%CV).

**Table 1:** Summary of pharmacokinetic parameters of plasma omeprazole following single oral doses of omeprazole 40 mg delayed-release capsule formulation and Losec® capsule (2 x 20 mg).

| Parameter (Units) | Geometric Mean | | Ratio (%)[a] | 90% CI |
|---|---|---|---|---|
| | Losec® (Reference treatment) | Omeprazole (Test treatment) | | |
| $AUC_{last}$ (ng*h/mL) | 3883.6 | 3898.4 | 100.4 | 90.8–110.9 |
| $AUC_{inf}$ (ng*h/mL) | 3976.4 | 4011.3 | 100.9 | 91.1–111.7 |
| $C_{max}$ (ng/mL) | 1346.4 | 1216.5 | 90.4 | 81.2–100.6 |

[a]Ratio of adjusted geometric mean for Test treatment (omeprazole 40 mg delayed-release capsule) versus Reference treatment (2 x Losec® 20 mg capsule).

**Table 2:** Ratio of the adjusted geometric means and associated 90% confidence intervals (CIs) for omeprazole plasma pharmacokinetic parameters following single oral doses of omeprazole 40 mg delayed-release capsule formulation and Losec® capsule (2 x 20 mg).

of product quality since differences in therapeutic equivalence might be reflected in clinical outcome. BE is defined as the absence of a significant difference in the *in vivo* performance between formulations under standardized therapeutic conditions. In general, for regulatory registration purposes, generic formulations require BE studies to determine their use in healthy subjects or patients, in order to provide a link to the performance of the drug product used in clinical trials and thus to the database containing evidence of safety and efficacy.

The primary objective of this study was to establish BE of a new omeprazole delayed-release capsule formulation to the reference marketed Losec® capsule at 40 mg in healthy Filipino subjects under fasted conditions. We showed that the bounds of the 90% CIs for the ratios of adjusted geometric means for the primary exposure comparisons $AUC_{last}$ and $C_{max}$, were contained within the established BE limits of 80 to 125%. Based on these results, the omeprazole 40 mg delayed-release capsule is bioequivalent to the Losec® (2x20 mg) capsule.

Concomitant intake of food significantly reduces rate and extent of omeprazole systemic exposure, and, hence, omeprazole bioavailability is significantly impaired by the presence of food [6]. However, previous pharmacokinetic studies have shown that food intake did not influence the bioavailability of omeprazole (in terms of AUC), when given as an enteric-coated tablet under repeated dosing [13,14]. In consultation with the local regulatory agency in the Philippines, it was deemed acceptable to conduct the present study with the new delayed-release omeprazole capsule only under fasted conditions.

In our study, the total exposures ($AUC_{last}$ and $AUC_{inf}$) of omeprazole were similar for the 40 mg delayed-release capsule and the 40 mg (2

x 20 mg) Losec® capsule, as were the terminal elimination half-lives ($t_{1/2}$). The maximum plasma concentration of omeprazole ($C_{max}$) was slightly higher following administration of the Losec® capsule than after the omeprazole delayed-release capsule; however, absorption (median time to reach maximal concentrations) of Losec® was slightly faster (at 2.5 h) compared with that of the omeprazole delayed-release capsule (at 3.0 h). Similar or slightly different values in PK exposure parameters were reflected in the BE results of the two formulations (omeprazole 40 mg delayed-release capsule versus Losec® 2x20 mg capsule).

No subject in this study receiving the omeprazole delayed-release capsule reported any AEs. Both omeprazole delayed-release and Losec® capsule formulations were safe and well tolerated in healthy volunteers.

## Conclusions

Based on the results of this bioequivalence study in healthy adult Filipino subjects, the new omeprazole 40 mg delayed-release capsule and the established marketed Losec® capsule (2x20 mg) are bioequivalent and may be anticipated to be therapeutically equivalent. Omeprazole 40 mg delayed-release capsule formulation was safe and well tolerated.

### Acknowledgement

### Conflict of Interest

This study was sponsored by Pfizer Inc. All authors are employees of Pfizer Inc, with the exception of R.G Alvero who was the principal investigator for the study, and C. Ernst who was the Clinical Project Manager for the study and an employee of ExecuPharm. ExecuPharm is a paid contractor to Pfizer Inc. in connection with the study. The study sponsor, Pfizer Inc., and the manuscript authors were involved in the writing of the manuscript, and in the decision to submit the manuscript for publication.

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