Clinical Study Report Synopsis	
Drug Substance	Prilosec/Omeprazole
Study Code	D9584C00010
Edition Number	1.0
Date	
NDA Number	19-810

An Open-label, Randomized, Single-center, 4-way Crossover, Single-dose Bioequivalence Study Comparing Omeprazole 20 and 40 mg Aqueous-solvent Based Capsules Manufactured by AstraZeneca with Omeprazole 20 and 40 mg Organic-solvent Based Capsules Manufactured by Merck

Study dates: First subject enrolled: 14 August 2013
Last subject last visit: 15 November 2013

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study center

One study center; .

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Bioequivalence	To demonstrate the bioequivalence of omeprazole 20 mg aqueous-solvent based capsules versus omeprazole 20 mg organic-solvent based capsules	AUC, $AUC_{(0-t)}$, C_{max}
Primary	Bioequivalence	To demonstrate the bioequivalence of omeprazole 40 mg aqueous-solvent based capsules versus omeprazole 40 mg organic-solvent based capsules	AUC, $AUC_{(0-t)}$, C_{max}
Secondary	PK	To evaluate the PK of 2 enteric-coated formulations after a single dose of 20 mg omeprazole	AUC, $AUC_{(0-t)}$, C_{max}, λ_z, $t_{1/2,}$ t_{max}
Secondary	PK	To evaluate the PK of 2 enteric-coated formulations after a single dose of 40 mg omeprazole	AUC, $AUC_{(0-t)}$, C_{max}, λ_z, $t_{1/2,}$ t_{max}
Secondary	Safety	To evaluate the safety and tolerability of omeprazole in subjects	AEs, clinical laboratory parameters, vital signs, 12-lead ECGs, and physical examinations

AEs adverse events; AUC area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0-t)}$ area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration; C_{max} maximum plasma concentration; ECG electrocardiogram; λ_z terminal rate constant; PK pharmacokinetics; $t_{1/2}$ terminal half-life; t_{max} time to reach maximum plasma concentration

Study design

This was an open-label, randomized, single-center, 4-way crossover, single-dose bioequivalence study. The study consisted of 4 treatment periods and a washout period of at least 5 days between each treatment. Subjects participated in a screening period of at most 28 days and were admitted to the study center on Day -1. Subjects were randomized to a treatment sequence predose on Day 1 of Period 1. The subjects received each treatment on

Day 1 and were released on the same day after completion of all procedures. The subjects returned to the study center for a follow-up visit 7 to 10 days after discharge in Period 4.

Each subject received each of the following 4 treatments according to the randomization scheme generated by Quintiles using the AstraZeneca randomization system:

- Treatment A: a single oral dose of omeprazole 20 mg aqueous-solvent based capsules (AstraZeneca)
- Treatment B: a single oral dose of omeprazole 20 mg organic-solvent based capsules (Merck)
- Treatment C: a single oral dose of omeprazole 40 mg aqueous-solvent based capsules (AstraZeneca)
- Treatment D: a single oral dose of omeprazole 40 mg organic-solvent based capsules (Merck)

The subjects were allocated to 1 of 4 treatment sequences according to a William´s Latin Square design for a 4-treatment, 4-period study design. Serial blood samples for PK analysis were collected for 10 hours postdose.

Target subject population and sample size

Approximately 54 healthy male or female subjects aged 18 to 55 years (inclusive), with a body mass index between 18 and 30 kg/m^2 (inclusive) and a weight of at least 50 kg and no more than 100 kg (inclusive) were to be randomized to the study in order to reach 48 completed and evaluable subjects.

Planned: Approximately 54 subjects
Randomized: 54 subjects
Treated: 54 subjects
Completed: 49 subjects

Investigational product and comparator: dosage, mode of administration and batch numbers

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Lot ID	Expiry date
Omeprazole	20 mg aqueous-solvent based capsules	AstraZeneca	MAAB	September 2014
Omeprazole	40 mg aqueous-solvent based capsules	AstraZeneca	KAAB	February 2014
Omeprazole	20 mg organic-solvent based capsules	Merck	H013300	June 2014

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Lot ID	Expiry date
Omeprazole	40 mg organic-solvent based capsules	Merck	J004828	April 2015

Duration of treatment

The 2 different dose levels for both aqueous-solvent based capsules (AstraZeneca) and organic-solvent based (Merck) were investigated in 4 treatment periods (over 2 days each). A washout period of at least 5 days between treatment periods was applicable. Total study duration was approximately 8 weeks.

Statistical methods

The analyses were performed using Standard Operating Procedures and Work Instructions. SAS® Version 9.2 (SAS Institute, Inc., Cary, North Carolina, United States) was used for all analyses and preparation of tables and listings.

All adverse events (AEs) were collected for each subject from the time of investigational medicinal product administration on Day 1 of Period 1 until the follow-up visit. Adverse events that occurred before investigational product administration were included in a listing of all AEs (and clearly identified) but not included in any summary table of AEs. Adverse events were summarized for each dosing regimen by System Organ Class (SOC) and Preferred Term (PT) using medical dictionary for regulatory activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) and AEs that led to withdrawal were made and the number of subjects who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity were summarized.

Where appropriate, tabulations and listings of data for vital signs (blood pressure and pulse rate), clinical laboratory tests, electrocardiograms (ECGs), and physical examination findings were presented. Where applicable, data were summarized for the absolute value at each scheduled assessment, and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each subject were presented with abnormal or out-of-range values flagged.

Pharmacokinetic parameters in plasma were derived using noncompartmental methods with Phoenix® WinNonlin® (Pharsight Corp., Mountain View, California, United States).

Bioequivalence was assessed between Treatments A (test) and B (reference) and between Treatments C (test) and D (reference).

The analyses for omeprazole were performed using a linear mixed-effects analysis of variance model using the natural logarithm of the area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC), area under the plasma concentration-time curve from

time zero to time of the last quantifiable concentration [$AUC_{(0-t)}$], and maximum plasma concentration (C_{max}) as the response variables, sequence, period, treatment as fixed effects, and subject nested within sequence as a random effect. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2-sided 95%) for AUC, $AUC_{(0-t)}$, and C_{max} were estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) were estimated and presented. Also, within- and between coefficient of variation (CVs) plus 90% CIs were calculated and presented. No adjustments were made for multiplicity.

For each omeprazole comparison separately, if the 90% CI for AUC (or $AUC_{(0-t)}$) was entirely contained within 80.00% and 125.00% and the 90% CI for C_{max} was entirely contained within 70.00% and 143.00%, it was concluded that the 2 formulations are bioequivalent. However, the Food and Drug Administration (FDA) Guidance is that for registration purposes the 90% CI for C_{max} must also be entirely contained within the same limits specified above for AUC to be considered bioequivalent. If the 90% CI for AUC or C_{max} is not entirely contained within the above specified bioequivalence limits, it was concluded that the 2 formulations are not bioequivalent.

Subject population

In total, 54 subjects (83.3% males) were randomized into the study of which 49 (90.7%) completed treatment, while 5 (9.3%) were discontinued; 3 (5.6%) subjects were lost to follow-up while 2 (3.7%) subjects were discontinued due to protocol deviations.

Summary of pharmacokinetic results

Geometric mean plasma concentrations following single oral dose administration of omeprazole showed the first mean plasma concentration at 1 hour postdose and a monophasic decline that adequately characterized each treatment's plasma versus concentration profile.

Secondary PK parameters of the terminal rate constant (λ_z), terminal half-life ($t_{1/2}$), and median time to reach maximum plasma concentration (t_{max}) were very similar between all treatments (geometric mean λ_z ranged from 0.641 to 0.767 1/h, geometric mean $t_{1/2}$ ranged from 0.904 to 1.08 hours and median t_{max} ranged from 1.50 to 2.00 hours).

Statistical treatment comparisons of omeprazole following single dose administration between Treatment A omeprazole 20 mg aqueous-solvent based capsules and Treatment B omeprazole 20 mg organic-solvent based capsules the geometric least squares (LS) mean ratio for omeprazole AUC was 111.92% and the 90% CI was 106.39, 117.74 and was completely within the criteria for bioequivalence (90% CI 80.00% to 125.00%). The geometric LS mean ratio for omeprazole C_{max} was 148.71% and the 90% CI was 134.29, 164.69 and was not within the predetermined criteria for bioequivalence (90% CI 70.00% to 143.00%). However, the 90% CI for C_{max} was outside the interval of 80.00% to 125.00%, recommended by the FDA Guidance on bioequivalence.

Between Treatment C (omeprazole 40 mg aqueous-solvent based capsules) and Treatment D (omeprazole 40 mg organic-solvent based capsules) the geometric LS mean ratio for

omeprazole AUC was 108.10% and the 90% CI was 102.8, 113.67 and was completely within the criteria for bioequivalence (90% CI 80.00% to 125.00%). The geometric LS mean ratio for omeprazole C_{max} was 120.60% and the 90% CI was 108.71, 133.79 and was completely within the predetermined criteria for bioequivalence (90% CI 70.00% to 143.00%). However, the 90% CI for C_{max} was outside the interval of 80.00% to 125.00%, recommended by the FDA Guidance on bioequivalence.

Summary of safety results

No deaths, SAEs or withdrawals from the study due to AEs were reported. A total of 11 (20.4%) subjects reported AEs during the study.

Overall, more than 1 subject reported AEs in SOC Gastrointestinal Disorders (5.6%), General Disorders and Administration Site Disorders (3.7%) and Nervous System Disorders (3.7%). Of the 20.4% subjects with at least 1 AE, 16.7% was considered mild and 3.7% moderate.

No AEs were considered to be related to the investigational medicinal product and all events resolved.

No clinically important values or changes were reported for laboratory measurements, vital signs, ECG, physical examination.