AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961S
Study Code	D961SC00001
Edition Number	1
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A Phase I, Open Label, Randomized, Single Center, 2-way Cross-over Bioequivalence Study Comparing D961S (a Fixed-dose Combination Capsule of Esomeprazole 20 mg and Acetylsalicylic Acid 81 mg) with a Free Combination of Esomeprazole Capsule 20 mg+Buffered Acetylsalicylic Acid Tablet 81 mg After Repeated Oral Administration in Japanese Healthy Male Subjects

Study dates:	First subject enrolled: 06 January 2012 Last subject last visit: 10 March 2012
Phase of development:	Clinical pharmacology (I)

Study center

This was a single-center study conducted in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate whether D961S was bioequivalent to a free combination of esomeprazole capsule 20 mg+buffered ASA tablet 81 mg following repeated oral doses, by assessment of area under the plasma concentration versus time curve during the dosing interval (AUC_{τ}) and maximum plasma concentration at steady state ($C_{max,ss}$) of esomeprazole and ASA on Day 5.	AUC_{τ} and $C_{max,ss}$ of esomeprazole and ASA on Day 5	PK
Secondary	**Secondary**	
To evaluate the PK properties of D961S and of a free combination of a esomeprazole capsule 20 mg+buffered ASA tablet 81 mg following a repeated oral dose.	Assessment of $AUC_{0\text{-}t,ss}$, MRT, $t_{max,ss}$, and $t_{1/2,ss}$ of esomeprazole and ASA on Day 5, and AUC_{τ}, $C_{max,ss}$, $AUC_{0\text{-}t,ss}$, MRT, $t_{max,ss}$, and $t_{1/2,ss}$ of salicylic acid on Day 5	PK
To evaluate the safety and tolerability of esomeprazole in combination with ASA by assessment of AEs, clinical laboratory tests, BP, pulse rate, and body temperature.	Assessment of AEs, clinical laboratory tests, blood pressure, pulse rate, and body temperature	Safety

AEs Adverse events; ASA Acetylsalicylic acid; $AUC_{0\text{-}t,ss}$ Area under the plasma concentration time curve from time zero to the last quantifiable time point at steady state; AUC_{τ} Area under the plasma concentration time curve during the dosing interval; BP Blood pressure; $C_{max,ss}$ Maximum plasma concentration at steady state; CSP Clinical study protocol; MRT Mean residence time; PK Pharmacokinetics; $t_{1/2,ss}$ Apparent elimination half life at steady state; $t_{max,\ ss}$ Time to reach $C_{max,ss}$ after dosing at steady state.

Study design

This study was an open-label, randomized, 2-way cross-over study consisting of 2 treatment periods to assess the PK after repeated oral administration of D961S once in the morning (om) on Day 1 to Day 5 or a free combination of esomeprazole capsule 20 mg+buffered Acetylsalicylic acid (ASA) tablet 81 mg on Days 1 to Day 5 in Japanese healthy male subjects.

Target subject population and sample size

The target population included 48 healthy Japanese male subjects between 20 and 45 years of age, classified as homozygote extensive metabolizer (homo-EM) of CYP 2C19, with a Body Mass Index (BMI=weight/height^2) of 19 to 27 kg/m^2 and a body weight of 50 to 85 kg.

Investigational product and comparator(s): Dosage, mode of administration, and batch numbers

D961S: Fixed dose combination capsule for oral use containing Aspirin 81 mg and esomeprazole 20 mg (22.3 mg for esomeprazole magnesium hydrate) provided as a hard gelatine capsule; manufactured by AstraZeneca R&D Sweden, Batch no. 11-002763AZ.

Esomeprazole capsule 20 mg: HPMC capsule containing esomeprazole 20 mg (22.3 mg for esomeprazole magnesium hydrate); manufactured by AstraZeneca R&D Sweden, Batch no. 00410.

Buffered ASA tablet 81 mg: Tablets containing Aspirin 81 mg; manufactured by Lion Corporation, Batch no. 12821.

Duration of treatment

Two treatment periods, each consisting of 5 days, with a wash-out period of at least 14 days between treatment periods.

Statistical methods

- **Pharmacokinetics**

The log-transformed area under the plasma concentration time curve during the dosing interval (AUC_{τ}) and maximum plasma concentration at steady state ($C_{max,ss}$) for esomeprazole, ASA, and Salicylic acid (SA) were analyzed using a linear mixed effect model including factors of treatment, treatment period, and treatment sequence as fixed effect and a factor of subject nested with treatment sequence as random effect in order to compare the PK parameters between the 2 treatments (D961S and free combination of esomeprazole capsule 20 mg+buffered ASA tablet 81 mg).

The results were anti-logarithmized and stated for each of the variables as:

(a) Estimates (geometric means) for the 2 treatments and 95% confidence intervals (CIs) for the geometric means.

(b) Estimates of the ratios (D961S/free combination of esomeprazole capsule 20 mg+buffered ASA tablet 81 mg), 90% CIs for the true ratios.

If the 90% CIs for the ratios of geometric means for AUC_{τ} and $C_{max,ss}$ of esomeprazole and ASA were all contained in the interval of 0.80 to 1.25, then it was to be concluded that the D961S was considered bioequivalent to the free combination of esomeprazole capsule 20 mg+buffered ASA tablet 81 mg.

In addition, other pharmacokinetic parameters ($AUC_{0\text{-}t,ss}$, $t_{1/2,ss}$, and MRT) were analyzed using the above statistical method. The non-log-transformed values of $t_{max,ss}$ for the 2 formulations were summarized using descriptive statistics.

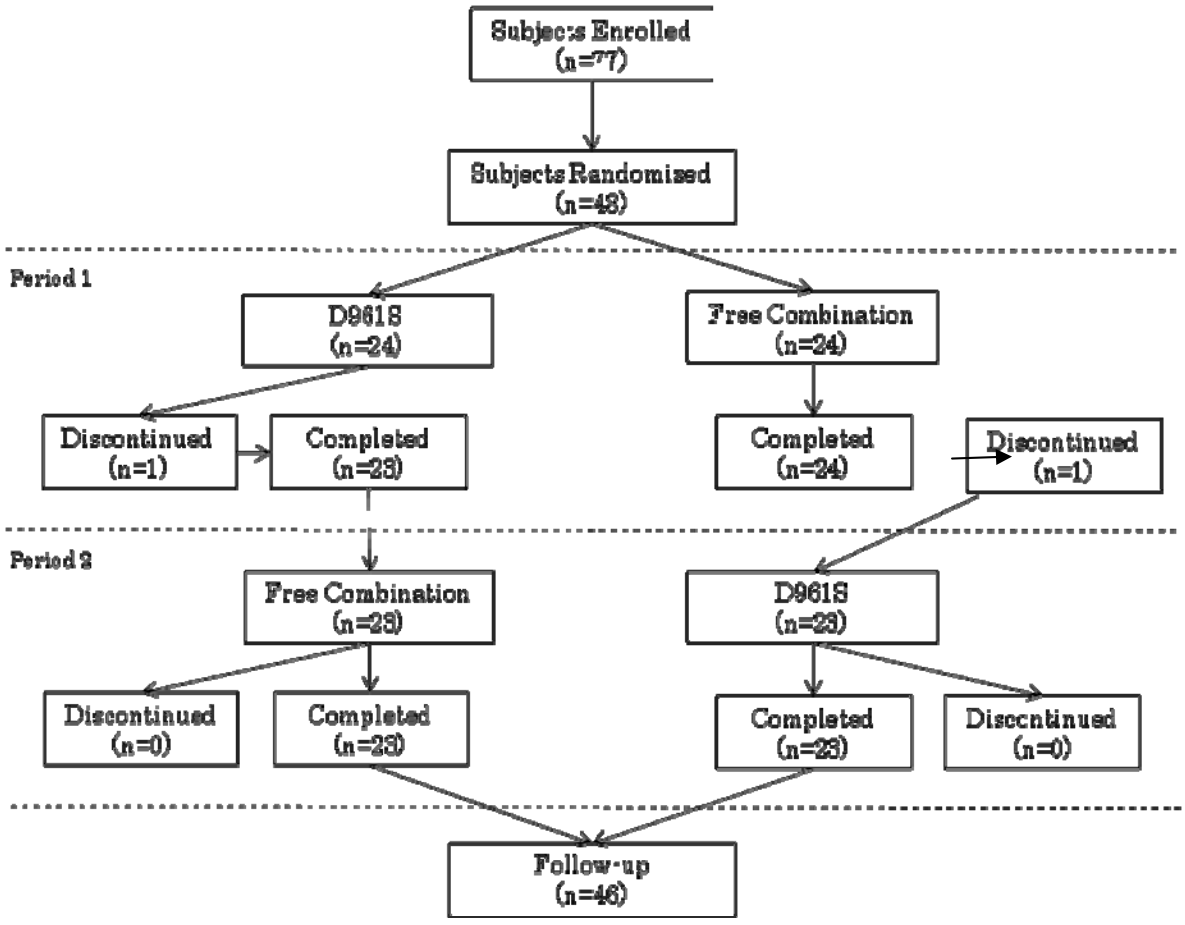
- **Safety**

Adverse events (AEs), laboratory variables, blood pressure, pulse rate, and body temperature were presented descriptively and separately for each treatment (D961S and free combination of esomeprazole capsule 20 mg+buffered ASA tablet 81 mg).

Subject population

A total of 77 Japanese male subjects were enrolled. Of these, 48 subjects were randomized to treatment. The mean age of the subjects randomized was 26.5 years (range: 20 to 44 years), with an average BMI of 22.05 kg/m^2 (range: 19.0 to 25.8 kg/m^2). Two subjects discontinued from the study: 1 due to influenza and 1 due to withdrawal of consent by the subject.
Figure S1 presents a summary of subject disposition.

Figure S1 Subject Disposition



Summary of pharmacokinetic results

PK parameters of esomeprazole, ASA, and SA, and the results of statistical comparisons between treatments, D961S and free combination, are summarized in Table S2.

The 90% CIs on the geometric least-squares mean ratios (treatment of D961S/treatment of free combination of esomeprazole capsule and buffered ASA tablet) for AUC_{τ} of both esomeprazole and ASA were contained in the range of 80 to 125%, but the corresponding values of $C_{max,ss}$ were not filled in the range of 80 to 125% and, thus, the D961S formulation is not bioequivalent to the free combination of esomeprazole capsule and buffered ASA tablet.

The 90% CIs on the geometric least-squares mean ratios (treatment of D961S/treatment of free combination of esomeprazole capsule and buffered ASA tablet) for $AUC_{0\text{-}t,ss}$, MRT, and $t_{1/2,ss}$ of esomeprazole were contained in the range of 80 to 125%. The median of $t_{max,ss}$ of esomeprazole (2.5 hours) was similar for treatment of D961S and treatment of free combination of esomeprazole capsule and buffered ASA tablet.

The 90% CIs on the geometric least-squares mean ratios (treatment of D961S/treatment of free combination of esomeprazole capsule and buffered ASA tablet) for $AUC_{0\text{-}t,ss}$ and $t_{1/2,ss}$ of ASA were contained in the range of 80 to 125%, but the corresponding values of MRT were not filled in the range of 80 to 125%. The median values of $t_{max,ss}$ of ASA for treatment of free combination of esomeprazole capsule and buffered ASA tablet (0.33 hours) were faster than for treatment of D961S (0.50 hours).

The 90% CIs on the geometric least-squares mean ratios (treatment of D961S/treatment of free combination of esomeprazole capsule and buffered ASA tablet) for AUC_{τ}, $AUC_{0\text{-}t,ss}$, MRT, and $t_{1/2,ss}$ of SA were contained in the range of 80 to 125%, but the corresponding value of $C_{max,ss}$ was not filled in the range of 80 to 125%. The median values of $t_{max,ss}$ of SA for treatment of free combination of esomeprazole capsule and buffered ASA tablet (1.00 hours) were faster than for treatment of D961S (1.75 hours).

Table S2 Summary of the results for PK variables using a linear mixed effect model (PK analysis set)

		D961S			Free Combination			Ratio of D961S to Free Combination	
Analyte	**Pharmacokinetic Parameter**	**n**	**LS Mean**	**95% CI**	**n**	**LS Mean**	**95% CI**	**LS Mean**	**90% CI**
Esomeprazole	$AUC_{0\text{-}t,ss}$(µmol-h/L)	46	4.05	3.62, 4.53	47	4.41	3.94, 4.93	0.92	0.88, 0.96
	AUC_{τ} (µmol-h/L)	46	4.12	3.68, 4.61	47	4.47	4.00, 5.00	0.92	0.88, 0.96
	$C_{max,ss}$(µmol/L)	46	1.85	1.68, 2.02	47	2.25	2.05, 2.46	0.82	0.76, 0.89
	MRT (h)	46	3.03	2.80, 3.28	47	3.13	2.90, 3.38	0.97	0.90, 1.05
	$t_{1/2,ss}$ (h)	46	0.98	0.92, 1.06	47	0.99	0.92, 1.06	1.00	0.96, 1.04

Table S2 Summary of the results for PK variables using a linear mixed effect model (PK analysis set)

		D961S			Free Combination			Ratio of D961S to Free Combination	
Analyte	**Pharmacokinetic Parameter**	**n**	**LS Mean**	**95% CI**	**n**	**LS Mean**	**95% CI**	**LS Mean**	**90% CI**
Acetyl Salicylic Acid	$AUC_{0\text{-}t,ss}$(µmol-h/L)	46	5.95	5.53, 6.40	47	5.81	5.40, 6.25	1.02	0.97, 1.08
	AUC_{τ} (µmol-h/L)	46	5.99	5.57, 6.45	47	5.83	5.43, 6.27	1.03	0.97, 1.09
	$C_{max,ss}$(µmol/L)	46	5.05	4.66, 5.48	47	8.24	7.60, 8.92	0.61	0.57, 0.66
	MRT (h)	46	1.15	1.09, 1.22	47	0.73	0.69, 0.77	1.58	1.47, 1.70
	$t_{1/2,ss}$ (h)	46	0.40	0.38, 0.42	47	0.35	0.33, 0.37	1.14	1.07, 1.22
Salicylic Acid	$AUC_{0\text{-}t,ss}$(µmol-h/L)	46	116.89	108.14, 126.34	47	119.76	110.80, 129.44	0.98	0.96, 0.99
	AUC_{τ} (µmol-h/L)	46	122.06	112.60, 132.32	47	124.08	114.47, 134.50	0.98	0.97, 1.00
	$C_{max,ss}$(µmol/L)	46	25.35	24.21, 26.54	47	32.28	30.84, 33.78	0.79	0.75, 0.82
	MRT (h)	46	3.72	3.52, 3.94	47	3.16	2.99, 3.34	1.18	1.15, 1.21
	$t_{1/2,ss}$ (h)	46	2.20	2.03, 2.38	47	2.15	1.99, 2.32	1.02	1.01, 1.04

$AUC_{0\text{-}t,ss}$ Area under the plasma concentration time curve from time zero to the last quantifiable time point at steady state; AUC_{τ} Area under the plasma concentration versus time curve during the dosing interval; CI: Confidence interval; $C_{max,ss}$ Maximum plasma concentration at steady state; LS Mean Least squares mean; MRT Mean residence time; PK Pharmacokinetics; $t_{1/2,ss}$ The apparent elimination half-life at steady state.

Summary of safety results

Table S3 presents the number of subjects who had at least 1 AE in any category for the entire study period**.**

D961S and the free combination of esomeprazole capsule 20 mg+buffered ASA tablet 81 mg were well tolerated in this study. In total, 2 AEs were reported during the study in 2 subjects. Of the 2 subjects, 1 subject reported AE of influenza in the D961S treatment period and other subject reported an AE of upper respiratory tract infection in the free combination treatment period. All the reported AEs were mild in intensity. There were no serious adverse events, deaths, and other adverse events reported in this study. No clinically significant changes in laboratory tests, blood pressure, pulse rate, or body temperature were observed.

Table S3 Number (%) of subjects who had at least 1 AE in any category for entire study period (Safety analysis set)

	Number (%) of Subjects[a]	
	D961S (N=47)	**Free Combination (N=47)**
AE category		
Any AE	2 (4.3)	1[c] (2.1)
Serious AEs leading to death	0 (0.0)	0 (0.0)
Serious AEs not leading to death	0 (0.0)	0 (0.0)
Discontinuation of study due to AEs	1 (2.1)	0 (0.0)
Other significant AEs[b]	0 (0.0)	0 (0.0)
Drug related AEs	0 (0.0)	0 (0.0)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.
[b] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as Other Significant AEs (OAEs).
[c] Subject E0001025 has been counted twice, for each treatment period.
AEs Adverse events; SAEs Serious adverse events.