AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961TC00001
Edition Number	1
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A Phase I, Open-Label, Randomized, Single-Center, 2-Way Cross-over Bioequivalence Study Comparing a Pellets Based Sachet Formulation of D961H 20 mg and a Commercial HPMC Capsule of D961H 20 mg After Repeated Oral Administration in Japanese Healthy Male Subjects

Study dates: First subject enrolled: 14 May 2012
Last subject last visit: 29 June 2012

Phase of development: Clinical pharmacology (I)

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

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 a D961H sachet 20 mg was bioequivalent to a D961H HPMC capsule 20 mg following repeated oral doses	AUC_{τ} and $C_{max,ss}$ of esomeprazole on Study Day 5	PK
Secondary	**Secondary**	
To evaluate the PK properties of a D961H sachet 20 mg and of a D961H HPMC capsule 20 mg following a repeated oral dose	Assessment of $AUC_{0\text{-}t,ss}$, MRT, $t_{max,ss}$, and $t_{1/2,ss}$ of esomeprazole on Study Day 5	PK
To evaluate the safety and tolerability of a D961H sachet 20 mg and D961H HPMC capsule 20 mg	Assessment of adverse events (AEs), clinical laboratory tests, blood pressure, pulse rate and body temperature	Safety

AUC_{τ} Area under the plasma concentration-time curve during the dosing interval; $AUC_{0\text{-}t,ss}$ Area under the plasma concentration-time curve from time zero to the last quantifiable time point at steady state; $C_{max,ss}$ Maximum plasma concentration at steady state; HPMC Hydroxypropyl methylcellulose; MRT Mean residence time; PK Pharmacokinetic; $t_{max,ss}$ Time to reach $C_{max,ss}$ after dosing at steady state; $t_{1/2,ss}$ Apparent elimination half-life at steady state.

Study design

This was an open-label, randomized, 2-way cross-over study, consisting of two 5-day treatment periods to assess the pharmacokinetics (PK) of D961H after repeated oral administration of a D961H sachet 20 mg once in the morning (om) on Study Day 1 to Day 5 or a D961H hydroxypropylmethylcellulose (HPMC) capsule 20 mg om on Study Day 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

D961H sachet 20 mg for oral use containing esomeprazole 20 mg (esomeprazole magnesium trihydrate 22.3 mg) and excipient granules filled into single-use aluminum sachets; manufactured by AstraZeneca AB; Batch no. 12-001234AZ.

D961H HPMC capsule 20 mg for oral use containing esomeprazole 20 mg (esomeprazole magnesium trihydrate 22.3 mg) provided as HPMC capsule; manufactured by AstraZeneca AB; Batch no. 00410.

Duration of treatment

Each subject participated in 2 treatment periods of 5 days each, with a wash-out period of at least 14 days between the 2 treatment periods.

Statistical methods

The log-transformed area under 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 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 (D961H sachet 20 mg and D961H HPMC capsule 20 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 (D961H sachet/D961H HPMC capsule), 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 were all contained in the interval of 0.80 to 1.25, then it was to be concluded that the D961H sachet 20 mg was considered bioequivalent to the D961H HPMC capsule 20 mg.

In addition, other PK parameters (area under the plasma concentration-time curve from time zero to the last quantifiable time point at steady state [$AUC_{0\text{-}t,ss}$], the apparent elimination half-life [$t_{1/2,ss}$], and mean residence time [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.

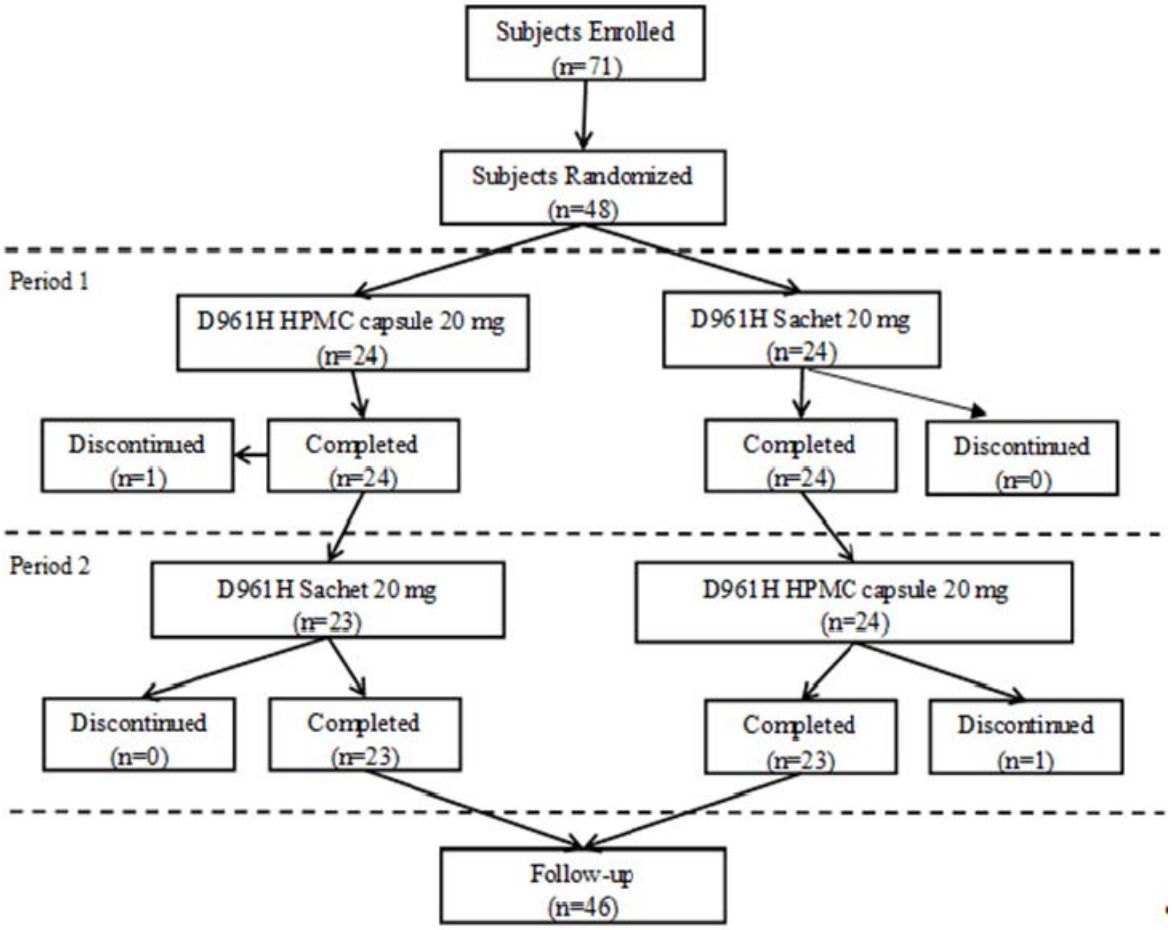
Safety

Adverse events (AEs), laboratory variables, blood pressure (BP), pulse rate, and body temperature were presented descriptively and separately for each treatment (D961H sachet 20 mg and D961H HPMC capsule 20 mg).

Subject population

A total of 71 subjects were enrolled at a single center in Japan. Of these, 48 Japanese male subjects were randomized to treatment. The mean age of the subjects enrolled was 28.3 years (range: 21 to 42 years), with an average BMI of 21.56 kg/m^2 (range: 19.2 to 26.3 kg/m^2). Figure S1 presents a summary of subject disposition.

Figure S1 Subject disposition



Summary of pharmacokinetic results

The geometric least-squares mean ratio (treatment of D961H sachet 20 mg/D961H HPMC capsule 20 mg) for AUC_τ of esomeprazole was 0.89 (90% CI: 0.85 to 0.94), which was contained in the range of 80% to 125% acceptance interval for bioequivalence (BE). However, the corresponding value of $C_{max,ss}$ was 0.82 (90% CI: 0.76 to 0.88), which was not contained in the range of 80% to 125%. Thus, in this study, the BE between D961H sachet 20 mg and D961H HPMC capsule 20 mg was not established according to the BE guideline in Japan.

The 90% CIs on the geometric least-squares mean ratios (treatment of D961H sachet 20 mg/D961H HPMC capsule 20 mg) for $AUC_{0\text{-}t,ss}$, mean residence time (MRT), and apparent elimination half-life ($t_{1/2,ss}$) of esomeprazole were contained in the range of 80% to 125%. The median values for $t_{max,ss}$ of esomeprazole (2.0 hours) were similar between D961H sachet 20 mg and D961H HPMC capsule 20 mg.

PK parameters for esomeprazole and the results of statistical comparisons between treatments (D961H sachet/D961H HPMC capsule) are summarized in Table S2.

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

		D961H Sachet			D961H Capsule			Ratio of D961H Sachet to D961H Capsule	
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)	47	3.93	3.46, 4.46	47	4.39	3.86, 4.98	0.90	0.85, 0.94
	AUC_{τ} (µmol*h/L)	47	3.99	3.52, 4.53	46	4.47	3.93, 5.07	0.89	0.85, 0.94
	$C_{max,ss}$(µmol/L)	47	1.91	1.73, 2.11	47	2.34	2.12, 2.59	0.82	0.76, 0.88
	MRT (h)	47	2.72	2.50, 2.95	47	2.87	2.64, 3.12	0.95	0.87, 1.03
	$t_{1/2,ss}$ (h)	47	0.94	0.86, 1.02	46	0.94	0.87, 1.03	0.99	0.96, 1.03

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

A total of 5 AEs were reported in 5 subjects (4 subjects in D961H sachet 20 mg and 4 subjects in D961H HPMC capsule 20 mg) during the study. There were no deaths, serious AEs, other significant AE or drug-related AEs. One subject (E00001058) discontinued the study due to an AE of tonsillitis during the D961H HPMC capsule 20 mg treatment in Treatment Period 2. No clinically significant changes in laboratory tests, BP, pulse rate, and 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]	
	D961H Sachet (N=47)	D961H Capsule (N=48)
AE category		
Any AE	4 (8.5)	4 (8.3)
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	0 (0.0)	1 (2.1)
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 were counted only once in that category. Subjects with events in more than 1 category were counted once in each of those categories.

[b] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which were of particular clinical importance, were identified, and classified as other significant AEs (OAEs).

AE Adverse event; SAE Serious adverse event.