Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961TC00004
Edition Number	1
Date	

An open label, randomised, single center, 2 way crossover study to assess bioequivalence between a commercial HPMC capsule of D961H 20 mg and a pellets based sachet formulation of D961H 20 mg by pharmacodynamics (intragastric pH) after once-daily repeated oral administration in Japanese healthy male subjects

Study dates: First subject enrolled: 19 Oct. 2013
Last subject last visit: 21 Dec. 2013

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PD	To investigate whether a pellets based sachet formulation of D961H 20 mg (D961H sachet 20 mg) was bioequivalent to a commercial HPMC capsule of D961H 20 mg (D961H HPMC capsule 20 mg) after repeated oral doses by the assessment of percentage of time with intragastric pH>4 during 24 hours after dose on Day 5	The percentage of time with intragastric pH>4 during 24 hours after dose on Day 5
Secondary	PD	To compare a D961H sachet 20 mg with a D961H HPMC capsule 20 mg after repeated oral doses by the assessment of percentage of time with intragastric pH>3 during 24 hours and 24-hour median pH after dose on Day 5	The percentage of time with intragastric pH>3 during 24 hours and 24-hour median intragastric pH after dose on Day 5
	PK	To compare PK properties of a D961H sachet 20 mg with those of D961H HPMC capsule 20 mg after repeated oral doses by the assessment of AUC_{τ}, $C_{max,ss}$, $AUC_{0-t,ss}$, MRT, $t_{max,ss}$, and $t_{1/2,ss}$ of esomeprazole after dose on Day 5	The plasma concentrations of esomeprazole after dose on Day 5 AUC_{τ}, $C_{max,ss}$, $AUC_{0-t,ss}$, MRT, $t_{max,ss}$, and $t_{1/2,ss}$ of esomeprazole after dose on Day 5
	Safety	To evaluate the safety and tolerability of a D961H sachet 20 mg and D961H HPMC capsule 20 mg by the assessment of adverse events, clinical laboratory tests, blood pressure (BP), pulse rate and body temperature	Adverse events, clinical laboratory tests, blood pressure (BP), pulse rate and body temperature

AUC_{τ} Area under the plasma concentration-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; $C_{max,ss}$ Maximum plasma concentration at steady state; HPMC Hydroxypropyl methylcellulose; MRT Mean residence time; PD Pharmacodynamics, 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 separated by a wash-out of at least 14 days to assess the pharmacodynamics (PD) (intragastric pH) and 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 hydroxypropyl methylcellulose (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 34 healthy Japanese male subjects between 20 and 45 years of age, classified as homozygote extensive metabolizer (homo-EM) of CYP 2C19, with *Helicobacter pylori* (*H.pylori*) negative, 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. TAAR.

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. PAAT.

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

PD and PK

The log-transformed PD and PK variables were analysed using a linear mixed effect model which accounts for factors of treatment, treatment period and treatment sequence as fixed effects and a factor of subject nested with the treatment sequence as a random effect.

The results indicated below were obtained for assessing the effects of the two treatments on the PD and PK variables.

- Estimates of geometric means of the variables for the two treatments and 95% confidence intervals (CIs) for the geometric means.
- Estimates of the ratios of the geometric means of the variables for the two treatments (D961H sachet/D961H HPMC capsule) and 90% CIs for the ratios.

Regarding the percentage of time with intragastric pH>4, if the 90% confidence intervals for the ratios of the geometric means for the two treatments were contained in the interval of 0.80-1.25, then it was to be concluded that the Treatment of D961H sachet 20 mg is considered bioequivalent to the Treatment of D961H HPMC capsule 20 mg.

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 41 subjects were enrolled at a single center in Japan. Of these, 34 Japanese male subjects were randomized to treatment. The mean age of the subjects enrolled was 26.4 years (range: 20 to 42 years), with an average BMI of 22.18 kg/m^2 (range: 19.0 to 26.7 kg/m^2). Table S2 presents a summary of subject disposition.

Table S2 Subject disposition

Disposition	Number (%) of subjects		
	D961H Sachet[b]	D961H Capsule[c]	Total
Subjects enrolled[a]	-	-	41
Subjects randomized	17 (100.0)	17 (100.0)	34 (100.0)
Subjects who were not randomized	-	-	7
Study discontinued due to withdrawal by subject	-	-	4
Study discontinued due to screen failure	-	-	2
Study discontinued due to other	-	-	1
Subjects who completed study	17 (100.0)	17 (100.0)	34 (100.0)

a Informed consent received
b Subjects randomized to treatment sequence D961H Sachet / D961H Capsule
c Subjects randomized to treatment sequence D961H Capsule / D961H Sachet
Data derived from Table 11.1.1.

Summary of pharmacodynamic results

Table S3 presents the results of statistical comparisons between treatments for the PD variables.

The geometric mean ratio (treatment of D961H sachet 20 mg/D961H HPMC capsule 20 mg) for percentage of time with intragastric pH>4 during 24 hours after dose on Day 5 was 0.96 (90% CI: 0.85 to 1.07), which was contained in the prespecified range of 0.80 to 1.25. This result demonstrated that the two formulations of D961H are bioequivalent in effects on

intragastric pH. For the percentage of time with intragastric pH>3 during 24 hours and 24-hour median intragastric pH after dose on Day 5, the ratios and their 90%CIs were 0.98 (90% CI : 0.92-1.05) and 0.97 (0.90-1.04), respectively, and the 90%CIs of the two PD variables were also contained in the range of 0.80 to 1.25, demonstrating that the two formulations of D961H are similar in effects on intragastric pH.

Table S3 Summary of analysis of PD variables on day 5 (PD analysis set)

Variables	D961H Sachet 20 mg			D961H Capsule 20 mg			Ratio of D961H Sachet to D961H Capsule	
	n	Estimate	95% CI	n	Estimate	95% CI	Estimate	90% CI
Percentage of time with pH>4 (%)	34	55.37	48.53, 63.18	34	57.96	50.79, 66.13	0.96	0.85, 1.07
Percentage of time with pH>3 (%)	34	70.36	64.71, 76.51	34	71.60	65.85, 77.85	0.98	0.92, 1.05
Median pH	34	4.57	4.22, 4.95	34	4.72	4.36, 5.11	0.97	0.90, 1.04

Note: Linear mixed effect model including factors of treatment, treatment period and treatment sequence as fixed effects and a factor of subject nested with the treatment sequence as random effect.
CI: Confidence Interval; PD; Pharmacodynamics.
Data derived from Table 11.2.2.6.

Summary of pharmacokinetic results

Table S4 presents the results of statistical comparisons between treatments for the PK parameters of esomeprazole.

The ratios (sachet formulation of D961H 20 mg / HPMC capsule of D961H 20 mg) of the geometric means for AUC_{τ}, $AUC_{0\text{-}t,ss}$, $C_{max,ss}$, MRT and $t_{1/2,ss}$ were 0.95 (90% CI : 0.92-0.99), 0.96 (0.93-1.00), 0.91 (0.83-0.99), 0.90 (0.81-1.00) and 0.99 (0.94-1.04), respectively, and the 90% CIs of the PK variables were contained in the range of 0.80-1.25, demonstrating that the two formulations of D961H are similar in effects on PK.

Table S4 Summary of analysis of PK variables on day 5 (PK analysis set)

PK variables (unit)	D961H Sachet 20 mg			D961H Capsule 20 mg			Ratio of D961H Sachet to D961H Capsule	
	n	Estimate	95% CI	n	Estimate	95% CI	Estimate	90% CI
AUC_{τ} (µmol·h/L)	34	4.50	3.76, 5.38	33	4.71	3.94, 5.63	0.95	0.92, 0.99
$AUC_{0\text{-}t,ss}$ (µmol·h/L)	34	4.43	3.70, 5.31	34	4.61	3.85, 5.53	0.96	0.93, 1.00
$C_{max,ss}$ (µmol/L)	34	2.06	1.80, 2.35	34	2.27	1.99, 2.60	0.91	0.83, 0.99
MRT (h)	34	2.71	2.46, 2.99	33	3.02	2.73, 3.33	0.90	0.81, 1.00
$t_{1/2,ss}$ (h)	34	1.03	0.93, 1.14	33	1.04	0.94, 1.15	0.99	0.94, 1.04

Note: Linear mixed effect model including factors of treatment, treatment period and treatment sequence as fixed effects and a factor of subject nested with the treatment sequence as random effect.
AUC_{τ} Area under the plasma concentration versus 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; CI Confidence interval; $C_{max,ss}$ Maximum plasma concentration at steady state; MRT Mean residence time; PK Pharmacokinetics; $t_{1/2,ss}$ Apparent elimination half-life at steady state.
Data derived from Table 11.2.1.5.

Summary of safety results

There were no AEs, deaths, serious AEs, discontinuation of study due to AEs, other significant AE or drug-related AEs. No clinically significant changes in laboratory tests, BP, pulse rate, and body temperature were observed.