AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961HC00009
Edition Number	1
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A randomised, single blind, two-way cross-over, single-centre study to assess the pharmacodynamics (intragastric pH) and pharmacokinetics after repeated oral administration of D961H 10 mg and omeprazole 10 mg in Japanese healthy male subjects

Study dates: First subject enrolled: 20 July 2010
Last subject last visit: 6 September 2010

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This study was conducted at Sumida Hospital, Medical Co. LTA in Japan. The first subject was enrolled on 20 July 2010 and the last subject completed on 6 September 2010.

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
Primary	
To assess the pharmacodynamics (intragastric pH) after repeated oral administration of D961H 10 mg, and omeprazole 10 mg in Japanese healthy male subjects who are classified by the genotype of CYP2C19 by the assessment of the 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 at pre-entry and after dose on day 5
Secondary	
1. To assess the pharmacodynamics (intragastric pH) after repeated oral administration of D961H 10 mg, and omeprazole 10 mg in Japanese healthy male subjects who are classified by the genotype of CYP2C19 by the assessment of the percentage of time with intragastric pH>3 during 24 hours and 24-hour median intragastric pH after dose on day 5	The percentage of time with intragastric pH>3 during 24 hours and 24-hour median intragastric pH at pre-entry and after dose on day 5
2. To assess the pharmacodynamics (intragastric pH) after repeated oral administration of D961H 10 mg, and omeprazole 10 mg in Japanese healthy male subjects who are classified by genotype of CYP2C19 by assessment of the percentages of time with intragastric pH>4 and pH>3, and median intragastric pH during the periods 0-12 hours and 12-24 hours after dose on day 5.	The percentages of time with intragastric pH>4 and pH>3, and median intragastric pH during the periods 0-12 hours and 12-24 hours after dose on day 5
3. To assess the pharmacokinetics after repeated oral administration of D961H 10 mg, and omeprazole 10 mg in Japanese healthy male subjects who are classified by the genotype of CYP2C19 by the assessment of the plasma concentrations, and AUC_t, AUC_τ, $C_{ss,max}$, t_{max}, and $t_{1/2}$ for D961H and omeprazole, after 10 mg doses of each compound on day 5.	The plasma concentrations of D961H and omeprazole after dose on day 5 AUC_t, AUC_τ, $C_{ss,max}$, t_{max}, $t_{½}$ for D961H and omeprazole after dose on day 5
4. To assess the safety and the tolerability after repeated oral administration of D961H 10 mg, and omeprazole 10 mg in Japanese healthy male subjects who are classified by the genotype of CYP2C19 by the assessment of adverse events, laboratory variables, pulse rate, blood pressure, body temperature and 12-lead ECG.	Adverse events, laboratory tests (clinical chemistry, haematology and urinalysis), ECG and vital signs (blood pressure, pulse rate, body temperature)

Study design

This study was carried out as a randomised, single-blind, two-way cross-over study consisting of two treatment periods separated by a wash-out of at least 14 days in Japanese healthy male subjects. The subjects were enrolled and randomised according to the genotype of CYP2C19.

Target subject population and sample size

In total, 42 Japanese healthy male subjects between 20 and 45 years of age:
14 homozygote extensive metabolisers (homo-EMs), 14 heterozygote extensive metabolisers (hetero-EMs) and 14 poor metabolisers (PMs) of the CYP2C19 genotype.

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

The following investigational products were supplied:

- D961H capsule 10 mg (batch number: 10-002787AZ)
- D961H capsule placebo (batch number: 09-004155AZ)
- omeprazole tablet 10 mg (batch number: 22000)
- omeprazole tablet placebo (batch number: 020010)

D961H capsule 10 mg or omeprazole tablet 10 mg were given once daily for 5 days. The placebo for D961H capsule or omeprazole tablet was given simultaneously as the double dummy.

Duration of treatment

Each subject took part in two treatment periods separated by a wash-out period of at least 14 days, and received either D961H 10 mg or omeprazole 10 mg once daily for 5 days in each treatment period.

Statistical methods

Pharmacodynamics: The mean differences of the percentage of time with pH>4 and pH>3, and the median intragastric pH during the periods 0-24, 0-12 and 12-24 hours between D961H 10 mg and omeprazole 10 mg with their two-sided 95% confidence intervals were estimated by using a mixed-effect ANCOVA model in consideration of the effect of CYP2C19 genotype on the pharmacodynamic profile of D961H and omeprazole.

Pharmacokinetics: The ratios of geometric means of AUC_t, AUC_τ, and $C_{ss,max}$, between D961H 10 mg and omeprazole 10 mg with their two-sided 95% confidence intervals were estimated by using a mixed-effect ANOVA model in consideration of the effect of CYP2C19 genotypes on the pharmacokinetic profile of D961H and omeprazole.

Safety: Adverse events, laboratory variables, ECG and vital signs were presented descriptively and separately for each treatment.

Subject population

Of 123 subjects enrolled, 42 subjects were randomised. Each subject took part in two treatment periods, and received either D961H 10 mg or omeprazole 10 mg once daily for 5 days in each treatment period. No subjects discontinued this study. There were no protocol deviations in this study. Demography and baseline characteristics were well balanced among the genotypes of CYP2C19.

Table S2 Subject population and disposition

Demographic or baseline characteristic		CYP2C19 genotype			Total
		homo-EM	hetero-EM	PM	
Demographic characteristics					
Number of planned		14	14	14	42
Number of randomised		14	14	14	42
Age (years)	Mean (SD)	25.4 (4.8)	27.9 (4.9)	28.5 (6.6)	27.3 (5.5)
	Range	22-37	21-37	20-39	20-39
Height (cm)	Mean (SD)	171.7 (4.6)	173.8 (5.4)	171.9 (5.3)	172.5 (5.1)
	Range	165-178	165-183	164-181	164-183
Weight (kg)	Mean (SD)	61.0 (5.6)	62.4 (4.9)	63.2 (5.8)	62.2 (5.4)
	Range	53-72	56-74	53-73	53-74
BMI (kg/m^2)	Mean (SD)	20.66 (1.29)	20.69 (1.49)	21.37 (1.49)	20.91 (1.43)
	Range	19.1-23.0	19.2-24.7	19.0-24.4	19.0-24.7
Number of completed		14	14	14	42
Number analysed for PD		14	14	14	42
Number analysed for PK		14	14	14	42
Number analysed for safety		14	14	14	42

Data derived from Table 11.1.1, Table 11.1.2, Table 11.1.3, and Table 11.1.4

Summary of pharmacodynamic results

The mean percentages of time with intragastric pH>4 during 24 hours on day 5 for D961H 10 mg in all subjects, homo-EMs, hetero EMs and PMs were 47.50%, 26.99%, 51.14% and 64.36%, respectively. The corresponding values for omeprazole 10 mg were 42.74%, 16.65%, 41.19% and 70.37%, respectively (Table S3).

The estimated differences in the means of percentage of time with intragastric pH>4 during 24 hours on day 5 between D961H 10 mg and omeprazole 10 mg in homo-EMs, hetero-EMs and PMs were 10.34, 9.94 and -6.01 percentage points, respectively (Table S4). The corresponding values for the percentage of time with intragastric pH>3 during 24 hours were 14.47, 10.01 and -4.76 percentage points, respectively. The corresponding values for 24-hour median intragastric pH were 0.58, 0.48 and -0.30, respectively. The corresponding values for the percentage of time with intragastric pH>4, pH>3 and median intragastric pH during the periods 0-12 and 12-24 hours were a similar pattern to described above.

Table S3 Descriptive statistics of percentages of time with intragastric pH>4 during 24 hours following once daily oral administration of D961H 10 mg and omeprazole 10 mg for 5 days to Japanese healthy male subjects classified by CYP2C19 genotypes (PD analysis set)

CYP2C19 genotype	Treatment	n	Arithmetic mean	SD
All	Pre-entry	42	6.10	5.33
	D961H 10 mg	42	47.50	22.55
	omeprazole 10 mg	42	42.74	26.49
homo-EM	Pre-entry	14	4.50	4.36
	D961H 10 mg	14	26.99	18.49
	omeprazole 10 mg	14	16.65	13.10
hetero-EM	Pre-entry	14	6.33	4.72
	D961H 10 mg	14	51.14	14.76
	omeprazole 10 mg	14	41.19	15.59
PM	Pre-entry	14	7.47	6.60
	D961H 10 mg	14	64.36	16.44
	omeprazole 10 mg	14	70.37	15.50

Data derived from Table 11.2.2.1.1

Table S4 Estimated differences and 95% CIs for arithmetic means of the percentage of time with intragastric pH>4 during 24 hours between the treatments of D961H 10 mg and omeprazole 10 mg (PD analysis set)

Treatments	CYP2C19 genotype	Estimated	95% CI	
			Lower	Upper
(D961H 10 mg) - (omeprazole 10 mg)	homo-EM	10.34	4.03	16.66
	hetero-EM	9.94	4.58	15.30
	PM	-6.01	-11.76	-0.27

CI : confidence interval
Based on mixed effect ANCOVA model with fixed effects for sequence, period, treatment, covariate of the values at pre-entry and a random effect for subject nested within sequence.
Data derived from Table 11.2.2.5.1

Summary of pharmacokinetic results

The estimated ratios of the geometric means for AUC_t and AUC_τ for D961H and omeprazole were 1.57 and 1.58 for homo-EMs, 1.62 and 1.60 for hetero-EMs, and 0.78 and 0.77 for PMs, respectively. The corresponding values for $C_{ss,max}$ were 1.10 for homo-EMs, 1.16 for hetero-EMs and 0.82 in PMs. The $t_{1/2}$ values tended to be somewhat longer for D961H 10 mg than for omeprazole 10 mg in homo-EMs and hetero-EMs, whereas those for D961H 10 mg was shorter in PMs comparing to omeprazole 10 mg. The t_{max} values were approximately the same following 10 mg doses of both compounds. These data support the pharmacodynamic observation.

Summary of safety results

In total, 1 subject reported 1 AE which was of mild intensity during the study period. There were no deaths, serious AEs, discontinuations due to AEs, other significant AEs, or drug-related AEs in this study. No clinically significant changes in laboratory tests, ECG, blood pressure, pulse rate or body temperature were observed.