AstraZeneca

Clinical Pharmacology Study Report

Drug Substance	D961H
Study Code	D961HC00004
Edition Number	1
Date	12 February 2008

A randomised, single blind, three-way cross-over, single-centre study to assess the pharmacodynamics (intragastric pH) and pharmacokinetics after repeated oral administration of D961H 20 and 40 mg, and omeprazole 20 mg in Japanese healthy male subjects

Study dates:	First subject enrolled:	4 June 2007
	Last subject completed:	4 September 2007
Phase of development:	Clinical Pharmacology (I)	

This study was performed in compliance with Good Clinical Practice

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A randomised, single blind, three-way cross-over, single-centre study to assess the pharmacodynamics (intragastric pH) and pharmacokinetics after repeated oral administration of D961H 20 and 40 mg, and omeprazole 20 mg in Japanese healthy male subjects

Study centre(s)

This study was conducted at Tokyo Heart Center, Osaki Hospital in Japan.

Study dates		**Phase of development**
First subject enrolled	4 June 2007	Clinical pharmacology (I)
Last subject completed	4 September 2007	

Objectives

Primary objective:

To assess the pharmacodynamics (PD) (intragastric pH) after repeated oral administration of D961H 20 mg and 40 mg, and omeprazole 20 mg in Japanese healthy male subjects who were classified by the genotype of CYP2C19 by the assessment of percentage of time with intragastric pH>4 during 24 hours after dose on day 5.

Secondary objectives:

1. To assess the PD (intragastric pH) after repeated oral administration of D961H 20 mg and 40 mg, and omeprazole 20 mg in Japanese healthy male subjects who were classified by the genotype of CYP2C19 by the assessment of percentage of time with intragastric pH>3 during 24 hours and 24-hour median intragastric pH after dose on day 5.

2. To assess the PD (intragastric pH) after repeated oral administration of D961H 20 mg and 40 mg, and omeprazole 20 mg in Japanese healthy male subjects who were classified by genotype of CYP2C19 by assessment of 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 (PK) after repeated oral administration of D961H 20 mg and 40 mg, and omeprazole 20 mg in Japanese healthy male subjects who were classified by the genotype of CYP2C19 by the assessment of plasma concentrations and, AUC_t, AUC_τ, $C_{ss,max}$, t_{max}, and $t_{1/2}$ for D961H 20 mg and 40 mg, and omeprazole 20 mg after dose on day 5.

4. To assess the safety and the tolerability after repeated oral administration of D961H 20 mg and 40 mg, and omeprazole 20 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.

Study design

This study was carried out as a randomised, single-blind, three-way cross-over study consisting of three study 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 at Tokyo Heart Center, Osaki Hospital in Japan:
14 homozygote Extensive Metabolisers (homo-EM), 14 heterozygote Extensive Metabolisers (hetero-EM) and 14 Poor Metabolisers (PM) of the CYP2C19 genotype

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

The following investigational products were supplied:

- D961H capsule 20 mg, batch number H 1189-04-01-13
- D961H capsule 40 mg, batch number H 1222-04-01-17
- D961H capsule placebo, batch number H 0459-06-03-15
- omeprazole tablet 10 mg, batch number 020240
- omeprazole tablet placebo, batch number 020010

D961H 20 or 40 mg capsule, or two omeprazole 10 mg tablets were given once daily for 5 days. The placebo for D961H capsule or omeprazole tablets were given simultaneously as the double dummy.

Duration of treatment

Each subject took part in three study periods, and D961H 20 mg or 40 mg, or omeprazole 20 mg was given once daily for 5 days in each study period.

Variables

- **PK**

  Plasma concentrations of D961H and omeprazole after dose on day 5
  AUC_t, AUC_τ, $C_{ss,\,max}$, t_{max}, $t_{½}$ for D961H 20 mg, 40 mg and omeprazole 20 mg after dose on day 5

- **PD**

  24-hour intragastric pH after dose on day 5:
  Percentages of time with intragastric pH>4 and pH>3 during 24 hours, and median 24-hour intragastric pH at pre-entry and after dose on day 5
  Percentages of time with intragastric pH>4 and pH>3, and median intragastric pH during the periods 0-12 hours and 12-24 hours at pre-entry and after dose on day 5

- **Safety**

  Adverse events, laboratory tests (biochemistry, haematology and urinalysis), ECG and vital signs (blood pressure, pulse rate, body temperature)

Statistical methods

PK:

The ratio of geometric means of AUC_t, AUC_τ, and $C_{ss,\,max,}$ between all pairs of the three treatment with their two-sided 95% confidence intervals were estimated by using a repeated measures model in consideration of the effect of CYP2C19 genotype on the PK profile of D961H and omeprazole.

PD:

The mean differences of the percentages of time with pH>4 and pH>3 during 24 hours and 24-hour median intragastric pH between all pairs of the three treatment with their two-sided 95% confidence intervals were estimated by using a repeated measures model in consideration of the effect of CYP2C19 genotype on the PD profile of D961H and omeprazole.

Safety:

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

Subject population

The first subject was enrolled on 4 June 2007 and the last subject completed on 4 September 2007. Of 65 subjects enrolled, 42 subjects were randomised. Each subject was to take part in three study periods, and D961H 20 mg or 40 mg, or omeprazole 20 mg was given once daily for 5 days in each study period and assessed for safety and tolerability, PK and PD.

There were 3 subjects who had a protocol deviation, however all protocol deviations were minor and did not lead to exclusion of data from the PK, PD or safety summaries.

Table S1 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 and treated[a]		14	14	14	42
Age (years)	Mean (SD)	31.4 (7.81)	26.2 (5.34)	30.5 (4.67)	29.4 (6.36)
	Range	23-45	22-41	23-40	22-45
Height (cm)	Mean (SD)	169.9 (6.03)	170.6 (6.20)	171.8 (7.32)	170.8 (6.43)
	Range	160-177	160-179	164-184	160-184
Weight (kg)	Mean (SD)	61.8 (7.15)	60.7 (5.80)	65.1 (7.19)	62.5 (6.85)
	Range	53-75	51-72	53-75	51-75
BMI (kg/m^2)[b]	Mean (SD)	21.34 (1.447)	20.84 (1.590)	22.11 (2.312)	21.43 (1.854)
	Range	19.7-23.9	18.8-24.3	19.4-26.8	18.8-26.8
Number completed		13	12	12	37
Number analysed for PK		13	14	13	40
Number analysed for PD		13	14	13	40
Number analysed for safety		14	14	14	42

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing.
[b] BMI of all randomised subjects were above 19, when the study centre's standard calculation method was used for confirmation of the inclusion criterion. However, since the different effective digit was used for statistical analysis, BMI of one subject was below 19.

Data derived from Table 11.1.1, Table 11.1.5 and Table 11.1.3.

Summary of PD results

In both homo-EM and hetero-EM, the percentage of time with intragastric pH>4 was higher for D961H 20 mg than for omeprazole 20 mg. On the other hand, in PM, the percentage of time with intragastric pH>4 was higher for omeprazole 20 mg than for D961H 20 mg. There was a dose-related increase in PD response from D961H 20 mg to 40 mg in homo-EM, while there was only minor increase in hetero-EM and PM. The results for percentage of time with intragastric pH>3 and median pH were similar to those for pH>4.

The difference in the PD variables among genotypes diminished with D961H as compared to omeprazole and with the increase of D961H dose from 20 mg to 40 mg. The values of PD variables for D961H 40 mg in homo-EM and hetero-EM were similar to those in PM. This corresponded to the results of PK variables, and D961H 40 mg was less subject to the polymorphism of CYP2C19 genotype and D961H 40 mg gave the highest PD effect.

The inter-individual variability in the PD variables for D961H 40 mg was smaller than that for D961H 20 mg and omeprazole 20 mg. The inter-individual variability in the PD variables for D961H 20 mg was smaller than that for omeprazole 20 mg.

The percentage of time with pH>4 escalated with increase of AUC_t and AUC_τ, it reached to plateau at around 5-10 μmol*h/L.

Summary of PK results

In homo-EM, AUC_t and AUC_τ values were about 80% higher for D961H 20 mg than for omeprazole 20 mg. For twofold dose of D961H from 20 mg to 40 mg, the AUC_t, AUC_τ and $C_{ss,\,max}$ values increased 2.64 to 3.03 times. In hetero-EM, AUC_t and AUC_τ values were 29% higher for D961H 20 mg than for omeprazole 20 mg. For twofold dose of D961H from 20 mg to 40 mg, the AUC_t, AUC_τ and $C_{ss,\,max}$ values increased 2.28 to 2.39 times. In PM, the situation was opposite, AUC_t and AUC_τ values were 29% lower for D961H 20 mg than for omeprazole 20 mg. For twofold dose of D961H from 20 mg to 40 mg, the AUC_t, AUC_τ and $C_{ss,\,max}$ values increased 1.97 to 2.07 times.

Overall, inter-individual variability in PK variables (AUC_t, AUC_τ, $C_{ss,max}$ and $t_{1/2}$) was less pronounced for D961H 20 mg compared to omeprazole 20 mg.

Summary of safety results

In total, 7 subjects reported 16 AEs during the study period. Four SAEs were reported by one subject and they were assessed as non-related to study drugs by the investigator. One subject was discontinued from study treatment due to AEs, which were assessed as non-related to study drugs by the investigator. All AEs except for the SAEs were of mild intensity, and assessed as non serious. There were two subjects whose AST and ALT increased slightly. These were assessed to relate to D961H 40 mg by the investigator. No clinically significant changes in ECG, blood pressure, pulse rate, body temperature were observed.

D961H 20 mg and 40 mg, and omeprazole 20 mg were well tolerated.