AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961HC00008
Edition Number	1
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Open label, Randomized, Single center, 2-way Crossover Bioequivalence Study Comparing Gelatine Capsule 40 mg D961H and HPMC Capsule 40 mg D961H After Repeated Oral Administration in Japanese Healthy Male Subjects

Study dates: First subject enrolled: 20 June 2009
Last subject last visit: 29 August 2009

Phase of development: Clinical pharmacology

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

Study centre(s)

This study was conducted at one centre in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S-1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate whether HPMC capsule of D961H 40 mg is bioequivalent to gelatine capsule of D961H 40 mg, by assessment of area under the plasma concentration-time curve during one dose interval (τ) after a steady state is reached (AUC_τ) and maximum observed plasma concentration at steady state on Day 5 ($C_{ss,max}$).	- AUC_τ - $C_{ss,\ max}$	Pharmacokinetics
Secondary	**Secondary**	
To evaluate the pharmacokinetic (PK) properties of HPMC capsule of D961H 40 mg and gelatine capsule of D961H 40 mg following repeated oral doses, by assessment of plasma concentrations, mean residence time (MRT), time to maximum plasma concentration (t_{max}), and half-life ($t_{1/2}$) on Day 5.	- plasma concentrations - MRT - t_{max} - $t_{1/2}$	Pharmacokinetics
To evaluate the safety and tolerability of HPMC capsule of D961H 40 mg and gelatine capsule of D961H 40 mg by assessment of adverse events, clinical laboratory tests ECG, blood pressure, pulse rate and body temperature.	- Adverse events - Laboratory tests (clinical chemistry, haematology and urinalysis) - ECG - Blood pressure - Pulse rate - Body temperature	Safety

Study design

This study was carried out as a single-centre, open, randomised, 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 classified as homozygote Extensive Metabolisers (homo-EM) of the CYP2C19 genotype.

Target subject population and sample size

48 Japanese healthy male subjects classified as homo-EM.

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

The following investigational products were supplied:

- D961H gelatine capsule 40 mg
- D961H HPMC capsule 40 mg

The subjects received D961H gelatine capsule 40 mg or D961H HPMC capsule 40mg once in the morning (om) on day 1-4 and om under fasting condition on day 5, in each of the two treatment periods.

Duration of treatment

Each subject took part in two treatment periods, and received D961H gelatine capsule 40 mg or D961H HPMC capsule 40 mg on day 1-5 in each treatment periods.

Statistical methods

- Pharmacokinetics:

The log-transformed AUC_{τ}, and $C_{ss,max}$ for D961H were analysed using a linear mixed effect model including factors of formulation, treatment period and treatment sequence as fixed effect and a factor of subject as random effect in order to compare the PK parameters between the two formulations (D961H HPMC capsule and D961H gelatine capsule).

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

(a) Estimates (geometric means) for the two formulations and 95 % confidence intervals (CIs) for the geometric means.

(b) Estimates of the ratios (D961H HPMC capsule/ D961H gelatine capsule), 90% CIs for the true ratios and p-values for the corresponding tests.

If the 90% CIs for the ratios of geometric means for AUC_{τ}, and $C_{ss,max}$ were all contained in the interval of 0.80-1.25, then it was to be concluded that the D961H HPMC capsule was considered bioequivalent to the D961H gelatine capsule.

In addition, other pharmacokinetic parameters ($t_{1/2}$ and MRT) were analysed using the above statistical method. The non log-transformed values of t_{max} for two formulations were compared using Wilcoxon signed rank test.

- Safety:

Adverse events, laboratory variables, ECG, blood pressure, pulse rate and body temperature were presented descriptively and separately for each formulation (D961H gelatine capsule and D961H HPMC capsule).

Subject population

First subject was enrolled on 20 June 2009 and the last subject completed on 29 August 2009. Of 248 enrolled subjects, 48 healthy male subjects classified as homo-EM were randomised in this study. Each subject took part in 2 treatment periods separated by a wash-out of at least 14 days, and HPMC capsule of D961H 40 mg or gelatine capsule of D961H 40 mg was be given for 5 days.

All randomised subjects completed 2 treatment periods according to the protocol. There was no cessation or overdosage of D961H.

Table S-2 Subject population and disposition

Disposition		Number of subjects
Subjects randomised		48
Subjects who completed study		48
Subjects who discontinued study		0
Subjects included in safety analysis set		48
Subjects included in PK analysis set		48
Age (years)	n	48
	Mean (SD)	27.7 (6.6)
	Median	25.0
	Min – Max	20 - 43
Height (cm)	n	48
	Mean (SD)	170.9 (6.0)
	Median	171.0
	Min – Max	156 - 185
Weight (kg)	n	48
	Mean (SD)	64.4 (6.4)
	Median	64.0
	Min – Max	52 - 82
BMI (kg/m^2)	n	48
	Mean (SD)	22.06 (1.99)
	Median	21.75
	Min – Max	19.2 - 26.6

Data derived from Section 11, Table 11.1.1, Table 11.1.3, Table 11.1.4

Summary of pharmacokinetic results

The estimated geometric means and 95% CIs for AUC_τ and $C_{ss,max}$ of D961H following repeated oral doses of HPMC capsule of D961H 40 mg and gelatine capsule of D961H 40 mg in healthy Japanese male subjects are presented in Table S-3. The estimated ratios of the geometric means (HPMC capsule/gelatine capsule) and the 90% CIs for the AUC_τ and $C_{ss,max}$ following repeated oral doses of HPMC capsule of D961H 40 mg and gelatine capsule of D961H 40 mg in healthy Japanese male subjects are presented in Table S-4.

As shown in Table S-4, the 90% CIs for the ratios of the geometric means (HPMC capsule/gelatine capsule) of AUC_τ and $C_{ss,max}$ were contained in the range of 0.8 to 1.25, which is the stated criterion for bioequivalence.

As for the secondary variables MRT and $t_{1/2}$, the 90% CIs for the ratios of the geometric means (HPMC capsule/gelatine capsule) were 1.04 (0.95-1.14) and 1.00 (0.98-1.02), respectively. The median of t_{max} was 2.0 hours for two formulations. The plasma concentrations-time profiles were similar for the HPMC capsule of D961H 40 mg and the gelatine capsule of D961H 40 mg.

Table S-3 Estimates and 95% CIs for the adjusted geometric means of pharmacokinetic variables AUC_τ and $C_{ss,max}$ following repeated oral doses of HPMC capsule of D961H 40 mg and gelatine capsule of D961H 40 mg in healthy Japanese male subjects

Variable	Formulation	Estimate	95% CI	
			Lower	Upper
AUC_τ (μmol·h/L)	HPMC capsule	11.570	10.579	12.655
	gelatine capsule	11.471	10.488	12.546
$C_{ss,max}$ (μmol/L)	HPMC capsule	4.839	4.492	5.213
	gelatine capsule	5.133	4.765	5.530

Data derived from Section 11, Table 11.2.5.2

Table S-4 Ratios (HPMC capsule/ gelatine capsule) of the adjusted geometric means and 90% CIs for AUC_τ and $C_{ss,max}$ following repeated oral doses of HPMC capsule of D961H 40 mg and gelatine capsule of D961H 40 mg in healthy Japanese male subjects

Variable	Ratio	Estimate	90% CI		p value
			Lower	Upper	
AUC_τ	HPMC capsule/ gelatine capsule	1.01	0.96	1.06	0.775
$C_{ss,max}$	HPMC capsule/ gelatine capsule	0.94	0.87	1.02	0.211

Data derived from Section 11, Table 11.2.5.3.

Summary of safety results

HPMC capsule of D961H 40 mg and gelatine capsule of D961H 40mg were well tolerated in this study.

1. Three subjects reported 4 adverse events during the study period. No adverse events were judged by investigator as drug related to the investigational product.

2. All adverse events were of mild intensity, and assessed as non serious.

3. There were no deaths, serious adverse events, discontinuations due to adverse events, or other significant adverse events in the study.

4. No clinically significant changes in clinical laboratory, vital signs or ECG were observed.