AstraZeneca

Clinical Study Report Synopsis

Drug Substance	D961H
Study Code	D961HC00007
Edition Number	1
Date	26 November 2008

A single-centre, open, randomised, three-way cross-over drug-drug interaction study of D961H capsule and loxoprofen tablet after repeated oral administration in Japanese healthy male subjects

Study dates: First subject enrolled: 11 April 2008
Last subject completed: 9 July 2008

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 Osaka Pharmacology Clinical Research Hospital in Japan. The first subject was enrolled on 11 April 2008 and the last subject completed on 9 July 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective was to study the pharmacokinetic profile of D961H during repeated oral administration with and without co-administration of loxoprofen and the pharmacokinetic profile of loxoprofen during repeated oral administration with and without co-administration of D961H by assessment by AUC_{τ}, $C_{ss,max}$, t_{max}, $t_{1/2}$ and plasma concentrations of D961H, loxoprofen and trans-hydroxy metabolite of loxoprofen after dose on day 5.

The secondary objective was to evaluate the safety of D961H with and without co-administration of loxoprofen by assessment of adverse events, clinical laboratory tests (clinical chemistry, haematology, urinalysis and haemoccult test), ECG, blood pressure, pulse rate and body temperature.

Study design

This study was carried out as a single-centre, open, randomised, three-way cross-over study consisting of three 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, 30 Japanese healthy male subjects between 20 and 45 years of age:
12 homozygote Extensive Metabolisers (homo-EM), 12 heterozygote Extensive Metabolisers (hetero-EM) and 6 Poor Metabolisers (PM) of the CYP2C19 genotype.

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

The following investigational product was supplied:

- D961H capsule 20 mg (batch number: H 1189-04-01-14)

Loxoprofen was selected as the target drug. LOXONIN® tablet 60 mg manufactured by Daiichi-Sankyo was used in this study.

Thirty healthy subjects received D961H capsule 20 mg om (once in the morning, after breakfast) on Days 1-4 and om (once in the morning, under fasting condition) on Day 5, loxoprofen 60 mg tid (3 times after meal a day) on Days 1-4 and om (once in the morning,

under fasting condition) on Day 5 or the two drugs concomitantly on Days 1-5 in each of the three treatment periods.

Duration of treatment

Each subject took part in three treatment periods separated by a wash-out period of at least 14 days, and received D961H 20 mg, loxoprofen 60 mg or the two drugs concomitantly on Days 1-5 in each treatment periods.

Criteria for evaluation - pharmacokinetics (main variables)

AUC_{τ}, $C_{ss,max}$, t_{max} and $t_{1/2}$, plasma concentrations of D961H, loxoprofen and trans-hydroxy metabolite of loxoprofen after dose on Day 5 in each treatment periods

Criteria for evaluation - safety (main variables)

Adverse events, laboratory tests (clinical chemistry, haematology, urinalysis and faecal haemoccult test), ECG, blood pressure, pulse rate and body temperature

Statistical methods

Pharmacokinetics:

The log-transformed AUC_{τ}, $C_{ss,max}$ and $t_{1/2}$ for D961H, loxoprofen and trans-hydroxy metabolite of loxoprofen were analysed using a repeated measures model with the covariance structure of "compound symmetry" in consideration of the effect of CYP2C19 genotype on the PK parameters of D961H and loxoprofen to compare the PK parameters between of drug alone and of the drug in combination. D961H, loxoprofen and trans-hydroxy metabolite of loxoprofen were analysed separately.

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

a) Estimates (geometric means) for the drug alone and for the combination and 95% confidence intervals for the true geometric means.

b) Estimates of the ratios (the combination/the drug alone), 95% confidence intervals for the true ratios and p-values for the corresponding tests.

Safety:

Adverse events, laboratory variables, ECG, blood pressure, pulse rate and body temperature were presented descriptively and separately for each treatment (D961H only, loxoprofen only and D961H + loxoprofen).

Subject population

Of 52 subjects enrolled, 30 subjects were randomised. Each subject was to take part in three study periods, and received D961H 20 mg, loxoprofen 60 mg or the two drugs concomitantly on Days 1-5 in each treatment periods.

There were no subjects who had a protocol deviation.

The genotypes were balanced in terms of demography and baseline characteristics.

Table S1 Subject population and disposition

Demographic or baseline characteristic		CYP2C19 genotype			Total
		Homo-EM	Hetero-EM	PM	
Demographic characteristics					
Number of planned		12	12	6	30
Number of randomised and treated [a]		12	12	6	30
Age (years)	Mean (SD)	24.5 (4.3)	26.1 (4.2)	25.0 (2.8)	25.2 (4.0)
	Range	21-36	21-34	21-29	21-36
Height (cm)	Mean (SD)	173.8 (4.2)	170.8 (5.8)	171.0 (4.7)	172.1 (5.0)
	Range	168-183	162-181	163-176	162-183
Weight (kg)	Mean (SD)	62.8 (4.6)	62.4 (6.2)	59.2 (5.1)	61.9 (5.4)
	Range	56-69	53-71	51-66	51-71
BMI (kg/m^2) [b]	Mean (SD)	20.78 (1.34)	21.40 (1.88)	20.22 (1.32)	20.91 (1.59)
	Range	19.4-23.2	18.9-25.1	19.0-22.1	18.9-25.1
Number completed		11	12	6	29
Number analysed for PK		12	12	6	30
Number analysed for safety		12	12	6	30

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 11.1.3 and Table 11.1.5

Summary of pharmacokinetic results

After five days of oral administration of D961H capsule 20 mg om and in combination of D961H capsule 20 mg om and loxoprofen 60 mg tid, there was no statistically significant changes observed in AUC_{τ}, $C_{ss,max}$ and $t_{1/2}$ of D961H regardless of the genotype of CYP2C19.

In case of loxoprofen, statistically significant changes were observed in AUC_{τ}, $C_{ss,max}$ and $t_{1/2}$ of unchanged compound but not in the pharmacokinetic parameters of active metabolite, trans-hydroxy loxoprofen. The changes in AUC_{τ} and $C_{ss,max}$ were 9% or less, and the 95% confidence intervals were entirely within the equivalence range of 0.8 to 1.25. Therefore, the changes in AUC_{τ} and $C_{ss,max}$ are unlikely to have any clinical relevance. It was also suggested that the changes in $t_{1/2}$ of loxoprofen would not be clinically significant since the exposures of active metabolite, trans-hydroxy loxoprofen, were not changed by the co-administration with D961H.

Consequently, it is concluded that there is no clinically significant drug-drug interaction between D961H and loxoprofen.

Summary of safety results

In total, 18 subjects reported 44 AEs during the study period. There were no deaths, serious AEs, discontinuations due to AEs, or other significant AEs in the study. All AEs were of mild intensity. No clinically significant changes in laboratory tests, ECG, blood pressure, pulse rate, body temperature were observed.

Date of the report

26 November 2008