AstraZeneca

DRUG PRODUCT	MUPS	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	H 199/18	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	DC-QBE-0001		
VERSION NO.	01		
STUDY CODE	DC-QBE-0001		
DATE	30 April, 1999		

A bioequivalence study with 20 mg H 199/18 comparing a new tablet formulation with a capsule formulation in healthy subjects

INVESTIGATOR

STUDY CENTRE(S)

Single centre study at
Quintiles AB, Phase I Services
Islandsgatan 2
S-753 18 Uppsala, Sweden

STUDY PERIOD

- DATE OF FIRST SUBJECT ENROLLED 2 June, 1998
- DATE OF LAST SUBJECT COMPLETED 23 July, 1998

PHASE OF DEVELOPMENT

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OBJECTIVES

To investigate if a Phase III capsule formulation and a MUPS tablet formulation of 20 mg H 199/18 are bioequivalent under non-fasting conditions during single and repeated dose administration.

STUDY DESIGN

The study was an open, randomised, two-way cross-over trial.

MAIN CRITERIA FOR INCLUSION

Healthy adult male and female subjects of normal weight.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 MUPS tablet, 20 mg, batch no. H 1370-01-01-01, was given orally once daily immediately following breakfast.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 capsule with enteric coated pellets, 20 mg, batch no. H 1189-04-01-04, was given orally once daily immediately following breakfast.

DURATION OF TREATMENT

Two periods of five days each, separated by a wash-out period of at least 13 days.

MAIN VARIABLES

- PHARMACOKINETIC

  The total area under the plasma concentration versus time curve (AUC), area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC_t) and the observed maximum concentration of H 199/18 in plasma (C_{max}) were calculated for days 1 and 5 in each period.

STATISTICAL METHODS

Data from day 1 and day 5 were analysed separately. Analysis of variance (ANOVA) was performed on log-transformed AUC, AUC_t and C_{max}. By applying the antilogarithm transformation, the 94% CI (corresponds to 90% CI, adjusted for interim analysis) for the geometric mean of each parameter and formulation and the 94% CIs for the ratios (Test/Comparator) of the geometric means were obtained. The estimated geometric means and CIs and the estimated ratios and CIs were corrected for the content of H 199/18 in the formulations. An interim analysis was performed after the first step of the study. The range for bioequivalence (C_{max}: ratio of the geometric means, AUC and AUC_t: 94% CI for the ratio of the geometric means) in the interim analysis and final analysis was 0.80 – 1.25. Analysis of variance (ANOVA) was performed on the elimination rate constant (λ), $t_{½}$ as well as t_{max}. The laboratory results and adverse events were presented descriptively.

SUBJECTS

	Total
No. planned	80 in total with 40 in the first step
No. randomised and treated	40
Males/Females	27/13
Mean age (range)	25 years (20-34)
No. analysed for pharmacokinetics	37
No. analysed for safety	40
No. completed	37

SUMMARY - CONCLUSION(S)

- PHARMACOKINETIC RESULTS

As the interim analysis showed that the stated criteria for bioequivalence was not fulfilled the study was stopped after completion of the first step. The geometric mean with 94% CI for each main variable and formulation and the ratios of the geometric means (MUPS tablet/capsule) with 94% CIs for day 1 and day 5 are shown in Tables 1 and 2, respectively.

The CIs for the ratios of the geometric means for AUC and AUC_t, expressing extent of absorption, and the ratio of the geometric means for C_{max}, expressing both extent and rate of absorption, were outside the range of bioequivalence (0.80 – 1.25) both for day 1 and day 5.

Table 1. Geometric means and ratios for *AUC (µmol· h/L*; n = 30), *AUC_t (µmol· h/L*; n = 37) and *C_{max} (µmol/L*; n = 37) for H 199/18 following a single oral administration of 20 mg as a MUPS tablet or as a capsule to healthy subjects under non-fasting conditions. Drug potency corrected estimates, 94% CIs and p-values for test of equal geometric means are presented.

Day 1	Geometric mean	94% confidence interval		p-value
		lower	upper	
AUC[A]				
MUPS	1.08	0.96	1.20	
Capsule	0.99	0.89	1.10	
MUPS/Capsule	1.09	0.93	1.27	0.29
AUC_t				
MUPS	0.89	0.79	1.01	
Capsule	0.73	0.64	0.82	
MUPS/Capsule	1.23	1.03	1.45	0.026
C_{max}				
MUPS	0.52	0.44	0.61	
Capsule	0.36	0.30	0.42	
MUPS/Capsule	1.45	1.15	1.84	0.004

[a] The AUC values for the MUPS tablet and/or the capsule estimated for subjects 4, 5, 7, 19, 31, 34 and 36 were regarded as uncertain (less than three plasma concentrations after C_{max} or an AUC_{extr} exceeding 20%). These subjects were therefore excluded from the calculation of the geometric means of AUC.

Table 2. **Geometric means and ratios for *AUC (µmol· h/L*; n = 35), *AUC_t (µmol· h/L*; n = 37) and *C_{max} (µmol/L*; n = 37) for H 199/18 following oral once daily administration of 20 mg for five days as MUPS tablets or as capsules to healthy subjects under non-fasting conditions. Drug potency corrected estimates, 94% CIs and p-values for test of equal geometric means are presented.**

Day 5	Geometric mean	94% confidence interval lower	upper	p-value
AUC[a]				
MUPS	2.49	2.21	2.81	
Capsule	1.77	1.57	2.00	
MUPS/Capsule	1.41	1.19	1.67	<0.001
AUC_t				
MUPS	2.29	1.99	2.64	
Capsule	1.50	1.31	1.73	
MUPS/Capsule	1.53	1.25	1.86	<0.001
C_{max}				
MUPS	0.95	0.82	1.10	
Capsule	0.58	0.50	0.67	
MUPS/Capsule	1.65	1.34	2.02	<0.001

[a] The AUC values for the capsule estimated for subjects 7 and 31 were regarded as uncertain (less than three plasma concentrations after C_{max} and/or an AUC_{extr} exceeding 20%). These subjects were therefore excluded from the calculation of the geometric means of AUC.

On study day 1, the median time for reaching maximum plasma concentrations (t_{max}) was 4.5 hours for both formulations. The mean elimination half-lives ($t_{1/2}$) were 0.9 and 1.1 hours for the tablet and the capsule, respectively. On study day 5, the median t_{max} was 3.0 and 4.5 hours for the tablet and capsule, respectively. The mean $t_{1/2}$ was 1.1 and 1.2 hours for the tablet and the capsule, respectively.

- SAFETY RESULTS

  In total, 130 AEs were reported during the study. There were no serious adverse events (SAEs) and the adverse events (AEs) reported were mostly mild; only 12 AEs of moderate intensity were reported. No AEs with severe intensity were noted. The AEs were representative for a group of healthy subjects with headache as the most commonly reported symptom.

- CONCLUSION(S)

  The Phase III capsule formulation and the MUPS tablet formulation of 20 mg H 199/18 were not bioequivalent with respect to AUC, AUC_t and C_{max} under non-fasting conditions, neither during single nor repeated dose administration. Repeated doses of H 199/18 were well tolerated in this study.

DATE OF THE REPORT

30 April 1999