2.0 SYNOPSIS

Name of Company: AstraZeneca LP	**Individual Study Table Referring to Item of the Submission** N/A	**(For National Authority Use only)**
Name of Finished Product:	**Volume:** N/A	
Name of Active Ingredient: H 199/18	**Page:** N/A	

Title of Study: A Randomized, Single-Center, Open-label, Two-period Cross-over, Pharmacokinetic Study, to Evaluate the Bioequivalence of a single 40 mg H 199/18 Dose Administered as an Intact Capsule and as an Open Capsule in Healthy Male and Female Volunteers.

Study Center(s):
MDS Harris Laboratories
621 Rose Street
Lincoln, NE 68501

Publication (reference): N/A

Studied Period (years): (first subject enrolled) 23 May 1999 (last subject completed) 23 June 1999	**Phase of development:** Phase I

Objectives:
The objective of this study was to determine whether the content of a single 40 mg dose of H 199/18 administered in applesauce is bioequivalent to that dose administered as an intact capsule in healthy male and female volunteers.

Methodology:
This was a randomized, single-center, open-label, two-period crossover study consisting of two study days separated by a washout period of 7 days. Forty five subjects (21 males and 24 females) received in a randomized sequence 40 mg of H 199/18 as an intact capsule or as the capsule contents mixed with applesauce. Blood samples for the determination of H 199/18 concentration in plasma were collected at specified intervals up to 12 hours post-dose. During that time, subjects were fed standardized meals. Adverse events were recorded throughout the study.

Number of Patients (Planned and Analyzed):

No. planned	36
No. randomized and treated	45
Males/Females	21/24
Mean age (range)	28 (19-45)
No. analyzed for pharmacokinetics	41
No. analyzed for safety	45
No. completed	41

Diagnosis and Main Criteria for Inclusion:
Healthy male or female volunteers between the ages of 18 and 45 years with a body weight not more than 15% above or below the ideal weight for their height and frame were included in the study.

Test Product, Dose and Mode of Administration, Batch or Lot Number:
H 199/18 capsule 40 mg, batch no. H 1222-04-01-05, single oral dose of 40 mg

Duration of Treatment:
Two single doses separated by at least 7 days

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
N/A

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Main variables:

Pharmacokinetics

The total area under the plasma concentration vs time curve (AUC), the area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC_t) and the observed maximum concentration (Cmax) of H 199/18 in plasma are the main variables.

Statistical Methods: For AUC (extrapolated to infinity), AUC_t, and C_{max}, an analysis of variance model, which included the factors of treatment, period, subject, and sequence, was employed to obtain treatment least square means on a logarithmic scale. The results were retransformed using antilogarithms to obtain estimates of the treatment geometric means with the corresponding 95% confidence limits, and of the ratio of the geometric means of the capsule opened in applesauce relative to the intact capsule, together with the corresponding 90% confidence limits.

Analyses for t_{max} and $t_{½}$ were also performed, using the same ANOVA model as that used for AUC. No logarithmic transformation was made. The estimates of the treatment least square means and their 95% confidence intervals, and of the difference between the means (capsule opened in applesauce minus intact capsule), together with the corresponding 95% confidence limits, are provided.

Secondary analyses included tests for carryover effect and gender for AUC.

SUMMARY

PHARMACOKINETIC RESULTS:

The ratios of the geometric means with 90% confidence intervals for AUC and C_{max} are shown in Table 1. The confidence intervals for AUC and C_{max} lie within the interval 0.80 to 1.25, indicating that the intact capsule and the capsule opened in applesauce are bioequivalent. The results for AUC_t were virtually identical to those obtained for AUC.

The elimination half-life ($t_{½}$) was similar for intact and opened capsule in applesauce (approximately 0.9 h). The time to the maximum plasma concentration (t_{max}) was approximately 2.3 hours for intact capsule and opened capsule in applesauce.

Table 1
Ratios of Geometric Means with 90% Confidence Intervals of AUC and C_{max} of H 199/18, 40 mg, Administered as Intact Capsule and Capsule Opened in Applesauce to Healthy Subjects (n=41)

	Ratio of Geometric Means	90% Confidence Limits
AUC (Open/Intact)	0.99	(0.94, 1.04)
C_{max} (Open/Intact)	0.93	(0.86, 1.01)

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SUMMARY

SAFETY RESULTS:
AEs were reported for 11 of the 45 subjects during the entire study (including wash-out period). One subject experienced headaches, stomach cramps, loose stools and vomiting, during the wash-out period 6 days following the single dose of intact capsule of H 199/18, and decided to discontinue the study. No subject experienced a serious adverse event. H 199/18 was well tolerated as an intact capsule and opened capsule in applesauce.

Date of the Report:
17 September 1999