2.0 SYNOPSIS

Name of Company: Astra Pharmaceuticals, L.P.	**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: An Interaction Study Between H 199/18 and Phenytoin in Epileptic Patients

Study Center(s): Two investigator sites initiated and enrolled patients

Publication (reference): N/A

Studied Period (years): (date of first enrollment) 24 June 1998 (date of last completed) 03 November 1998	**Phase of development:** Phase I

Objectives:
The objective of this study was to determine the effect of H 199/18 on the steady-state trough serum concentration of phenytoin in epileptic patients

Methodology:
The study was a randomized, double-blind, placebo controlled parallel group study. Subjects had three trough phenytoin concentrations measured during the baseline period. If these concentrations were stable, ie, Week 1 and Week 2 phenytoin concentrations were each within 20% of the level at Week 0 and subject's highest concentration was not more than 40% higher than the lowest concentration, then subjects were randomized to receive 40 mg of H 199/18 capsule or placebo capsule, once daily for two weeks. Subjects were also instructed to continue their usual phenytoin treatment throughout the study. Blood samples for determination of phenytoin in serum were collected before, during, and after the double-blind treatment period. Twenty-four epileptic patients were included in the study. Adverse events were recorded throughout the study.

Number of Subjects (Planned and Analyzed):

No. planned	24
No. randomized and treated	24
Males/Females	16/8
Mean age (range)	41 (22-65)
No. analyzed for clinical pharmacology	23
No. analyzed for safety	24
No. completed	24

Diagnosis and Main Criteria for Inclusion: Confirmed diagnosis of epilepsy (any seizure type) and continuous and stable phenytoin therapy for the preceding two months

Test Product, Dose and Mode of Administration, Batch or Lot Number:
H 199/18 capsule 40 mg, batch no. H 1222-04-01-05, oral dose of 40 mg daily for 14 days.
comparator product, batch number, dosage and mode of administration
Placebo, batch no. H 0459-06-03-05, oral dose daily for 14 days.

Duration of Treatment: Two weeks
Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
Placebo capsule, batch no. H 0459-06-03-05, oral dose.

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Main variables:
-Pharmacokinetics
The steady-state trough serum concentration of phenytoin was the primary variable.

Statistical Methods: The change from baseline to the end of study drug administration in serum phenytoin concentrations was analyzed with a two-way analysis of variance (ANOVA) model, which included treatment and investigator as fixed effects. Tests were based on two-sided alternative hypotheses.

SUMMARY
PHARMACOKINETIC RESULTS:
The means and mean changes from baseline in serum concentrations of phenytoin (µg/mL) to the end of the study drug administration at Week 2 are summarized in the following table.

		Baseline		Week 2		Change from Baseline	
Treatment	N	Mean	SD	Mean	SD	Mean (% Change in Means)	SD
H 199/18 40 mg	11	13.89	7.13	15.70	6.19	1.80 (13.0%)	3.47
Placebo	12	14.39	3.82	13.88	3.74	-0.51 (-3.6%)	2.16

At Week 2, the mean serum concentration of phenytoin increased 1.8 µg/mL (an increase of 13.0% over the baseline mean) in the H 199/18 treatment group compared with a decrease of 0.5 µg/mL (a decrease of 3.6% from the baseline mean) in the placebo group. The significance level for the difference between the treatment groups is p=0.074.

SAFETY RESULTS:
Nine AEs were reported for 4 of the 12 subjects during treatment with H 199/18 in combination with phenytoin and 8 AEs were reported for 6 of the 12 subjects during placebo treatment in combination with phenytoin. All AEs reported were mild to moderate intensity. No subject experienced a serious adverse event. No subject discontinued due to an AE.

Date of the Report: 25 May 1999