ASTRA
ASTRA HÄSSLE

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	H 199/18 capsule	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0012		
VERSION NO.	01		
STUDY CODE	SH-QBE-0012		
DATE	28 May, 1999		

A placebo-controlled study on the efficacy of on demand treatment with H 199/18 40 mg in maintaining control of symptoms in patients with gastroesophageal reflux disease without macroscopic esophagitis - A multicentre study

STUDY CENTRE(S)

Multicentre study including 65 centres in France, Germany and Switzerland.

PUBLICATION (REFERENCE)

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- DATE OF FIRST PATIENT ENROLLED	October 23, 1997	IIIA
- DATE OF LAST PATIENT COMPLETED	October 16, 1998	

OBJECTIVES

Primary:

- To compare the efficacy of on-demand treatment with H 199/18 40 mg or placebo over a 6-month period following initial complete resolution of heartburn, in the study SH-QBE-0011.

Secondary:

- To compare the efficacy of on-demand treatment with H 199/18 40 mg or placebo over a 6-month period with regard to time to discontinuation due to insufficient control of heartburn.
- To study the patients' dosing habits with on demand treatment.
- To evaluate the safety and tolerability of H 199/18.

STUDY DESIGN

Double-blind, randomised, placebo controlled and parallel group designed study with H199/18 40 mg or placebo.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients with complete resolution of heartburn, defined as no heartburn during the last 7 days of the 4 week treatment in the study SH-QBE-0011, were eligible to enter this study.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

H 199/18 40 mg capsule once daily on demand, batch numbers: H 1222-04-01-04, H 1222-04-01-05 and H1222-04-01-6.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Placebo capsule once daily on demand, batch number: H 0459-06-03-06, H0459-06-03-05

DURATION OF TREATMENT

Double blind on-demand treatment for six months or until discontinuation.

MAIN VARIABLE(S):

- EFFICACY

  The primary variable was time to study discontinuation due to unwillingness to continue.

  Secondary variable was time to study discontinuation due to insufficient control of heartburn.

- SAFETY

  Adverse events (AE), laboratory assessments and vital signs.

STATISTICAL METHODS

For the primary and the secondary variables the two treatment groups were compared using Life Table methods for graphic presentation and a logrank test with stratification based on *H.pylori* (*Helicobacter pylori*) status

Both Intention to treat (ITT) and Per protocol (PP) analyses were made for the primary variable.

Patients' dosing habits were described using descriptive statistics and frequency tables as assessed by Medical Event Monitoring System (MEMS®) containers.

Laboratory data was presented in terms of the number of patients with median, mean and standard deviations. A cross table showing the number of patients with values below, within

or above the normal range at baseline (visit 1 in SH-QBE-0011) versus the same classification at the last visit was provided for each laboratory variable. Graphs showing last visit values versus the baseline values were presented for each treatment group and each laboratory variable.

PATIENTS

	Placebo	H199/18 40mg	Total
No. planned	160	160	320
No. randomised and treated	192	191	383*
Males/Females (ITT)	89/100	86/101	175/201
Mean age (range) (ITT)	50.0 (21-83)	50.0 (19-77)	50.0 (19-83)
No. analysed for efficacy (ITT)	189	187	376
No. analysed for safety	187	184	371**
No. completed	108	152	260

* 7 patients were excluded from all analyses due to inability to confirm the quality and reliability of the data.
** an additional 5 patients were excluded from the safety analysis because no post randomisation data was available.

SUMMARY

- EFFICACY RESULTS

Eighty patients discontinued due to unwillingness to continue and of these, 59 discontinued due to insufficient control of heartburn as shown in Table 1. The logrank test showed a statistically significant difference between the treatment groups ($p<0.0001$) in favour of H 199/18 40 mg (Figure 1).

Table 1. Number (%) of patients by outcome, ITT.

	H 199/18 40 mg	Placebo	All
Total	187(100%)	189(100%)	376(100%)
Discontinued due to unwillingness to continue			
No	169(90%)	127(67%)	296(79%)
Yes	18(10%)	62(33%)	80(21%)
Unwilling due to insufficient control of heartburn	11(6%)	48(25%)	59(16%)
Unwilling due to adverse event	0(0%)	1(1%)	1(0%)
Unwilling due to other reason	7(4%)	13(7%)	20(5%)

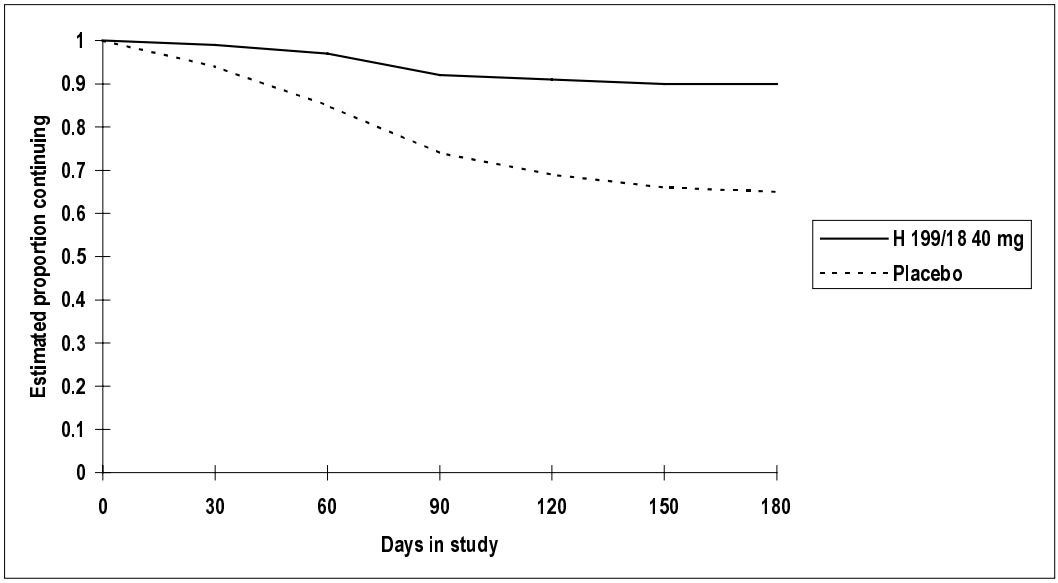

Figure 1. Time to discontinuation due to insufficient control of heartburn, ITT.

The mean number of doses of H 199/18 40 mg taken per day was 0.24, i.e. on average one capsule every fourth day.

- SAFETY RESULTS

On-demand treatment with H 199/18 was safe and well tolerated. No specific differences between the treatment groups were seen, especially when taking into consideration the longer exposure times in the H 199/18 group compared with the placebo group. The laboratory profiles were similar for the two treatment groups with small deviations during the study period.

DATE OF THE REPORT

28 May, 1999