1. TITLE PAGE

CONFIDENTIAL

CLINICAL STUDY REPORT

Clinical Study Report Code: M/00EBS/18

Name of the Investigational product: Ebastine
Indication studied: N/A (Bioequivalence Study)
Phase of the study: I

"RANDOMIZED, UNICENTRIC, CROSS-OVER CLINICAL TRIAL TO EVALUATE THE BIOEQUIVALENCE OF TWO ORAL FORMULATIONS (10 mg TABLETS) OF EBASTINE IN HEALTHY VOLUNTEERS"
(Protocol No. M/00EBS/18; Eudract No. 2006-002936-13)

Safety Statistical Report date: 02-Nov-2006
Pharmacokinetics Statistical Report date: 30-Oct-2006
Analytical Report No.: FC/06/009
Date of initiation of the study: 12-Jul-06
Date of early study termination (if applicable): N/A
Date of completion of the study: 02-Aug-06
Date of completion of this Report: 13-Nov-2006

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The study was performed in accordance with Good Clinical Practices (GCP) including the archiving of essential documents

2. SYNOPSIS

Name of Sponsor / Company: Almirall Prodesfarma, S.A **Name of Finished Product:** Kestin® and Ebastine Alter® **Name of Active Ingredients:** Ebastine	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Title of Study: RANDOMIZED, UNICENTRIC, CROSS-OVER CLINICAL TRIAL TO EVALUATE THE BIOEQUIVALENCE OF TWO ORAL FORMULATIONS (10 mg TABLETS) OF EBASTINE IN HEALTHY VOLUNTEERS		
Investigators: Principal Investigator: [redacted]		
Study centre (s): [redacted] (Dos de Maig Hospital), Barcelona, Spain		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 12-Jul-06 Date study finalized (last patient last visit): 02-Aug-06	**Phase of development:** I	
Objectives: Primary: To evaluate the bioequivalence of two oral formulations (tablets) of ebastine in healthy volunteers Secondary: To evaluate the safety of the formulations used		
Methodology: Randomized, two-way, cross-over, open-label bioequivalence study conducted in healthy subjects. There was at least 1 week separating the treatment periods. Reference medication consisted of Ebastine [10 mg micronised ebastine tablets, Laboratorios Almirall S.A.S, France (Kestin®)] as one tablet single dose, and experimental medication consisted of Ebastine [10 mg tablets, Laboratorios Alter, Spain (Ebastine Alter ®)] as one tablet single dose.		
Number of subjects (planned and analyzed): Planned: 24 Screened: 39 Randomized: 24 Completed study: 24 Evaluated for pharmacokinetics: 24 Evaluated for safety: 24		
Diagnosis and main criteria for inclusion: Healthy subjects (male and female) meeting all the inclusion and none of the exclusion criteria of the study.		
Test product , dose and mode of administration, batch number, expiry date: Name: Ebastine Alter ® Administration route: Oral Dosage form: 10 mg tablets Dose and regimen: One tablet (single dose) Batch number: Z01 Expiry date: Jan/2008		
Duration of treatment: One single dose for each treatment (test plus reference) separated at least 1 week (washout period)		
Reference therapy, dose and mode of administration, batch number, expiry date: Name: Kestin ® Administration route: Oral Dosage form: 10 mg micronised ebastine tablets Dose and regimen: One tablet (single dose) Batch number: Z40B Expiry date: Apr/2009		

Name of Sponsor / Company: Almirall Prodesfarma, S.A **Name of Finished Product:** Kestin® and Ebastine Alter® **Name of Active Ingredients:** Ebastine	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Criteria for evaluation:

Pharmacokinetics:
Plasma concentrations of carebastine (main ebastine metabolite) at observed sampling-times [pre-dose, every hour during the first 8 hours, and at 12h, 16h, 24h, 36h, 48h, 72h and 96h post-dose (16 extractions)] were measured by LC/MS/MS (LLOQ: 3 ng/mL) for the calculation of the following pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$,, C_{max} C_{max}/AUC, T_{max}., $T_{1/2}$, λ_z, CL/f and Vz/f.

Assessment criteria	Main parameters	AUC_{0-t} and C_{max} Log-transformed data and parametric approach	80 – 125 %
	Secondary parameters	$AUC_{0-\infty}$ and $C_{max}/AUC_{0-\infty}$ Log-transformed data and parametric approach	80 – 125 %
		T_{max} (un-transformed) Hauschke's non-parametric approach	70 – 130 %
		$T_{1/2}$, λ_z, CL/f and Vz/f	Descriptive only

Safety:
Safety evaluations included adverse events, vital signs (heart and respiratory rate, blood pressure, temperature), 12-lead ECGs, clinical laboratory, and physical examination.

Statistical methods:
An analysis of variance (ANOVA) was used to evaluate treatment, sequence and period effects. Bioequivalence was assessed using a parametric approximation for AUC_{0-t}, C_{max}, $AUC_{0-\infty}$ and $C_{max}/AUC_{0-\infty}$ after logarithmic transformation, with a 90 % parametric confidence interval (90%CI) defined for the ratio after log-transformation, using the residual variability obtained in the ANOVA. The parametric Schuirmann approach, by means of a two one-sided t-test was also performed. T_{max} was analyzed by a non-parametric (Hauschke's) approach. The effect of sex and sex-by-formulation interaction were analyzed for exploratory purposes. The statistical significance was established at $p \leq 0.05$.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:
Carebastine data from 24 volunteers with data from both study periods.

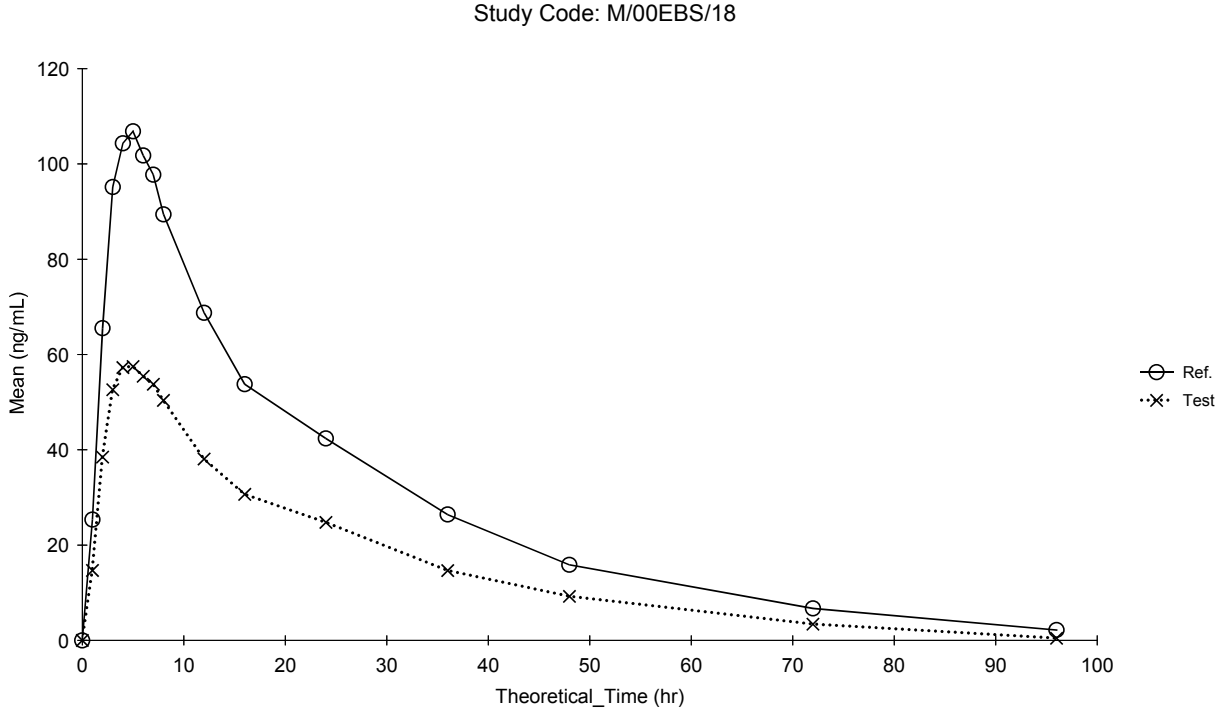
Parameter	Test[¥] (T) Ebastine Alter® N=24	Reference[¥] (R) Kestin® N=24	T/R Ratio[†] (%)	90%CI[†]
AUC_{0-t} (ng*h/mL), mean(SD)	1396.823 (526.402)	2565.124 (499.428)	52.4	(47.3, 58.0)
C_{max} (ng/mL), mean(SD)	61.721 (22.601)	117.229 (44.043)	52.6	(46.6, 59.4)
$AUC_{0-\infty}$ (ng*h/mL), mean(SD)	1524.507 (528.439)	2690.304 (503.914)	54.9	(49.9, 60.4)
T_{max} (h) , median (range)	4.000 (2.000-8.000)	4.000 (3.000-8.000)	100.0	(84.3, 106.9)
$C_{max}/AUC_{0-\infty}$ (h^{-1}), mean(SD)	0.041 (0.009)	0.043 (0.011)	95.8	(91.1, 100.8)
$t_{1/2}$ (h), mean(SD)	18.446 (3.264)	19.475 (3.344)	Not applicable	
λ_z, (h^{-1}), mean(SD)	0.039 (0.007)	0.037 (0.006)		
Cl/f (mL/h), mean(SD)	7187.812 (2040.168)	3844.957 (726.990)		
Vz/f (mL), mean(SD)	188455.873 (54075.117)	107960.466 (28505.453)		

[¥]Un-transformed descriptive data

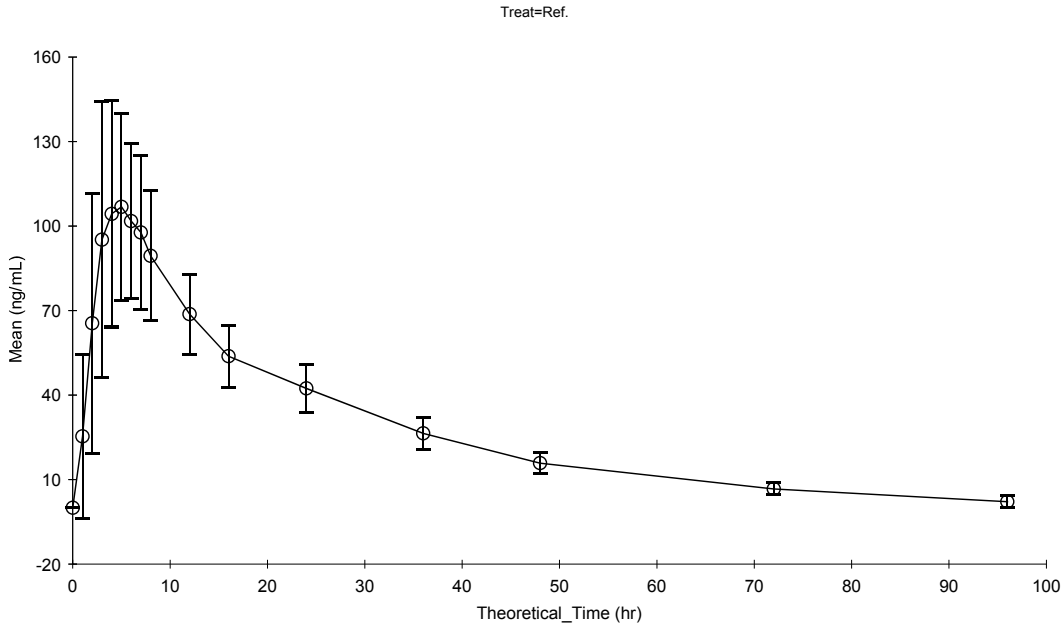
[†]Log-transformed data for ratios and CI except for T_{max}. The Hauschke non-parametric method was used for T_{max}

Ref.: Ebastine Almirall.

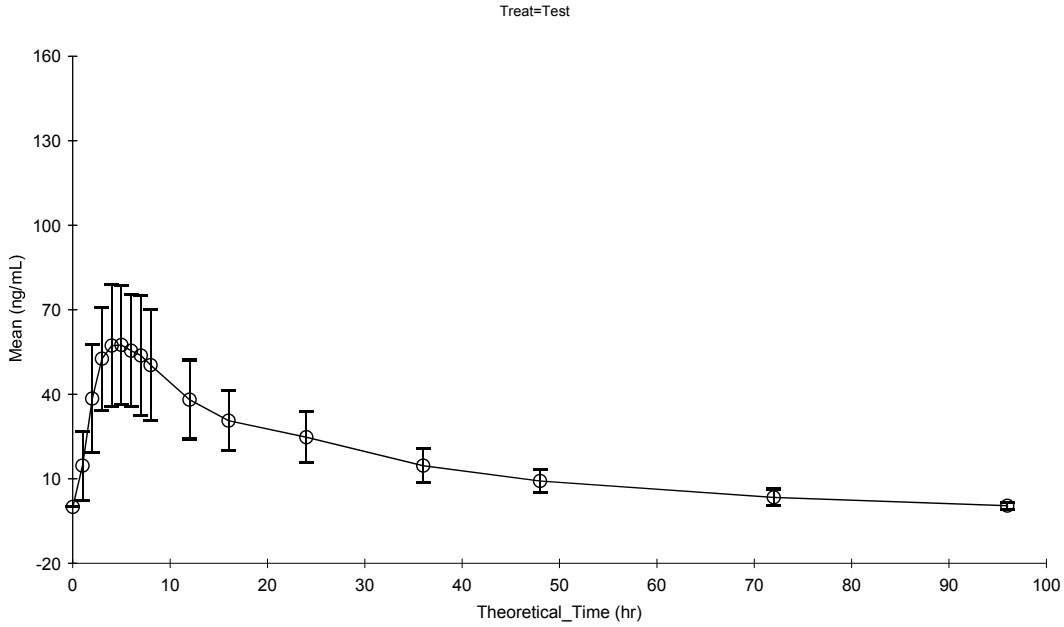
Test: Ebastine Alter.



Mean concentration vs time curve of carebastine



Mean (±SD) concentration vs time curve of carebastine for the reference formulation



Mean (±SD) concentration vs time curve of carebastine for the test formulation

Safety Results:

A total of 17 treatment emergent adverse events (AEs) occurred during the study.

Eight (8) AEs occurred in 8 subjects (33.3%) after one single dose Ebastine Alter®, and 9 AEs in 7 subjects (29.2%) after one single dose of Kestin® (Ebastine Almirall)

Body system	**Adverse event Preferred term**	**Test** Ebastine Alter® N=24	**Reference** Kestin® N=24	**Total** N=24*
		Events/Subjects	Events/Subjects	Events/Subjects
Any body system	Any event	8/8	9/7	17/12
Nervous System	Headache	4/4	5/4	9/7
	Somnolence	1/1	1/1	2/2
Blood and Lymphatic	Anaemia	1/1	2/2	3/3
Investigations	Blood Creatinine Increased	0/0	1/1	1/1
Gastro-intestinal	Dyspepsia	1/1	0/0	1/1
	Diarrhoea	1/1	0/0	1/1

(*) One Subject reported 2 episodes of headache (Ref) and 3 subjects reported AEs with both study drugs .
Source: App. 17.5, Table 49 and Listing 28

Overall, the most frequently reported AE was headache (5 AEs -2 episodes in one subject- after Kestin® and 4 after Ebastine Alter®) followed by anaemia (2 AEs after Kestin® and 1 after Ebastine Alter®) and Somnolence (1 AE after Kestin® and 1 after Ebastine Alter®)

No serious or severe AE occurred and no withdrawals occurred due to AEs.

Most of AEs (11 of 17) were assessed as being related to the study drug by the Investigator. All AEs were of mild intensity except 4 AEs that were moderate: two (2) anaemia (assessed as not related with the study drug by the investigator), one (1) creatinine increased (assessed as not related with the study drug by the investigator) and one (1) headache (see Table 16 and Table 17).

No relevant findings concerning physical examination, vital signs and ECGs were reported.

CONCLUSIONS:

No statistically significant period or sequence effects were detected. All test/reference ratio estimates and 90%CI of AUC_{0-t}, C_{max} and $AUC_{0-\infty}$ lay entirely below the pre-established margins of bioequivalence. Therefore, according to the results obtained from the statistical analysis of the pharmacokinetic parameters, it can be concluded that the test Ebastine Alter® 10 mg tablets are not bioequivalent to the reference Kestin® 10 mg micronised ebastine tablets, and that Ebastine Alter® 10 mg shows approximately half of the bioavailability of Kestin® 10 mg micronised ebastine tablets.

None of the few reported AEs were serious, and no withdrawals occurred due to AEs.
The safety profile was similar in both formulations (test and reference) and matched with the expected ebastine safety profile.

DATE OF REPORT:
13-Nov-06