***CONFIDENTIAL***

**FINAL REPORT**

**Final report code: M/EBSFD/05**

**Name of test drug: Ebastine**
**Indication studied: n/a**
**Study phase: I (IV)**

**Title: "A DOUBLE BLIND, RANDOMIZED, UNICENTRIC, CROSSOVER AND PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE INHIBITORY EFFECT OF EBASTINE 20 mg (ORAL LYOPHILISATE) AND DESLORATADINE 5 mg ON THE HISTAMINE INDUCED SKIN REACTION IN HEALTHY VOLUNTEERS".**

## (Protocol Code: M/EBSFD/05)

**Date of study beginning (first treatment administration): April 25, 2005**
**Date of study end (last treatment administration): June 8, 2005**
**Date of report: 22 December 2005**

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

# 2.- SYNOPSIS

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|---|---|---|
| **Name of Sponsor / Company:**<br>Almirall Prodesfarma, S.A.<br>**Name of Finished Product:**<br>Ebastel® Forte Flas<br>**Name of Active Ingredients:**<br>Ebastine | **Individual Study Table Referring to Part of the Dossier**<br>**Volume:** N/A<br>**Page:** N/A | **(For use by National Authorities only)** |

**Title of Study:**
A double-blind, randomized, unicentric, cross-over and placebo-controlled clinical trial to evaluate the inhibitory effect of ebastine 20 mg (oral lyophilisate) and desloratadine 5 mg on histamine induced skin reaction in healthy volunteers.

**Principal Investigators:**
[redacted]

**Study centre(s):**
Research Institute. Drug Research Area. Clinical Pharmacology Dept. Hospital de la Santa Creu i Sant Pau. 08025 Barcelona (Spain). [redacted]

**Publication (reference):**
N/A

| **Study period (years):** | **Phase of development:** |
|---|---|
| April-June2005 | I (IV) |

**Aims:**
The main aim of the trial was to compare the pharmacodynamic effect of Ebastine 20 mg (oral lyphilisate), Desloratadine 5 mg and Placebo administered once daily for 5 days. The main variable studied was the percentage reduction from baseline of histamine-induced wheal 24 hours after a 5 days treatment period. Secondary variables were the evaluation of: pharmacodynamic effect of drugs after the first dose administered, onset of action of the administered treatments as well as the oral lyophilisate acceptability and treatments tolerability.

**Methodology:**
Double blind, double dummy, crossover and placebo-controlled clinical trial with randomised treatment sequences.
Intracutaneous histamine challenge was conducted on different occasions during the study: Once at the screening visit to asses volunteer's eligibility; Repeatedly at day 1 of each study period (prior and during 2 hours after the 1$^{st}$ dose administered) to evaluate the "onset of action"; One at day 2 of each study period to assess IMP efficacy 24h post one dose; and one at day 6 of each study period to assess IMP efficacy 24h post five consecutive doses. On day 1, a subjective evaluation of heat, itching and pain perception was also conducted after each histamine injection.
The skin reactivity tests were performed in the ventral surface of forearms using 0.05 ml of a solution of 100 μg/ml of histamine and following the area/time/volunteer random generated for this study in order to avoid bias due to the possible different sensitivity of the cutaneous areas. The wheal surface was recorded (15 minutes after histamine inoculation) by planimetry using the scanner and Prick-Scan® software (Inmunotek S.L.).
Itching, heat and pain perception was also evaluated on day 1 (10 minutes after histamine inoculation) by means of Visual Subjective Scales.
Laboratory tests, vital signs, complete physical examination by systems and ECG recordings were performed on day 0 and day 6 of each treatment period.
The process was repeated with each of the study drugs after a washout period between treatments of 7 to 10 days.
Concomitant medication and all adverse events reported during the study were recorded.
At the end of study, all subjects were required to evaluate its experience of the lyophilisate pharmaceutical form via a multiple-choice closed questions questionnaire.

**Number of subjects (planned and analysed):**
36 healthy Caucasian volunteers of both sexes were included of whom 35 completed the study (14 men and 21 women). Pharmacodynamic analysis was performed with those subjects who completed the three treatment periods. Safety analysis was performed with all the data available of all the subjects included in the study.

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**Diagnosis and main criteria for inclusion:**

Healthy Caucasian volunteers of both sexes aged from 18 to 40 years not presenting positive dermatographism.

**Test product, dose and administration route, batch number and expiry date:**

Oral lyophilisate form of ebastine 20 mg, batch number: 248120 and with expiry date in January 2007.

**Duration of treatment:**

5 days in each of the 3 treatments.

**Reference product, dose and administration route, batch number and expiry date:**

Oral capsules of Desloratadine 5 mg (batch number: 020F0034) and Desloratadine placebo (batch number: 019F0033) and oral lyophilisate form of Ebastine Placebo (batch number: 257700).

Desloratadine 5 mg and Desloratadine Placebo were presented in gelatine capsules to maintain the double blind condition.

**Evaluation criteria:**

Main variable:

- Percentage of reduction from baseline value of the wheal area at +24 hours after the 5$^{th}$ dose administered.

Secondary variables:

- Percentage of reduction from baseline value of the wheal area at +24 hours after the 1$^{st}$ dose administered.
- Percentage of reduction from baseline value of the wheal area at +20', +40', +1h, +1h 20', +1h 40' and +2h after the 1$^{st}$ dose administered.
- Change from baseline of the heat, itching and pain scores obtained at +20', +40', +1h, +1h 20', +1h 40' and +2h after the 1$^{st}$ dose administered by means of visual analogical scales.
- Scores obtained in the acceptability questionnaire at the end of the study (taste acceptability, convenience and preference).

**Safety:**

The study protocol included vital signs, physical examination, standard laboratory tests (biochemistry, haematology, urinalysis), ECG recordings and monitoring of possible adverse events.

**Statistical methods**:

The statistical analyses were performed by means of bilateral approach using the SAS v8 statistical program. The statistically significant level was established at 5% ($\alpha$=0.05).

Activity variables were evaluated following the "per protocol" criteria. The safety analysis population consisted of those volunteers who received at least one dose of one of the 3 treatments.

The analyses of percentage reduction from baseline of the wheal area at +24 hours after the 5$^{th}$ dose and at +24h after the 1$^{st}$ dose, consist on an analysis of covariance (ANCOVA) for crossover designs, with baseline value of wheal area as a covariant and including the following factors: treatment, period, sequence and subject within sequence. The treatment effects, the inter-treatment differences, their standard errors and 95% confidence intervals were estimated by means of Least Squares (LS) means.

The "onset of action" (objective and subjective variables) was analysed by means of an ANCOVA model with baseline value of wheal area as a covariant and including the following factors: sequence, subject within sequence, period, time, treatment and treatment by time interaction. The treatment effects on each evaluation time, the differences between treatments on each evaluation time, their standard errors and 95% confidence intervals were estimated by means of Least Squares (LS) means.

Descriptive analyses were applied to the variables obtained in the oral lyophilisate acceptability questionnaire (taste acceptability, convenience, preference).

The tolerability variables were also analised descriptively. In either case, the results evaluation was made in terms of "clinically relevant changes".

**Pharmacodynamic Results:**

MAIN VARIABLE

Wheal area percentage reduction at +24h after the 5$^{th}$ dose administered:

After 5 days of treatment (at +24h after the five dose administered) Ebastine 20 mg induced a percentage of reduction from baseline of the wheal area significantly greater than the percentage of reduction induced by Desloratadine 5 mg (LS mean = 29.03; $p < 0.0001$) and Placebo (LS mean = 43.66; $p < 0.0001$). Statistically significant differences were also found in the comparison between Desloratadine 5 mg and placebo (LS mean = 14.63; $p = 0.0013$).

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SECONDARY VARIABLES

Wheal area percentage reduction at +24h after the 1st dose administered:

At +24 hours after the first dose administered, Ebastine 20 mg induced a percentage of reduction from baseline of the wheal area significantly greater than the percentage of reduction induced by Desloratadine 5 mg (LS mean = 37.02; $p < 0.0001$) and Placebo (LS mean = 36.97; $p < 0.0001$). No statistically significant differences were found between Desloratadine 5 mg and Placebo.

"Onset of action":

Although Ebastine 20 mg showed the largest skin reactivity inhibition over 2 hours after the 1st dose administered, no statistically significant differences were found. No significant differences were also found for the subjective assessment of the itching, heat and pain perception after histamine inoculation.

Oral lyophilisate acceptability:

Almost all the subjects were quite or very satisfied with the initial and final taste of the new oral lyophilisate formulation (86% and 77% of the subjects, respectively). The 91.5% of the subjects considered their convenience as "very or quite convenient" and the 80 % of the subjects reported their preference for this new formulation.

**Safety Results:**

No Serious Adverse Events ot other Expeditedly Reportable Events as defined by protocol were observed. Nine volunteers (25%) reported a total of 14 AE. Four were of mild intensity and 10 of moderate intensity. The causal relationship with the study drugs was considered "unlikely" in 6 cases and "possible" in the remaining 8 cases. Five occurred during the period of treatment with Ebastine 20 mg (intermittent somnolence, pharyngolaringeal pain, pyrexia, back pain and oral pain), 5 occurred during the period of treatment with Desloratadine 5 mg (asthenia (2), dry mouth, somnolence and back pain) and 4 occurred during the treatment with placebo (diarrhoea (2), drowsiness and headache).

No clinically significant changes were found regarding vital signs, physical examination, ECG and laboratory parameters.

**Conclusions:**

Ebastine 20 mg showed a significant superior antihistamine activity compared to those obtained with Desloratadine 5 mg at +24h after the 5th dose and at +24h after the 1st dose administered, also reaching statistical significance compared to Placebo. In contrast, the percentage of skin reactivity inhibition obtained with Desloratadine 5 mg was of lower magnitude than Ebastine 20 mg and only reached statistical significance in comparison to Placebo at +24 hours after the 5th dose administered.

No significant differences between study drugs were found in the "onset of action" evaluations (neither objective nor subjective).

The oral lyophilisate form acceptability was very good.

The drugs evaluated were safe and well tolerated.

**Date of report:** 22 December 2005