2. SYNOPSIS

Company name: ACRAF S.p.A	Tabular format referring to	(For National Authority Use Only)
Name of the finished product: Tantum Pomata Forte	Volume:	
Name of the active substance: Benzydamine	Page:	

Title of the study: A randomized, double-blind, placebo-controlled trial of benzydamine hydrochloride cream in the treatment of plaque psoriasis: a proof-of-concept and dose-finding study

[redacted]

Study centre(s): Multicentre study [redacted]

Publication (reference): not applicable

Study period (years): 2009-2010	**Clinical Phase:** II

Objectives: The aim of the study was to assess the safety and efficacy of benzydamine hydrochloride 5% cream (test product 1) and benzydamine hydrochloride 3% cream (test product 2) in comparison with placebo in treating mild to moderate chronic plaque psoriasis.

Methodology: Randomized, double blind, placebo controlled, parallel groups study. Seven visits were scheduled over a maximum period of 113 days (including window periods), to evaluate efficacy and tolerability of treatments. The treatment period lasted 28 days (from Visit 0 to Visit 3). A 58-day (±7) observation period (FU1 and FU2) followed-up the treatment period to assess relapses.

Number of subjects (total and per treatment): Ninety-five patients (43 females, 52 males; age range 19-77 years) were enrolled and randomized (32 in the benzydamine 3% group, 30 in the benzydamine 5% group, and 33 in the placebo group).

Diagnosis and inclusion criteria: Patients with mild to moderate chronic plaque psoriasis. Inclusion criteria: men and women ≥ 18 and ≤ 70 years old; clinical diagnosis of chronic plaque psoriasis for at least 12 months; mild to moderate psoriasis, defined as a PASI score ≤10 and a BSA ≤12; subjects legally capable to give their consent to participate in a clinical study; women of childbearing potential had to agree not to start a pregnancy from the signature of the informed consent up to 30 days after the last administration of the investigational product; sexually active men had to commit not to start a pregnancy with their partner/wife from the first dose of investigational product up to 30 days after the last administration of the investigational product.

Test product 1, dose, mode of administration, batch No.: benzydamine 5% cream (skin application into the affected area) once daily. Manufacturer batch no. 00110IP02 (expiry dates: 31/01/10; 31/08/10)

Test product 2, dose, mode of administration, batch No.: benzydamine 3% cream (skin application into the affected area) once daily. Manufacturer batch no. 00111IP02 (expiry dates: 31/01/10; 31/08/10)

Duration of treatment: 28 days

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Reference therapy, dose, mode of administration, batch No.: placebo cream (skin application into the affected area) once daily. Manufacturer batch no. 00115IP02 (expiry dates: 31/01/10; 31/08/10)

Assessment criteria:

The efficacy of the test drug was assessed on the basis of the clinical and statistical endpoints. The drug was considered effective from a clinical viewpoint if a reduction ≥ 75% and/or ≥ 90% of the Psoriasis Area and Severity Index (PASI) with respect to the patient's baseline was detected (within patient analysis). From a statistical point of view, the drug was considered effective if a difference of at least 50% between the placebo arm and either one out of the two treatment groups, in the number of patients showing a reduction ≥ 50% in the PASI score, was detected. Additional efficacy parameters were the Body Surface Area (BSA), the Index Lesions Visual Assessment (ILVA), and a Visual Analogue Scale (VAS)for Itching. Safety was assessed on the basis of the prevalence of adverse events, and changes in vital signs (heart rate and blood pressure), physical examinations, and laboratory exams.

Statistical methods:

Efficacy analyses were performed on the Intention To Treat (ITT) population, defined as all randomised subjects who received at least one dose of the investigational product, and had at least one post-baseline efficacy evaluation. Missing values were replaced by the last observation available (LOCF, Last Observation Carried Forward). A description of the population characteristics was performed on all randomised subjects. The response rate in PASI score was analyzed using the chi-square test, comparing each benzydamine group with the placebo group. The Fisher exact test could be used, if more appropriate. Secondary efficacy endpoints were analysed by using parametric or non-parametric analysis. The VAS score was compared with an analysis of variance using, if necessary, the baseline values as covariate.

All randomised patients treated with at least one dose of the investigational product were included in the safety population. Adverse events were tabulated by body system accordingly to the MedDRA categorization. The Chi-square or Fisher's exact test were as regards the percentage of subjects with adverse events. Changes in physical examination and vital signs were descriptively evaluated. Laboratory examinations were evaluated according to the Investigator's interpretation and the normal ranges.

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SUMMARY – CONCLUSION

Efficacy results:

No patients had a reduction of at least 75% in the PASI score at Visits 1 and 2 compared to baseline, but one patient in the benzydamine 3% treatment group. Thus, from a clinical point of view the drug was effective in only one patient at the end of the treatment period. At the follow-up 1, two, three and three patients in the benzydamine 5%, benzydamine 3% and placebo group respectively, had a reduction of at least 75% in the PASI score. At follow-up 2, no patients had a reduction of at least 75% in the PASI score. When the percentage of patients showing a reduction ≥ 50% in the PASI score is considered, a difference of at least 50% between the placebo arm and either one out of the two treatment groups was not reached, and no statistically significant differences between groups were detected. The BSA showed a substantial constancy throughout the study, without significant statistical differences between groups or when compared with their own baseline. In the ILVA scores, statistical analysis applied to the Refractory and Trunk Areas evidenced some significant changes from baseline. No significant differences between groups were detected in the Refractory Area, while in the Trunk Area some significant differences between groups were detected. The VAS mean change from baseline for itching did not show any significant difference between groups, while statistically significant changes from baseline were detected.

Safety results:

During the study 3 serious AEs, including one death for myocardial infarction, occurred in three patients of the placebo arm. No deaths or serious adverse events occurred in patients treated with the test product.

The highest number of AEs was recorded in the placebo group (9 AEs), followed by benzydamine 3% (8 AEs), and benzydamine 5% (6 AEs). Most of the AEs were of mild intensity in benzydamine 3% and 5% treatment groups, whereas most were of moderate intensity in the placebo treatment group (Table 14.12). Only three and two AEs in the benzydamine 3% and placebo groups respectively, were severe in intensity.

The assessment of urinalysis, hematology and serum chemistry tests did not show clinically significant alterations or signals referable to the administration of the test product. Similarly, no significant changes in vital signs and physical examination were detected.

Conclusion:

Study results did not demonstrate the efficacy of benzydamine 3% and 5% creams in comparison with placebo in patients with plaque psoriasis. On the other hand, the very good safety profile of topical applied benzydamine 3% and 5% creams was confirmed.

Date of report: November 4th, 2011