2 Synopsis

Name of Sponsor/Company: Ursapharm Arzneimittel GmbH & Co. KG, Industriestr. 35, 66129 Saarbrücken, Germany	*Individual Study Table Referring to Part of the Dossier* *Volume:* *Page:*	*(For National Authority Use Only)*
Name of finished product: Bromelain-POS®		
Name of active ingredients: Bromelain		

Title of study:
Reduction of Pain under Pressure of an Experimentally Induced Hematoma in Healthy Volunteers by two Bromelain Preparations (Bromelain-POS® and Traumanase® forte)

Investigator(s):
Michael-W. Kleine, MD, Egenhofenstr. 18, 82152 Planegg, Germany

Study center:
Michael-W. Kleine, MD, Egenhofenstr. 18, 82152 Planegg, Germany

Publication (reference/s):
n/a

Studied period (mo./years): *date of first enrolment:* *date of last completed:*	1 month June 24, 2006 July 13, 2006	*Phase of development:* Clinical study phase III

Objectives:
To demonstrate equivalent efficacy of Bromelain-POS® and Traumanase® forte in the model of an experimentally induced hematoma as a substitute for bioequivalence testing.

Methodology:
Double-blind, randomized clinical study with two parallel groups, balanced for males and females by separate randomization.
The hematomas were induced by injection of own blood subcutaneously into one forearm.
Measurements of reduction of pain under pressure using a special pressure gauge; reduction of hematoma by judgment of change of color.

Number of subjects (planned and analyzed):
140 planned, 140 included, 140 evaluated (70 Bromelain-POS® group, 70 Traumanase® forte group), balanced for each 35 males and 35 females per group.

Diagnosis and main criteria for inclusion:
Main inclusion criteria: Healthy subjects of either sex; 18-40 years; written informed consent signed; willing to fulfill the study requirements. – Main exclusion criteria: no forbidden concomitant medication; no intolerability of test drugs or ingredients; no pregnant or nursing female; limited absolute and difference values during screening pain threshold measurements.
(Detailed inclusion and exclusion criteria: cf. 9.3.1 and 9.3.2)

Test product, dose and mode of administration, batch number:
Bromelain-POS® : bromelain 500 F.I.P. units (66.7-100 mg), as a genuine mixture of bromelain A and bromelain B; 1 tablet orally b.i.d. (= 2 tablets per day), batch no.: 007 036;
4 matching placebo tablets orally b.i.d. (= 8 tablets per day), batch no. P001101

Duration of treatment:
11 days

Reference therapy, dose and mode of administration, batch number:
Traumanase® forte: 40 mg bromelain standardized to 100 F.I.P. units per tablet; 5 tablets orally b.i.d. (= 10 tablets per day), batch no. 50291

Synopsis – page 2

Name of Sponsor/Company: Ursapharm Arzneimittel GmbH & Co. KG, Industriestr. 35, 66129 Saarbrücken, Germany	*Individual Study Table Referring to Part of the Dossier*	*(For National Authority Use Only)*
Name of finished product: Bromelain-POS®	*Volume:*	
Name of active ingredients: Bromelain	*Page:*	

Criteria for evaluation:

Efficacy:

Main endpoint was the sum of the reduction of pain under pressure from day 0 through day 10. Secondary endpoint was the reduction of the hematoma.

Safety:

Frequency and kind of adverse events during treatment; standardized laboratory parameters measured before and after end of treatment; subjective judgment of tolerance by the subjects.

Statistical methods:

The Student's t-test on equivalence has been performed on the main endpoint to compare the two bromelain groups. A level of significance of $\alpha < 0.05$ was defined. The test was performed two-sided. 90% confidence intervals were calculated. A range of ± 20% of the sum of the pain thresholds in the control group (Traumanase® forte) was defined to be accepted as equivalent. This range is small enough, as a value of > 100% higher in a placebo group is known from other studies.

SUMMARY – CONCLUSIONS:

EFFICACY RESULTS

As main endpoint on equivalence, the sum of differences of pain under pressure from day 0 through day 10 was evaluated. It was calculated from the daily differences between the pain thresholds of the hematoma carrying arm and the control arm. In the Bromelain-POS® group this sum was 5.21 kp/cm² on average (range 1.1 – 9.8 kp/cm²), in the Traumanase® forte group 5.35 kp/cm² on average (range 1.5 – 10.7 kp/cm²). The statistical evaluation by means of the Student's t-test yielded a Mann-Whitney estimator of 0.5193 with a 90% confidence interval between 0.4393 and 0.5984. Both limits lay in between the range of equivalence (benchmarks 0.36 – 0.64). Consequently, the equivalence of both groups has been proved according to the conditions predefined in the protocol with an acceptable difference between the groups of $\delta \leq 20\%$.

SAFETY RESULTS

Adverse events (AEs) were reported in both treatment groups, with comparable frequency, type and severity: in the Bromelain-POS® group in seven subjects (4 males, 3 females), and in the Traumanase® forte group in five subjects (3 males, 2 females). Two (Bromelain-POS® group) and one (Traumanase® forte group) AEs were probably or possibly related to the study drug.
Also the global judgments of the tolerance both by the investigator and by the subjects were comparable: it was judged as "very good" or "good" in all (Bromelain-POS® group) or in 69/70 (Traumanase® forte group) cases, respectively, by the investigator, and in 68 (Bromelain-POS® group) or 69 (Traumanase® forte group) cases, respectively, by the subjects.

CONCLUSIONS

The results have proved equivalent efficacy of Bromelain-POS® in the main endpoint. The difference between the groups was 2.4% (90%-CI: -7.9% - 12.9%), which is clearly below the predefined acceptable equivalence range of $\delta \leq 20\%$.

Date of the report:

23 October 2006