ICH E3-Report BRODOS09 – Synopse – EudraCT-No. 2009-015804-24

Name of Sponsor: URSAPHARM Arzneimittel GmbH, Industriestr. 35, 66129 Saarbrücken, Germany	
Name of Finished Product: Bromelain-POS	
Name of Active Substance: Bromelain	
Title of Study: Perioperative oedema therapy with bromelain after extraction of wisdom teeth – Test for efficacy as a function of different doses (dose-finding study)	
Investigators: PD Dr Kai-Hendrik Bormann Sandra Haas (née Meckfessel) Heike Kloppenburg Pia Staude (née Edel)	
Study centre: Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie Medizinische Hochschule Hannover Carl-Neuberg-Strasse 1 30625 Hannover, Germany	
Publication: -	
Studied period **Date of first enrolment:** 01/10/2010 **Date of last completed:** 01/08/2014	**Phase of development: II**
Objectives: The objective of this investigation is to test the efficacy of bromelain at different doses under standardised conditions for preventing oedema after the operative extraction of wisdom teeth.	
Methodology: Prospective, randomised, placebo-controlled, three-armed, double-blind crossover study	
Number of patients (planned and analyzed): 72 patients planned, 75 analyzed	
Diagnosis and main criteria for inclusion: Inclusion criteria: • Patients with fully retained molars in positions 18, 28, 38 and 48 (wisdom teeth) • Male and female patients aged 15 to 40 years old • Indication for a tooth extraction • Provision of information and written consent of the patient or parent/legal guardian • Willingness to accept the additional effort for the study Exclusion criteria: • Patients who do not fulfil all of the above-named inclusion criteria • Known allergy to the investigational medicinal product or to its ingredients (also: known allergy to pineapple) • Blood clotting disorder • Treatment with anti-inflammatory drugs less than two weeks ago • Acute inflammation in the mouth area • Pregnancy and lactation • Chronic alcohol, medication or drug abuse within the last year	

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• Severe liver and/or kidney damage • Antirheumatic and anticoagulant medications • Participation in clinical trials within the last 30 days • Concomitant participation of another clinical trial • Neurological diseases • Patients for whom poor compliance is expected • Patient does not want to refrain from using local measures such as cooling or applying anti-inflammatory topical creams • An expected deviation of more than 10 minutes in the operation times of the first and second operations (intraindividual comparison) • Bearded persons (because the 3D scan is not possible)
Test product, dose and mode of administration, batch number: **Preparation A:** Test product Bromelain-POS 500 F.I.P. bromelain/tablet **Preparation B**: Placebo The placebo has the size and appearance of the test product (Bromelain-POS); the content of the active substance is replaced by microcrystalline cellulose **Treatment group 1:** 1,000 F.I.P. bromelain/day Preparations A and B (test product / placebo): 1 tablet preparation A (test product) and 2 tablets preparation B (placebo) in the morning and evening and 3 tablets preparation B (placebo) midday, for 9 days; in crossover to placebo (3 tablets preparation B three times daily) **Treatment group 2:** 3,000 F.I.P. bromelain/day Preparations A and B (test product / placebo): 2 tablets preparation A (test product) three times daily and 1 tablet preparation B (placebo) three times daily for 9 days; in crossover to placebo (3 tablets preparation B three times daily) **Treatment group 3:** 4,500 F.I.P. bromelain/day Preparation A (test product): 3 tablets three times daily for 9 days; in crossover to placebo (3 tablets preparation B three times daily) Take: 3 tablets three times daily (total of 9 tablets/day) with some liquid approx. 30 minutes before the main meals <u>Batches used for Bromelain-POS®:</u> Batch-No.: 006010 (Exp.: 01/2013) Batch-No.: 205980 (Exp.: 08/2015)
Duration of treatment: 9 days, start on day before wisdom teeth surgery
Reference therapy, dose and mode of administration, batch number: Placebo medication

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Batches used for Placebo:

Batch-No.: P001020 (Exp.: 01/2013)

Batch-No.: 206702 (Exp.: 08/2015)

Dose and mode of administration: refer to section above ("Test product, dose and mode of administration")

Criteria for evaluation:

Efficacy:

The primary efficacy parameter is the extent of swelling of the cheeks over time measured as AUC postoperatively on examination days 2, 4 and 7 in comparison to the baseline.

Secondary:

- Pain
- Maximum extent of swelling
- Postoperative use of analgesics
- Symptom assessment (difficulty in swallowing) by the patient

Safety:

- Spontaneous reporting of clinically relevant AE
- Overall clinical impression from the point of view of the investigator and patient
- Tolerability

Statistical methods:

The therapeutic effect (as difference to placebo) is estimated for each dose group through the crossover study design. In an ordered system of hypotheses, it will be first tested whether there is a dose-response relationship. The dose-response relationship is demonstrated if the estimated therapeutic effect from the pooled treatment groups 2 and 3 is greater than that of treatment 1. After rejecting this global hypothesis, it will be tested whether treatment 2 is superior to treatment 1 in a second step. If this hypothesis can also be rejected, it will then be tested whether treatment 3 is superior to treatment 1.

All analyses will be adjusted for periods. The primary analysis is performed in the mITT population for all patients for whom measurements could be made in both periods. The type 1 error is defined as 5% (two-sided).

Summary - Conclusions:

Efficacy results:

No significant difference between treatment 1 (1000 F.I.P.) and the pooled treatment groups 2 and 3 (3000 and 4500 F.I.P.) (estimated difference: -0.63, confidence interval: [-25.2; 23.9], p-value = 0.960) was observed. Therefore, the global primary hypothesis of dose-response-relationship was rejected, and a superiority of higher dosages (3000 F.I.P. and 4500 F.I.P.) as compared to the registered dose (1000 F.I.P.) has not been established.

Analysis of secondary efficacy endpoints (extent of swelling of the cheeks (AUC), maximal swelling, pain, use of analgetics and difficulties in swallowing) did not yield significant results, as well. However, all estimates of the difference between the treatment groups tend to show better results for bromelain as compared to placebo. Statistical significance was nearly reached in the main parameter "Extent of swelling of the cheeks" (p = 0.0892), with an average decrease in swelling of approximately 20% under bromelain treatment as compared to placebo when all dose

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groups were combined for the analysis. **Safety results:** There were no events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, or deaths due to intake of the study medication. Adverse events under bromelain treatment did not occur more frequently as compared to placebo treatment, even though this study was performed in a perioperative setting and in spite of the administration of high daily dosages in the Bromelain 3000 F.I.P. and Bromelain 4500 F.I.P. treatment groups. **Conclusion:** A superiority of higher dosages (3000 F.I.P. and 4500 F.I.P.) as compared to the registered dose (1000 F.I.P.) could not be established in this study and indication. The effects observed in this clinical trial, conducted with a limited number of patients included, yet support the beneficial effect of perioperative bromelain treatment and are considered as clinically relevant. A positive risk-benefit profile can be altogether concluded given the good safety and tolerability profile of bromelain as observed in this clinical trial.
I hereby confirm that the data in the results report were collected properly and are correct. **Date of the report: 22.07.2015** **Print Name:** PD Dr Kai-Hendrik Bormann **Signature:**