2. SYNOPSIS

Name of Sponsor/Company: Ursapharm Arzneimittel GmbH Industriestraße 35 D-66129 Saarbrücken	Individual Study Table Referring to Part of Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Bromelain tablets hysan®		
Name of Active Ingredient: Bromelain		

Title of Study:
Efficacy and tolerabilty of Bromelain tablets hysan® in patients with chronic rhinosinusitis.
A prospective, double-blind, randomized, placebo-controlled multi-centre trial.
A proof of concept study.

Investigators:
Prof. Dr. med. Ralph Mösges
Peter Hinterkausen
Taufik Shahab
Dr. med. Martin Sondermann
Dr. med. Norbert Pasch
Dr. med. Uta Thieme
Facharzt f. HNO-Heilkunde (Physician was not ready to publish his name.)
HNO-Abteilung eines Krankenhauses (Physician was not ready to publish his name.)

Study centres:
Steppenbergerallee 12, 52074 Aachen, Ralph Mösges, Norbert Pasch
Lindenthalgürtel 2, 50935 Köln, Peter Hinterkausen
Neumarkt 41, 50667 Köln, Taufik Shahab
Auf der Ell 1-3, 52078 Aachen, Martin Sondermann
Mercatorstraße 10, 47051 Duisburg , Uta Thieme
478xx Krefeld**,** Facharzt f. HNO-Heilkunde
890xx Ulm , HNO-Abteilung eines Krankenhauses

Publication (reference): -

Studied period:	**Phase of development:**
11 months Date of first enrollment: 11th March 2014 Date of last completed: 8th January 2015	Phase IIa

Objectives
The purpose of this clinical trial was to evaluate the efficacy and tolerability of Bormelain tablets hysan® (3,000 F.I.P./d) compared to placebo in patients suffering

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from chronic rhinosinusitis.

Primary efficacy parameter:
Assessment of the efficacy of the therapy with Bromelain tablets hysan® on a „**Total Rhinosinusitis Symptom and Rescue Medication Score (TRSSRMS)“** taking into account

- A “**Rhinosinusitis Symptom Score (RSSS)“**according to EPOS guidelines [1], of the four rhinosinusitis symptoms nasal obstruction, nasal discharge, facial pain/pressure and reduction or loss of smell.

And

- a “**Rescue Medication Score (RMS)**”, taking into account the use of paracetamol tablets as well as decongestant nasal spray (hysan® Schnupfenspray, Ursapharm)

Secondary efficacy parameters:

1. **Sino-Nasal-Outcome-Test-20 German Adapted Version (SNOT-20 GAV) [2, 3, 4]:** This test consisted of 20 items indicating the severity of symtoms on a scale of 0 (= no problem) to 5 (=no further worsening imaginable). The overall score (OS) was the sum of the values of the 20 items. The SNOT-20 GAV was used to assess the quality of life which was performed by the patient at visit V1 – V5.
2. **Course of Symptoms:** Nasal obstruction**,** nasal discharge**,** facial pain or facial pressure and reduction or loss of smell (hyposmia or anosmia).
3. **Cytokine diagnostics:** Effects of the treatment on the immune system were tested at Visits 1 and 2, by use of the TruCulture® blood collection and whole-blood culture device.
4. Measurement of **Peak Nasal Inspiratory Flow** (PNIF)
5. **Nasal examination and rhinoscopic inspection with optics**: A nasal examination (rhinoscopy) with a following diagnostic evaluation was performed at every visit. The nasal symptoms edema, secretion and redness were

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assessed by the investigator at each visit.

Safety
The safety of the treatment was documented by the physical examinations, the description of the adverse events (frequency, intensity, severity and duration of adverse events) and the safety laboratory data during the treatment with Bromelain hysan® tablets.

Methodology:
A prospective, double-blind, randomized, placebo-controlled, multicenter, phase IIa-study. A proof of concept study.

Number of patients (planned and analysed):
It was planned to recruit 40 patients in total, with 20 participants in each treatment group. A total number of 40 patients were recruited and screened for inclusion and exclusion criteria; 40 eligible patients were included into the statistical analyses.

Diagnosis and main criteria for inclusion:

Female or male patients aged 18 to 75 years with chronic rhinosinusitis diagnosed by the physician after an endoscopic and pre-existing CT examination. Furthermore, patients must have characteristic symptoms according to EPOS guidelines [1] composed of two or more symptoms which had to be diagnosed by a rhinoscopic and ENT-specific examination by the physician. One of these symptoms had to be either nasal obstruction or nasal discharge (anterior/posterior rhinorrhea),

± facial pain or facial pressure respectively headache

± loss of smell or change in perceptions of smell.

The Rhinosinusitis Symtome Score (RSSS) had to be ≥ 6.

Test product, dose and mode of administration, batch number:
Bromelain tablets hysan® in a dosage of 500 F.I.P. or placebo. Daily intake of six tablets.
Batch-no.: 209067/208701

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Duration of treatment:
84 days

Criteria for evaluation:

Assessment of the primary efficacy variable:

- For the RSSS (maximum daily score of 12) and the RMS (maximum daily score of 18), the daily values (as determined by the patients in their diary) were combined to a daily TRSSRMS by addition.
  All individual daily TRSSRMS-values were accumulated during the 84 days of treatment. Then, the mean daily scores during that period were calculated for both parameters (RSSS and RMS) and the combination TRSSRMS.

Assessment of the secondary efficacy variable:

- Sino-Nasal-Outcome-Test-20 German Adapted Version (SNOT-20 GAV): This test consisted of 20 items indicating the severity of symptoms on a 6-point scale of 0 (= no problem) to 5 (= no further worsening imaginable). The overall score (OS) was the sum of the values of the 20 items. The test was documented by the physicians at all visits V1-V5.
- Course of the symptoms nasal obstruction, nasal discharge, facial pain or facial pressure and reduction or loss of smell. The severity of symptoms was documented in the patient diaries.
- Cytokine diagnostics: Effects of the treatment on the immune system were tested at Visits V1 and V2 by use of the TruCulture® blood collection and whole-blood culture device. Cytokines were analysed via multiplex testing (Multi analyte profiles, MAP's A and B), and parameters tested for were:

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HumanCytokine MAP A		HumanCytokine MAP B	
GM-CSF	IL-8	BDNF	IL-15
IFN-gamma	IL-10	Eotaxin	IL-17
IL-2	MCP-1	ICAM-1	IL-23
IL-3	MIP-1alpha	IL-1alpha	MMP-3
IL-4	MIP-1beta	IL-1beta	SCF
IL-5	TNF-alpha	IL-1Ra	VEGF
IL-6	TNF-beta	IL-12p40	
IL-7		IL-12p70	

Cytokine concentrations observed before and after treatment were compared in order to evaluate the pharmacological effect of Bromelain and its potential important impact on the chronic inflammatory process.

- The Measurement of the Peak Nasal Inspiratory Flow (PNIF) determined the extent of nasal airway patency and was performed at every visit.
- A nasal examination (rhinoscopy) with a following diagnostic evaluation was performed at every visit. The three nasal symptoms edema, secretion and redness were assessed by the investigator, scored from 0=none to 3=severe and added to assess a rhinoscopy score with a maximum value of 9.

Safety:

The safety and tolerability of the investigational product was evaluated by the results of the physical examinations, safety laboratory data like hematology, clinical chemistry and coagulation status and description of adverse events (frequency, intensity, severity and duration of adverse events) during the treatment with Bromelain tablets hysan® compared to placebo.

Statistical methods:

This study aimed at demonstrating a therapeutic effect in patients suffering from chronic rhinosinusitis under treatment with Bromelain tablets hysan® compared to placebo. The primary endpoint was the TRSSRMS, taking into account the RSSS and the RMS. The null hypothesis was that there would not be any difference in

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efficacy between the two treatment groups, i.e. placebo and Bromelain tablets hysan® (500 F.I.P./tablet). The alternative hypothesis was that there would be a verifiable therapeutic efficacy in the group treated with Bromelain tablets hysan® with at least one difference to the placebo group. Differences between treatment groups were considered statistically significant at the 5 % level of significance using two-sided tests. The analyses were based on the original treatment assignment (Intent-to-Treat Principle).
If this overall test was statistically significant, both the individual **RSSS** and **RMS** mean scores would have been tested simultaneously by Wilcoxon-tests with a 2-sided α = 5 %.
By the closed testing procedure, the multiple level α was controlled.
A descriptive analysis was performed on all demographic and baseline characteristics as well as secondary efficacy variables to detect a possible difference between the two treatment groups (Bromelain tablets hysan® and placebo). For qualitative variables, a possible change from baseline was checked by means of a two-tailed Fisher´s Exact test, and for the ordinal and metric variables by means of a two-tailed Wilcoxon-Mann-Whitney test or a two-tailed t-Test or Fisher's exact test, respectively.

Summary - Conclusions

Efficacy results:
Regarding the TRSSRMS as the primary endpoint over the study period of 84 days, a statistically significant difference between the actively treated group receiving Bromelain tablets hysan® and the placebo group was not demonstrated.
Analysis of secondary objectives showed significantly higher levels of peak nasal inspiratory flow in the placebo group at all visits. The sniff tests, the SNOT-20 GAV and the rhinoscopic inspections revealed no statistically significant differences between treatment groups.
Cytokine diagnostics demonstrated statistically significant increase in concentrations of GM-CSF, ICAM-1 and VEGF in the Bromelain tablets hysan® group and significant increases in concentrations of Eotaxin-1 and MMP3 in the placebo group.

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Safety results:

A total of 18 treatment emergent adverse events (TEAE) were reported during the course of the trial. Of those, three AEs were regarded as possibly treatment related adverse events (TRAE), and occurred in the placebo group. One SAE (car accident, acute ischialgia, leading to hospitalization) was reported during the study, but was regarded as not treatment related. A discontinuation of the therapy due to an AE was documented seven times. There were neither significant changes in laboratory values (hematology, clinical chemistry and coagulation status) nor in the parameters weight, blood pressure and heart rate. The treatment was very well tolerated by the patients.

Conclusion:

In conclusion, the efficacy of the safe and well tolerated oral therapy with Bromelain tablets hysan® in terms of reduction of symptoms in patients with chronic rhinosinusitis could not be demonstrated in this trial.

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