



Clinical trial results:

Efficacy and tolerability of Bromelain tablets hysan® in patients with chronic rhinosinusitis.

A prospective, double-blind, randomized, placebo-controlled multi-centre trial.

A proof of concept study.

Summary

EudraCT number	2013-003896-37
Trial protocol	DE
Global end of trial date	08 January 2015

Results information

Result version number	v1 (current)
This version publication date	06 February 2016
First version publication date	06 February 2016
Summary attachment (see zip file)	Synopsis BroSin2013 (Synopse BroSin2013.pdf)

Trial information

Trial identification

Sponsor protocol code	BronSin2013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ursapharm Arzneimittel GmbH
Sponsor organisation address	Industriestraße 35, Saarbrücken, Germany, 66129
Public contact	Coordinating Investigator, Institut für Med. Statistik, Informatik u. Epidemiologie, 0049 2214783456, informatik@imsie.de
Scientific contact	Coordinating Investigator, Institut für Med. Statistik, Informatik u. Epidemiologie, 0049 680592920, p.meiser@ursapharm.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2015
Global end of trial reached?	Yes
Global end of trial date	08 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the efficacy of Bromelain tablets hysan® by the Total Rhinosinusitis Rescue Medication Score (TRSSRMS) taking in account the Rhinosinusitis Symptom Score (RSSS) of the four rhinosinusitis symptoms (nasal obstruction, nasal discharge, facial pain or facial pressure and reduction or loss of smell) and the Rescue Medication Score (RMS).

Protection of trial subjects:

Three blood samples were taken, two of them in order to monitor clinical safety laboratory parameters. Beyond this no invasive interventions were undertaken. Patients were allowed to take the analgesic paracetamol in case of pain sensation and to use a decongesting nasal spray if necessary. Vital signs, physical findings and other observations related to safety were evaluated in the beginning and at the end of the trial.

Background therapy:

Intake of paracetamol tablets and use of decongesting nasal spray (xylometazoline) were offered as rescue medication.

Evidence for comparator: -

Actual start date of recruitment	01 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	36
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited starting in February 2014. The first patient was enrolled on 11th March 2014, the last patient was completed on 8th January 2015.

Pre-assignment

Screening details:

Altogether 40 patients with chronic rhinosinuitis (=symptomatology more than 12 weeks without complete remission) diagnosed by the physician after a endoscopic and pre-existing Computer Tomography examination (CT) were assessed for eligibility for inclusion into the trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bromelain 3000 F.I.P.

Arm description:

Verum group

Arm type	Experimental
Investigational medicinal product name	Bromelain
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient was instructed to take two tablets thrice a day approximately half an hour before meals with 0.2 L of water for 12 weeks.

Arm title	Placebo
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Arm description:

Placebo treatment

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient was instructed to take two tablets thrice a day approximately half an hour before meals with 0.2 L of water for 12 weeks.

Number of subjects in period 1	Bromelain 3000 F.I.P.	Placebo
Started	21	19
Completed	18	16
Not completed	3	3
Adverse event, non-fatal	1	2
Lost to follow-up	-	1
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
Adults (18-64 years)	36	36	
From 65-84 years	4	4	
Gender categorical Units: Subjects			
Female	24	24	
Male	16	16	

End points

End points reporting groups

Reporting group title	Bromelain 3000 F.I.P.
Reporting group description:	
Verum group	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment	

Primary: Total Rhinosinusitis Symptom and Rescue Medication Score (TRSSRMS)

End point title	Total Rhinosinusitis Symptom and Rescue Medication Score (TRSSRMS)
End point description:	
End point type	Primary
End point timeframe:	
TRSSRMS was assessed at the start, after 2 weeks, after 4 weeks, after 8 weeks and at the end (12 weeks) of the treatment period (V1 - V5).	

End point values	Bromelain 3000 F.I.P.	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: Sum score				
arithmetic mean (standard deviation)	6.88 (\pm 4.057)	6.45 (\pm 4.723)		

Statistical analyses

Statistical analysis title	TRSSRMS
Statistical analysis description:	
The null hypothesis was that there is no difference in efficacy between the two treatment groups, i.e. placebo and Bromelain tablets hysan. The alternative hypothesis was that there is 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 to be statistically significant at the 5 % level of significance using two sided tests.	
Comparison groups	Bromelain 3000 F.I.P. v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	\leq 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed by the investigators at all visits.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Bromelain
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Bromelain	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Bromelain	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 21 (42.86%)	5 / 19 (26.32%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 19 (5.26%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1 0 / 21 (0.00%) 0	0 / 19 (0.00%) 0 2 / 19 (10.53%) 2	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Pharyngeal inflammation subjects affected / exposed occurrences (all) Nasal turbinate hypertrophy subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1	1 / 19 (5.26%) 1 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0	
Skin and subcutaneous tissue disorders Skin irritation subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1 0 / 21 (0.00%) 0	0 / 19 (0.00%) 0 1 / 19 (5.26%) 1	
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	2 / 21 (9.52%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Laryngitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	3 / 21 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Cough			
subjects affected / exposed	0 / 21 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported