Clinical trial results:
Perioperative Ödemtherapie mit Bromelain nach Weisheitszahnosteotomien – Überprüfung der Wirksamkeit in Abhängigkeit von unterschiedlichen Dosierungen (Dosisfindungsstudie)

Perioperative oedema therapy with bromelain after extraction of wisdom teeth – Test for efficacy as a function of different doses (dose-finding study)

Summary

EudraCT number	2009-015804-24
Trial protocol	DE
Global end of trial date	01 August 2014

Results information

Result version number	v1 (current)
This version publication date	04 July 2016
First version publication date	13 August 2015
Summary attachment (see zip file)	Synopsis BRODOS09 (BRODOS09_Synopse.pdf)

Trial information

Trial identification

Sponsor protocol code	BRODOS09

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
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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	22 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Ziel der vorliegenden Untersuchung ist die Überprüfung der Wirksamkeit von Bromelain in unterschiedlichen Dosierungen unter standardisierten Bedingungen bei der operativen Weisheitszahnentfernung.

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.

Protection of trial subjects:

No invasive interventions beyond the performed surgery were undertaken. Patients were allowed to take the analgesic paracetamol. In case of severe pain, prescription of paracetamol and codeine tablets as rescue medication was possible.

Background therapy:

Paracetamol tablets were provided as analgesic therapy for all treatment arms.
In case of severe pain, prescription of paracetamol and codeine tablets as rescue medication was possible.

Evidence for comparator:

Placebo was used as comparator for each individual tested (cross-over-design)

Actual start date of recruitment	01 October 2010
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: 75

Worldwide total number of subjects	75
EEA total number of subjects	75

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	17
Adults (18-64 years)	58
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients that were planed to undergo wisdom teeth extraction at MHH were continuesly screened for inclusion into the trial.

Pre-assignment

Screening details:

Altogether 94 patients were assessed for eligibility for inclusion into the trial. Suitable patients had to have four fully retained molars in positions 18, 28, 38 and 48, and had to accept the additional effort required for conduct of the study.

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 1000 F.I.P.

Arm description:

Bromelain 1000 F.I.P., cross-over against Placebo

Arm type	Cross-over Experimental-Placebo
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:

The preparations (Bromelain-POS and/or placebo, total of 3 tablets three times daily) should be taken with some liquid approx. 30 minutes before the main meals (morning, midday and evening).

Arm title	Bromelain 3000 F.I.P.

Arm description:

Bromelain 3000 F.I.P., cross-over against Placebo

Arm type	Experimental - Placebo
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:

3 tablets three times daily (total of 9 tablets/day) with some liquid approx. 30 minutes before the main meals.
Duration of treatment: 9 days, start on day before wisdom teeth surgery

Arm title	Bromelain 4500 F.I.P.

Arm description:

Bromelain 4500 F.I.P., cross-over against Placebo

Arm type	Experimental - Placebo

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:

The preparations (Bromelain-POS and/or placebo, total of 3 tablets three times daily) should be taken with some liquid approx. 30 minutes before the main meals (morning, midday and evening).

Number of subjects in period 1	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.
Started	25	24	26
Completed	25	24	26

Baseline characteristics

Reporting groups	
Reporting group title	Bromelain 1000 F.I.P.
Reporting group description:	
Bromelain 1000 F.I.P., cross-over against Placebo	
Reporting group title	Bromelain 3000 F.I.P.
Reporting group description:	
Bromelain 3000 F.I.P., cross-over against Placebo	
Reporting group title	Bromelain 4500 F.I.P.
Reporting group description:	
Bromelain 4500 F.I.P., cross-over against Placebo	

Reporting group values	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.
Number of subjects	25	24	26
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	6	6
Adults (18-64 years)	20	18	20
Gender categorical Units: Subjects			
Female	16	13	19
Male	9	11	7

Reporting group values	Total		
Number of subjects	75		
Age categorical Units: Subjects			
Adolescents (12-17 years)	17		
Adults (18-64 years)	58		
Gender categorical Units: Subjects			
Female	48		
Male	27		

End points

End points reporting groups

Reporting group title	Bromelain 1000 F.I.P.
Reporting group description:	
Bromelain 1000 F.I.P., cross-over against Placebo	
Reporting group title	Bromelain 3000 F.I.P.
Reporting group description:	
Bromelain 3000 F.I.P., cross-over against Placebo	
Reporting group title	Bromelain 4500 F.I.P.
Reporting group description:	
Bromelain 4500 F.I.P., cross-over against Placebo	
Subject analysis set title	Dose-dependency Bromelain 1000 vs. Bromelain 3000 + 4500
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Comparison of treatment arm Bromelain 1000 vs treatment arm Bromelain 3000 + treatment arm 4500 F.I.P.
This comparison aimed at a proof of a dose-dependent efficacy of bromelain-treatment and resembled the primary hypothesis of this study. For the primary hypothesis both higher treatment groups are pooled and compared to the lowest dose.
The number of subjects included into this subject analysis set thus results from the number of subjects included into arms 1-3 (n = 75).

Primary: Extent of swelling of the cheeks over time (AUC)

End point title	Extent of swelling of the cheeks over time (AUC)

End point description:

For each dose group the average of the differences in AUC with Bromelain and Placebo is calculated. The global primary hypothesis intends to show a dose-response relationship of Bromelain. This is demonstrated if the estimated therapeutic effect from the pooled treatment groups 2 and 3 (3000 and 4500 F.I.P.) is greater than that of treatment 1 (1000 F.I.P.). Dose-response relationship is given as subject analysis set.
Standard deviations are given for Bromelain treatment and thus do not refer to the mean values of the differences observed between bromelain and placebo treatment!

End point type	Primary

End point timeframe:

Extent of swelling of the cheeks over time measured as difference in AUC postoperatively on examination days 2, 4 and 7 in comparison to the baseline. The difference per patient in AUC is determined as AUC Bromelain – AUC Placebo.

End point values	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.	Dose-dependency Bromelain 1000 vs. Bromelain 3000 + 4500
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	25	24	26	75
Units: mL				
arithmetic mean (standard deviation)	-10 (± 26.71)	-2.31 (± 35.97)	-16.44 (± 28.9)	0.48 (± 34.85)

Statistical analyses

Statistical analysis title	Extent of swelling of the cheeks - AUC

Statistical analysis description:

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.

Comparison groups	Bromelain 4500 F.I.P. v Bromelain 3000 F.I.P. v Bromelain 1000 F.I.P. v Dose-dependency Bromelain 1000 vs. Bromelain 3000 + 4500
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Pain

End point title	Pain

End point description:

For each dose group the average of the differences in mm (VAS) with Bromelain and Placebo is calculated.
Standard deviations are given for Bromelain treatment and thus do not refer to the mean values of the differences observed between bromelain and placebo treatment!

End point type	Secondary

End point timeframe:

Pain was assessed postoperatively on examination days 2, 4 and 7 in comparison to the baseline by use of a Visual Analogue Scale (VAS). The difference per patient in mm is determined as mm Bromelain – mm Placebo.

End point values	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	26	
Units: mm				
arithmetic mean (standard deviation)	-1.03 (± 5.46)	-0.7 (± 8.74)	-0.1 (± 6.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Max swelling of the cheeks

End point title	Max swelling of the cheeks

End point description:

For each dose group the average of the differences in ml with Bromelain and Placebo is calculated.
Standard deviations are given for Bromelain treatment and thus do not refer to the mean values of the differences observed between bromelain and placebo treatment!

End point type	Secondary

End point timeframe:

Maximal swelling of the cheeks measured as difference in ml in comparison to the baseline. The difference per patient in ml is determined as ml Bromelain – ml Placebo.

End point values	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	26	
Units: ml				
arithmetic mean (standard deviation)	-3.13 (± 8.62)	0.18 (± 11.54)	-4.04 (± 9.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Use of analgetics

End point title	Use of analgetics

End point description:

For each dose group the average of the differences in the number of paracetamol tablets used with Bromelain and Placebo is calculated.
Standard deviations are given for Bromelain treatment and thus do not refer to the mean values of the differences observed between bromelain and placebo treatment!

End point type	Secondary

End point timeframe:

Number of paracetamol tablets used postoperatively until examination day 7.

End point values	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	26	
Units: Number of paracetamol tablets used				
arithmetic mean (standard deviation)	-0.05 (± 8.13)	-0.67 (± 8.06)	-1.46 (± 8.15)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed by the investigators at all visits.

Adverse event reporting additional description:

Adverse events also had to be reported by the patient by use of a daily questionnaire. Patients were encouraged to report on adverse events after finishing the respective treatment blocks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Bromelain 1000 F.I.P.

Reporting group description:

Bromelain 1000 F.I.P.

Reporting group title	Bromelain 3000 F.I.P.

Reporting group description:

Bromelain 3000 F.I.P.

Reporting group title	Bromelain 4500 F.I.P.

Reporting group description:

Bromelain 4500 F.I.P.

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Bromelain 1000 F.I.P.	Bromelain 3000 F.I.P.	Bromelain 4500 F.I.P.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 25 (72.00%)	6 / 24 (25.00%)	5 / 26 (19.23%)
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 25 (12.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	6	0	0
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Feeling cold			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
sleep disorder			

subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
External ear pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	1 / 26 (3.85%)
occurrences (all)	1	2	2
abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Hypoaesthesia oral			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Reflux gastritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin burning sensation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
pimples			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 75 (32.00%)		
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Feeling cold			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Discomfort			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
sleep disorder			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		

Ear and labyrinth disorders External ear pain subjects affected / exposed occurrences (all)	 0 / 75 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) abdominal pain subjects affected / exposed occurrences (all) Hypoaesthesia oral subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Reflux gastritis subjects affected / exposed occurrences (all)	 5 / 75 (6.67%) 7 2 / 75 (2.67%) 2 0 / 75 (0.00%) 0 2 / 75 (2.67%) 2 1 / 75 (1.33%) 2 1 / 75 (1.33%) 1		
Skin and subcutaneous tissue disorders Skin burning sensation subjects affected / exposed occurrences (all) pimples subjects affected / exposed occurrences (all)	 0 / 75 (0.00%) 0 2 / 75 (2.67%) 3		
Psychiatric disorders Disorientation subjects affected / exposed occurrences (all)	 0 / 75 (0.00%) 0		

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