



## Clinical trial results:

### **Efficacy and safety of Euminz® (10% ethanolic solution of peppermint oil for topical use) compared to placebo in patients with episodic tension-type headache (ETTH)**

#### **Summary**

EudraCT number	2011-004777-89
Trial protocol	DE
Global end of trial date	15 September 2015

#### **Results information**

Result version number	v1 (current)
This version publication date	22 May 2025
First version publication date	22 May 2025

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	CAS/B/016611
-----------------------	--------------

##### **Additional study identifiers**

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

Notes:

##### **Sponsors**

Sponsor organisation name	Cassella-med GmbH & Co. KG
Sponsor organisation address	Gereonsmuehlengasse 1, Cologne, Germany, 50670
Public contact	Clinical Operations, Cassella-med GmbH & Co.KG, clinical.operations@klosterfrau.de
Scientific contact	Clinical Operations, Cassella-med GmbH & Co.KG, clinical.operations@klosterfrau.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	27 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2015
Global end of trial reached?	Yes
Global end of trial date	15 September 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this prospective, multi-centre, double-blind, placebo-controlled, phase IV clinical trial is to demonstrate the efficacy of Euminz to reduce the intensity of headaches symptoms after topical use during episodic headache attack experienced by patients with episodic tension-type headache.

Protection of trial subjects:

Each subject was fully informed of all aspects of the study and provided informed consent prior to start of any study procedures. Subjects could withdraw from treatment at any time and for any reason. No specific additional measures were required to minimize distress given the nature of study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2013
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: 209
Worldwide total number of subjects	209
EEA total number of subjects	209

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)	0
Adults (18-64 years)	190
From 65 to 84 years	19
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Adult subjects were recruited in Clinical Complementary and Integrative Medicine Charité University and Immanuel Hospital Berlin, Germany from 15th February 2013 until 15th September 2015.

### Pre-assignment

Screening details:

Subjects were eligible for inclusion, if the main criteria were met: - signed and dated Informed Consent;  
- history of ETTH for at least one year and number of days per month with ETTH  $\geq 2$

### 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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Euminz
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	peppermint oil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous liquid
Routes of administration	Cutaneous use

Dosage and administration details:

At onset of a headache episode, when the intensity was assessed at least as moderate (3 on VPRS), the patient had to apply the IMP solution as broad bands on the temples and forehead to a skin area of about 100 to 140 cm<sup>2</sup>. In case of pericranial tenderness and neck pain the patient had to apply the IMP solution also on the neck. Application was to be repeated after 15 and 30 minutes, and if necessary after 45 and 60 minutes. Thus, 3 to 5 applications during one headache episode were allowed. Before each application, changes were to be recorded in the headache documentation form.

<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Cutaneous use

Dosage and administration details:

At onset of a headache episode, when the intensity was assessed at least as moderate (3 on VPRS), the patient had to apply the IMP solution as broad bands on the temples and forehead to a skin area of about 100 to 140 cm<sup>2</sup>. In case of pericranial tenderness and neck pain the patient had to apply the IMP solution also on the neck. Application was to be repeated after 15 and 30 minutes, and if necessary after 45 and 60 minutes. Thus, 3 to 5 applications during one headache episode were allowed. Before each application, changes were to be recorded in the headache documentation form.

<b>Number of subjects in period 1</b>	Euminz	Placebo
Started	105	104
Completed	90	89
Not completed	15	15
Consent withdrawn by subject	3	5
Adverse event, non-fatal	4	1
Lost to follow-up	6	5
Lack of efficacy	1	3
Protocol deviation	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Euminz
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Euminz	Placebo	Total
Number of subjects	105	104	209
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	45	47	
full range (min-max)	18 to 78	18 to 75	-
Gender categorical Units: Subjects			
Female	79	78	157
Male	26	26	52

### Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT set consists of all patients who were randomized and applied at least one dose of study medication.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The FAS consists of all patients in the ITT set with at least one evaluable headache episode.	

Reporting group values	ITT	FAS	
Number of subjects	209	189	
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median full range (min-max)	46 18 to 78	44.5 18 to 78	
Gender categorical Units: Subjects			
Female	157	146	
Male	52	43	

## End points

### End points reporting groups

Reporting group title	Euminz
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set consists of all patients who were randomized and applied at least one dose of study medication.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS consists of all patients in the ITT set with at least one evaluable headache episode.	

### Primary: VPRS responder rate for the first documented HE

End point title	VPRS responder rate for the first documented HE
End point description:	
VPRS responder rate for the first documented HE. A responder was defined as a patient whose baseline value (VPRS0) was $\geq 3$ and who reached a VPRS-value after treatment (VPRS1 at 120 min or LOCF) of $\leq 1$ . If the first documented HE was terminated due to inefficacy, the patient was to be rated as non-responder even if another HE was documented.	
End point type	Primary
End point timeframe:	
First documented HE between V1 and V2	

End point values	Euminz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94 <sup>[1]</sup>	95 <sup>[2]</sup>		
Units: number of patients	37	28		

Notes:

[1] - FAS

[2] - FAS

### Statistical analyses

Statistical analysis title	primary efficacy analysis hierarchical statistical
Statistical analysis description:	
This hypothesis was to be tested using the non-parametric Fisher's exact test at a 1-sided significance level of 2.5%. Confirmatory testing of the second hypothesis referring to VAS assessment of pain intensity was to be performed only if the null hypothesis of the first analysis could be rejected. Hence, no adjustment of significance levels was required.	
Comparison groups	Euminz v Placebo

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
P-value	≤ 0.025
Method	Fisher exact

Notes:

[3] - The latter hypothesis was to be tested using the non-parametric Mann-Whitney U Test (rank-sum test) at a 2-sided significance level of 5%. In case the first null hypothesis (H1-0) could not be rejected, i.e., statistical significance of the results could not be demonstrated, the second test was to be performed exploratory only.

### Primary: Assessment of Pain by VAS SPID at 120 min

End point title	Assessment of Pain by VAS SPID at 120 min
-----------------	---

End point description:

The second primary variable was the VAS sum of pain intensity differences (VAS SPID) at 120 min after start of treatment of the patient's first eHE recorded in the HDF. Pain intensity was assessed using a visual analogue scale (VAS) and SPID was calculated. SPID is the weighted sum of pain intensity differences (PID: difference of pain intensity recorded at baseline [t0] and pain intensity at assessment time [ti]). Higher VAS SPID values indicate higher differences in pain intensity over time, i.e., in the present setting a more pronounced reduction of pain.

End point type	Primary
----------------	---------

End point timeframe:

120min after start of treatment of the patient's first eHE.

End point values	Euminz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94 <sup>[4]</sup>	95 <sup>[5]</sup>		
Units: VAS SPID at 120 min				
median (full range (min-max))	1576.0 (-2505.0 to 7230.0)	1065.0 (-2910.0 to 8752.0)		

Notes:

[4] - FAS

[5] - FAS

### Statistical analyses

<b>Statistical analysis title</b>	second primary confirmatory endpoint
Comparison groups	Placebo v Euminz
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

### Secondary: Pain-free Rate at 120 min: first eHE by Number of Study Drug Applications

End point title	Pain-free Rate at 120 min: first eHE by Number of Study Drug Applications
-----------------	---



End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Study drug was to be applied 3 to 5 times during one eHE according to protocol.

End point values	Euminz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94 <sup>[6]</sup>	95 <sup>[7]</sup>		
Units: number of patients	36	28		

Notes:

[6] - FAS

[7] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: VPRS Sum of Pain Intensity Differences

End point title	VPRS Sum of Pain Intensity Differences
-----------------	--

End point description:

Differences in verbal pain rating between baseline and assessment times have been calculated and summed up to obtain VPRS SPID values for all eHEs and, separately, for the patients' first eHE. Furthermore, SPIDs have been assessed as means to give mSPID values defined as arithmetic mean of the SPIDs calculated per eHE in an individual patient.

End point type	Secondary
----------------	-----------

End point timeframe:

V1-V3

End point values	Euminz	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94 <sup>[8]</sup>	95 <sup>[9]</sup>		
Units: VPRS SPID and mSPID				
median (full range (min-max))				
all eHEs	100.0 (-120.0 to 435.0)	85 (-105.0 to 375.0)		
first eHE	105.0 (-120.0 to 435.0)	75.0 (-105.0 to 360.0)		
VPRS mSPID	105.0 (-120.0 to 327.5)	82.5 (-93.0 to 355.0)		

Notes:

[8] - FAS

[9] - FAS

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Visit 1 up until 1 week after Visit 3

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.1
--------------------	------

### Reporting groups

Reporting group title	Intent-to-treat
-----------------------	-----------------

Reporting group description:

The ITT set consists of all patients who were randomized and applied at least one dose of study medication.

Serious adverse events	Intent-to-treat		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 209 (0.96%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast cancer female			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Intent-to-treat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 209 (18.66%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Breast cancer female subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		
General disorders and administration site conditions Application site pain subjects affected / exposed occurrences (all)  Application site rash subjects affected / exposed occurrences (all)  Application site dryness subjects affected / exposed occurrences (all)  Discomfort subjects affected / exposed occurrences (all)  Feeling cold subjects affected / exposed occurrences (all)  Local swelling subjects affected / exposed occurrences (all)  Malaise subjects affected / exposed occurrences (all)	2 / 209 (0.96%) 2  2 / 209 (0.96%) 2  1 / 209 (0.48%) 1  1 / 209 (0.48%) 1  1 / 209 (0.48%) 1  1 / 209 (0.48%) 1  1 / 209 (0.48%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)  Dyspnoea subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1  1 / 209 (0.48%) 1		

Injury, poisoning and procedural complications Administration related reaction subjects affected / exposed occurrences (all)	2 / 209 (0.96%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Paraesthesia subjects affected / exposed occurrences (all)	2 / 209 (0.96%) 2  1 / 209 (0.48%) 1		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		
Eye disorders Eye irritation subjects affected / exposed occurrences (all)  Conjunctivitis allergic subjects affected / exposed occurrences (all)  Ocular discomfort subjects affected / exposed occurrences (all)	2 / 209 (0.96%) 2  1 / 209 (0.48%) 1  1 / 209 (0.48%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Abdominal distension subjects affected / exposed occurrences (all)  Diarrhoea	3 / 209 (1.44%) 3  3 / 209 (1.44%) 3  1 / 209 (0.48%) 1		

subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 209 (1.44%)		
occurrences (all)	3		
Flank pain			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 209 (0.48%)		
occurrences (all)	1		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 209 (3.35%) 7		
Acute sinusitis subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		
Bronchitis subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		
Sinusitis subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	1 / 209 (0.48%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2014	Amendment 1, dated 24 March 2014 concerned the change in the placebo manufacturer (Klosterfrau Berlin GmbH instead of Lichtenheldt GmbH) and a change in data management responsibility which was transferred to acromion GmbH, Frechen. Furthermore, responsibility for statistical analysis was transferred to Norman Bitterlich, PhD, Medizin und Services GmbH, Chemnitz.
09 September 2015	Amendment 2, dated 09 September 2015 concerned change of responsibility for statistical analyses which was transferred entirely to acromion GmbH, Frechen.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported