Clinical trial results:
Efficacy and safety of Sinusitis Hevert SL tablets compared to placebo in adult patients with acute, uncomplicated rhinosinusitis.
A multicenter, randomized, double-blind, placebo-controlled, parallel group phase IV study.

Summary

EudraCT number	2014-000907-29
Trial protocol	DE BG
Global end of trial date	24 April 2015

Results information

Result version number	v1 (current)
This version publication date	13 August 2022
First version publication date	13 August 2022
Summary attachment (see zip file)	SHDE-1 Synopsis (SHDE-1 - ATZ0901-08_ICH-130916_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	SHDE-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hevert-Arzneimittel GmbH & Co. KG
Sponsor organisation address	In der Weiherwiese 1, Nussbaum, Germany,
Public contact	Clinical Research, AtoZ-CRO, +49 220695990,
Scientific contact	Clinical Research, AtoZ-CRO, +49 220695990,

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	13 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the present clinical trial is to assess the efficacy, safety and tolerability of Sinusitis Hevert SL, compared to placebo, in adult patients with uncomplicated, acute rhinosinusitis

Protection of trial subjects:

As rescue treatment, water steam inhalation without any additives, maximally three times per day, was permitted. If medically indicated for symptomatic treatment, paracetamol, at a maximal dose of 4 gram per day (e.g. 1 – 2 tablets containing 500 or 1000 mg paracetamol up to 4 times daily), was also permitted as rescue medication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 November 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: 308
Worldwide total number of subjects	308
EEA total number of subjects	308

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)	288
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with acute uncomplicated or acute recurrent rhinosinusitis were recruited by primary care practitioners, commercial trial sites and specialists for otorhinolaryngology in Germany. Recruitment started on 24 NOV 2014. The last patient completed the study on 24 APR 2015.

Pre-assignment

Screening details:

After signing the informed consent form patients were screened for elegibility.

Period 1

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

Blinding implementation details:

Sinusitis Hevert SL and placebo were identical in appearance so that neither the CRO nor the investigators or the patients were aware of the identity of the treatment assigned to the patient. Study medication and fitting emergency envelopes were provided to the investigators and were stored in the Investigator Site Files (ISF). All emergency envelopes were collected during close-out from the investigational sites at the end of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sinusitis Hevert SL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing on day 0 varied depending on the time when the patient was included into the study. During the first week (days 1 – 7), 2 tablets of Sinusitis Hevert SL were taken 6 times daily. During the second week (days 8 – 14), 2 tablets had to be taken 4 times daily.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing on day 0 varied depending on the time when the patient was included into the study. During the first week (days 1 – 7), 2 tablets of Sinusitis Hevert SL were taken 6 times daily. During the second week (days 8 – 14), 2 tablets had to be taken 4 times daily.

Number of subjects in period 1	Test	Placebo
Started	153	155
Completed	128	140
Not completed	25	15
Consent withdrawn by subject	2	3
Adverse event, non-fatal	3	3
Cure	8	4
Problems with intake	1	-
Lost to follow-up	2	2
Protocol deviation	8	3
Lack of efficacy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	308	308	
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			
arithmetic mean	39.7		
standard deviation	± 14.7	-	
Gender categorical Units: Subjects			
Female	197	197	
Male	111	111	

End points

End points reporting groups

Reporting group title	Test
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full analysis set Test
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS consists of patients who have been enrolled in the study according to the inclusion / exclusion criteria and were treated	
Subject analysis set title	Valid case analysis set Test
Subject analysis set type	Per protocol
Subject analysis set description:	
The VCAS Test consists of patients who have been enrolled in the study according to the inclusion / exclusion criteria, were treated with Test and had completed the study without major protocol violations	
Subject analysis set title	Full analysis set Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS placbeo consists of patients who have been enrolled in the study according to the inclusion / exclusion criteria and were treated with placebo	
Subject analysis set title	Valid case analysis set Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
The VCAS placebo consists of patients who have been enrolled in the study according to the inclusion / exclusion criteria, were treated with lacebo and had completed the study without major protocol violations	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS consists of patients who have been enrolled in the study according to the inclusion / exclusion criteria and were treated	
Subject analysis set title	Valid case analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
The VCAS consists of patients who have been enrolled in the study according to the inclusion / exclusion criteria, were treated and had completed the study without major protocol violations.	

Primary: Responder rate

End point title	Responder rate
End point description:	
The first primary endpoint is the rate of responders which occur between baseline and treatment end after maximum 14 days. A response is defined as stable reduction of MRSSpat (sum of 5 main rhinosinusitis symptoms daily assessed by the patient) by at least 50%, i.e. reduction by at least 50% and no subsequent change from baseline > –50% up to treatment termination.	
End point type	Primary
End point timeframe:	
After maximum 14 days of treatment	

End point values	Full analysis set Test	Valid case analysis set Test	Full analysis set Placebo	Valid case analysis set Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	153	142	155	146
Units: patients	131	124	125	120

Statistical analyses

Statistical analysis title	Comparison responder rate FAS
Comparison groups	Full analysis set Test v Full analysis set Placebo
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.2438 [2]
Method	Chi-squared
Parameter estimate	Comparison of responder rate

Notes:

[1] - The test of superiority of Sinusitis Hevert SL in comparison with placebo with respect to the responder rate was performed one-sided on the overall significance level of alpha=0.025 in a two-step adaptive design according to Bauer and Köhne.
[2] - In the FAS, the responder rates amounted to
- Sinusitis Hevert SL : 131/153 (85.6%)
- Placebo : 125/155 (80.6%)
(Chi-sqaure^2 test: p=0.2438 in favor of Sinusitis Hevert SL).

Statistical analysis title	Comparison responder rate VCAS
Comparison groups	Valid case analysis set Test v Valid case analysis set Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.2262 [4]
Method	Chi-squared

Notes:

[3] - The test of superiority of Sinusitis Hevert SL in comparison with placebo with respect to the responder rate was performed one-sided on the overall significance level of alpha=0.025 in a two-step adaptive design according to Bauer and Köhn
[4] - In the VCAS, the responder rates amounted to
- Sinusitis Hevert SL : 124/142 (87.3%)
- Placebo : 120/146 (82.2%)
(Chi-square^2 test: p=0.2262 in favor of Sinusitis Hevert SL).

Primary: Remission rate

End point title	Remission rate

End point description:

End point type	Primary

End point timeframe:

Up to day 14

End point values	Full analysis set Test	Valid case analysis set Test	Full analysis set Placebo	Valid case analysis set Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	153	142	155	146
Units: Number				
number (not applicable)	48	47	58	58

Statistical analyses

Statistical analysis title	Remission rate FAS

Statistical analysis description:

The second primary endpoint is the rate of remitters which occur between baseline and treatment end after maximum 14 days. A remission is defined as complete disappearance of all 5 main rhinosinusitis symptoms with no subsequent reoccurrence of any symptom up to treatment termination.

Comparison groups	Full analysis set Test v Full analysis set Placebo
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2641 [5]
Method	Chi-squared
Parameter estimate	Comparison of remission rate

Notes:

[5] - In the FAS, the remission rates amounted to
- Sinusitis Hevert SL : 48/153 (31.4%)
- Placebo : 58/155 (37.4%)
(Chi-square^2 test: p=0.2641 in favor of placebo).

Statistical analysis title	Remission rate VCAS
Comparison groups	Valid case analysis set Test v Valid case analysis set Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.2427 [7]
Method	Chi-squared
Parameter estimate	Comparison of remission rate

Notes:

[6] - In the VCAS, the remission rates amounted to
- Sinusitis Hevert SL : 47/142 (33.1%)
- Placebo : 58/146 (39.7%)
(Chi-sqquare^2 test: p=0.2427 in favor of placebo).
[7] - In the VCAS, the remission rates amounted to
- Sinusitis Hevert SL : 47/142 (33.1%)
- Placebo : 58/146 (39.7%)
(Chi-sqquare^2 test: p=0.2427 in favor of placebo).

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From treatment to Day 14	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	Test
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Test	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Migraine	Additional description: Due to headache with vomiting the patient was admitted to hospital. The patient has left the hospital the following day.		
subjects affected / exposed	1 / 153 (0.65%)	0 / 155 (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: 1 %

Non-serious adverse events	Test	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 153 (15.69%)	22 / 155 (14.19%)	
Vascular disorders			
Vascular disorder			
subjects affected / exposed	2 / 153 (1.31%)	0 / 155 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Nervous system disorder			

subjects affected / exposed	4 / 153 (2.61%)	3 / 155 (1.94%)	
occurrences (all)	4	3	
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	1 / 153 (0.65%)	2 / 155 (1.29%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	5 / 153 (3.27%)	5 / 155 (3.23%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	2 / 153 (1.31%)	4 / 155 (2.58%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	1 / 153 (0.65%)	3 / 155 (1.94%)	
occurrences (all)	1	3	
Infections and infestations			
Infections			
subjects affected / exposed	9 / 153 (5.88%)	5 / 155 (3.23%)	
occurrences (all)	9	5	

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