2. SYNOPSIS

Name of sponsor	Hevert-Arzneimittel GmbH & Co. KG In der Weiherwiese 1, 55569 Nussbaum, Germany
Name of finished product	Sinusitis Hevert SL
Name of active ingredients	One tablet contains eleven homeopathic substances: ▪ Apis ▪ Baptisia (HAB 34), (HAB, Vorschrift 3a) ▪ Cinnabaris ▪ Echinacea ▪ Hepar sulfuris ▪ Kalium bichromicum ▪ Lachesis ▪ Luffa ▪ Mercurius bijodatus ▪ Silicea ▪ Spongia
Study title	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
Investigators	Twenty-seven centers in Germany were enrolled into the study, and 23 recruited patients at study end: ▪ Center 41 : Prof. Dr. med. Andreas Michalsen, Berlin Principal investigator pursuant to § 40 AMG ▪ Center 42 : Peter Hinterkausen, Köln ▪ Center 43 : Taufik Shahab, Köln ▪ Center 44 : Dr. med. Joachim Spaeth, Düren (no patients) ▪ Center 47 : Dr. med. Elke Hippke, Berlin ▪ Center 48 : PD Dr. med. Christian Geßner, Leipzig ▪ Center 49 : Dr. med. Andreas Horn, Heidelberg (Neuenheim) (no patients) ▪ Center 50 : Dr. med. Uta Thieme, Duisburg ▪ Center 51 : Prof. Dr. med. Ludger Klimek, Wiesbaden (no patients) ▪ Center 52 : Dr. med. Jürgen Palm, Röthenbach ▪ Center 53 : Dr. med. Thorsten Krause, Goch ▪ Center 54 : Dr. med. Petra El Naib, Chemnitz ▪ Center 55 : Dr. med. Udo Schäfer, Dresden ▪ Center 56 : Dr. med. Yury Yarin, Dresden ▪ Center 57 : Liana Vismane, Synexus Clinical Research GmbH, Berlin ▪ Center 58 : Olga Maus, Synexus Clinical Research GmbH, Leipzig ▪ Center 59 : Dr. med. Ulrich Neumann, Wolmirstedt (no patients) ▪ Center 60 : Dr. med. Florian Heimlich, Heidelberg ▪ Center 61 : Dr. med. Christiane Klein, Künzing ▪ Center 62 : Dr. med. Axel Schaefer, Essen ▪ Center 63 : Dr. med. Andrea Rinke, Synexus Clinical Research GmbH, Bochum ▪ Center 64 : Dr. med. Christel Contzen, Synexus Clinical Research GmbH, Frankfurt ▪ Center 65 : Dr. med. Markus Faghih, Essen ▪ Center 66 : Dr. med. Karsten Sperling, Hamburg ▪ Center 67 : Dr. med. Christine Grigat, Clinical Research Hamburg GmbH, Hamburg

Investigators *[cont.]*	▪ Center 68 : Dr. med. Dennes Barth, Gars am Inn ▪ Center 69 : Dr. med. Holger Samer, Haag
Publication (reference)	–
Study period	Date of first patient enrolled : 24/11/2014 Date of last patient completed : 24/04/2015
Phase of development	Phase IV
Objectives	To assess the efficacy, tolerability and safety of Sinusitis Hevert SL tablets versus placebo (at a dose of max 10 tablets day 1, 12 tablets/day week 1, 8 tablets/day week 2).
Methodology	Multicenter, randomized, double-blind, placebo-controlled, parallel group study
Number of patients	▪ Planned : N=320 ▪ Screened : N=315 ▪ Randomized : N=314 ▪ All-Patients-Treated Set (APTS) : N=308 ▪ Full Analysis Set (FAS) : N=308 ▪ Valid Case Analysis Set (VCAS) : N=288 ▪ Valid completers : N=265
Diagnosis and main criteria for inclusion	Acute, uncomplicated rhinosinusitis (ARS) or recurrent ARS
Test product	Sinusitis Hevert SL tablets
Dose	▪ Visit 1 (day 0) : max 5 times 2 tablets, depending on time of visit ▪ Day 1 – 7 : 6 times 2 tablets ▪ Day 8 – 14 : 4 times 2 tablets. One tablet contains: 10 mg Apis D4, 5 mg Baptisia D4, 5 mg Cinnabaris D3, 30 mg Echinacea D2, 10 mg Hepar sulfuris D3, 30 mg Kalium bichromicum D8, 10 mg Lachesis D8, 60 mg Luffa D4, 70 mg Mercurius bijodatus D9, 5 mg Silicea D2 and 10 mg Spongia D6. Further constituents comprise lactose, magnesium stearate and corn starch.
Mode of administration	per os
Batch no.	C1406008
Duration of treatment	Approximately 2 weeks: Day 0 patient inclusion and first dosage, followed by 14 days of treatment (± 4 days in total for compensation for visit schedule problems)
Reference product	Placebo tablets
Dose	Dose regimen was identical for Sinusitis Hevert SL and placebo group. Placebo tablets were of equal size and appearance, and they had also been manufactured by the sponsor.
Mode of administration	per os
Batch no.	C1406008

Criteria for evaluation

Efficacy

Primary endpoints

- 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 $MRSS_{pat}$ (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.
- 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.
- Both endpoints are analyzed as co-primary endpoints in an adaptive design according to Bauer and Köhne.

Secondary endpoints

- Time to response
- Time to remission
- Time to improvement in the individual $MRSS_{pat}$ symptoms (in case of positive baseline value)
- Time to disappearance in the individual $MRSS_{pat}$ symptoms (in case of positive baseline value)
- Change in the overall $MRSS_{inv}$ (sum of 5 main rhinosinusitis symptoms assessed by the investigator) at V2[1], V3[1], and V4[1], as well as in the time course of the study
- Change in the overall $MRSS_{inv}$ (sum of the remaining symptoms) at V2, V3, and V4, as well as in the time course of the study
- Change in the individual $MRSS_{inv}$ symptoms, between baseline and V2, V3, and V4, as well as in the time course of the study
- Change in the SNOT-20 GAV, in the Overall Score (OS) as well as in the subscores (PNS = Primary Nasal Symptoms, SRS = Secondary Rhinogenous Symptoms, GQOL = General Quality of Life) between baseline and V2, V3, and V4
- Change in the SNOT-20 GAV, individual symptoms, between baseline and V2, V3, and V4
- Change in the assessment of patient's health status with respect to ARS by the patient using a VAS_{pat} between baseline and V2, V3, and V4
- Change in the assessment of patient's health status with respect to ARS by the investigator using a VAS_{inv} between baseline and V4
- General assessment of efficacy (4-point rating scale) by the investigator at each visit from V2 to V4
- Use of antibiotics / rescue medication.

Safety and tolerability

- Rate and intensity of AEs
- Withdrawal due to AEs
- Clinically relevant new or worsening findings in physical examination as reported as adverse event
- Changes from baseline in physical examination and vital signs (blood pressure, pulse rate, body temperature)
- VAS assessment of tolerability by patient at each visit (V2, V3, and V4)
- VAS assessment of tolerability by investigator at end of treatment.

[1] V2 = Day 7, V3 = Day 10, V4 = Day 14

Statistical methods	▪ χ^2 test for the comparison of percentages ▪ Logrank test for the comparison of Kaplan-Meier plots of time to event data ▪ Mann-Whitney U test, t-test for the comparison of treatment groups with respect to continuous data (non-parametric or normal distributed case) ▪ Wilcoxon test for intragroup comparisons ▪ Logistic regression analysis with backward elimination on the 15% level ▪ MMRM analysis of covariance for repeated measures in mixed models (V2, V3, V4 vs. V1).

Efficacy results

CONFIRMATORY STATISTICS

At the first step of the adaptive design according to Bauer and Köhne the results of the one-sided tests Sinusitis Hevert SL versus placebo of the responder and the remission rate (i.e. both p-values) should be compared with two margins α_0=0.5 and α_1=0.0102 in order to make the following decision:

- If $p < \alpha_1$ for both p-values the study would have been successfully terminated on the overall limit α=0.025 **without** continuation at step 2.
- If $p > \alpha_0$ for at least one p-value the study would have been terminated due to insufficiency.
- If $p \leq \alpha_0$ for both p-values and $p \geq \alpha_1$ for at least one p-value the study would have been continued at step 2.

The test of the first primary endpoint (responder rate) provided an advantage in favor of Sinusitis Hevert SL and p=0.1219 (FAS; VCAS: p=0.1131) in the one-sided test versus placebo. However, the test of the second primary endpoint (remission rate) provided an advantage in favor of placebo and p=0.8680 (FAS; VCAS: p=0.8787) in the one-sided test versus placebo. Therefore, the study was terminated prematurely with negative result of the superiority test Sinusitis Hevert SL versus placebo. All p-values reported in the subsequent analyses are two-sided exploratory test results.

EXPLORATORY STATISTICS

- The $MRSS_{pat}$ responder rates showed a small tendency in favor of Sinusitis Hevert SL:
  - FAS (p=0.2438)
    - Sinusitis Hevert SL : 131/153 (85.6%)
    - Placebo : 125/155 (80.6%)
  - VCAS (p=0.2262)
    - Sinusitis Hevert SL : 124/142 (87.3%)
    - Placebo : 120/146 (82.2%).

- The $MRSS_{pat}$ remission rates showed a small tendency in favor of placebo:
  - FAS (p=0.2641)
    - Sinusitis Hevert SL : 48/153 (31.4%)
    - Placebo : 58/155 (37.4%)
  - VCAS (p=0.2427)
    - Sinusitis Hevert SL : 47/142 (33.1%)
    - Placebo : 58/146 (39.7%).

- An advantage in favor of Sinusitis Hevert SL with respect to the time of $MRSS_{pat}$ response was not significant (logrank test: p=0.1351 in the FAS and p=0.1081 in the VCAS).

- The time to $MRSS_{pat}$ remission showed no advantage in favor of Sinusitis Hevert SL.

- The $MRSS_{inv}$ summary score showed no deviating aspects in comparison with $MRSS_{pat}$.

- The single item analyses of $MRSS_{pat}$ and $MRSS_{inv}$ provided advantages in favor of Sinusitis Hevert SL with respect to rhinorrhea but slight disadvantages with respect to pain parameters – mean courses over time for facial pain / pressure and headache were, however, comparable.

- For SNOT-20 GAV marked differences in favor of Sinusitis Hevert SL were detected with respect to PNS (Primary Nasal Symptoms):
  - FAS (p=0.0603)
    - Sinusitis Hevert SL: –10.09 ± 5.32
    - Placebo : –8.99 ± 5.70
  - VCAS (p=0.0528)
    - Sinusitis Hevert SL: –10.48 ± 5.07
    - Placebo : –9.40 ± 5.41.

- The single item analysis of SNOT-20 GAV provided advantages in favor of Sinusitis Hevert SL with respect to runny nose, thick nasal discharge (significant), and loss of smell.

- Slight differences in favor of Sinusitis Hevert SL with respect to the VAS_{pat} were statistically not significant.

- Additional analyses (significant or nearly significant differences **in favor of Sinusitis Hevert SL**):
  - Superiority in male patients with respect to time to $MRSS_{pat}$ response (p=0.0120; VCAS).
  - $MRSS_{pat}$ responder rates for male patients (p=0.0258)
    - Sinusitis Hevert SL: 96.2%
    - Placebo : 83.0%.
  - Odds ratio of the treatment effect with respect to rhinorrhea in the global logistic regression model: 1.885 (p=0.0531).
  - $MRSS_{pat}$ responder rates for completers in the VCAS (p=0.0340)
    - Sinusitis Hevert SL: 92.1%
    - Placebo : 83.5%.
  - For completers in the VCAS all centers showed advantages in favor of Sinusitis Hevert SL or at least no disadvantages of Sinusitis Hevert SL.
  - Changes in SNOT-20 GAV PNS for completers in the VCAS (p=0.0081)
    - Sinusitis Hevert SL: –11.15 ± 4.47
    - Placebo : –9.53 ± 5.32.
  - The Mixed Model Repeated Measurement analysis of covariance provided significant interactions with respect to SNOT OS, PNS, and GQOL indicating an increasing treatment difference over time in favor of Sinusitis Hevert SL.

Safety results

Averse events were reported in

- Sinusitis Hevert SL: N=24 (15.7%; 37 events)
- Placebo : N=22 (14.2%; 41 events)

patients (χ^2 test: p=0.9347), predominantly as infections and infestations which occurred in

- Sinusitis Hevert SL: N= 9 (5.9%; 10 events)
- Placebo : N= 5 (3.2%; 6 events)

patients (χ^2 test: p=0.5346) and gastrointestinal disorders which occurred in

- Sinusitis Hevert SL: N= 5 (3.3%; 8 events)
- Placebo : N= 5 (3.2%; 7 events)

patients (χ^2 test: p=0.9998).

Adverse events at least possibly related to the IMP occurred in

- Sinusitis Hevert SL: N= 3 (2.0%; 5 events)
- Placebo : N= 4 (2.6%; 8 events)

patients (χ^2 test: p=0.9356).

Possible relationship upon treatment with Sinusitis Hevert SL was reported for 'heart condition' and 'skin itching, thigh on both sides' and a probable relationship for 'mild abdominal pain', 'nausea' and 'furry feeling on the tongue'. No adverse events with certain causality to study medication occurred.

Three Patients in the Sinusitis Hevert SL group ('heart condition', 'double vision', 'furry feeling on the tongue / skin itching, thigh on both sides'), and 3 patients in the placebo group ('feeling of pressure in the throat', 'feeling of pressure in the sinuses area / itching of the eyes, nose, ears, and the throat', 'pruritus generalized / allergic exanthema') terminated the study due to an adverse event as primary reason.

Serious adverse events were reported in one case (Sinusitis Hevert SL 'migraine') which was classified as 'unrelated' to IMP.

With regard to vital signs, physical examinations, and the VAS assessments of tolerability of patient and investigator no relevant treatment differences were detected.

Conclusions

This multicenter double-blind randomized placebo-controlled clinical study in adult patients with ARS revealed slight differences in favor of Sinusitis Hevert SL treatment on a descriptive level for the first primary endpoint response rate – defined by 50% reduction of the $MRSS_{pat}$ as compared to baseline and maintenance until study end. The responder rate for placebo was 80.6% and for Sinusitis Hevert SL 85.6%. This slight improvement is supported by further secondary efficacy variables such as the SNOT-20 GAV overall score and its subscores 'Primary Nasal Symptoms' and 'General Quality of Life', certain single items of these symptomscores (rhinorrhea, thick nasal discharge, loss of smell), patient's health status as well as time to response. However, the second strictly defined primary endpoint 'remission' – with '0' for all 5 key symptoms – revealed slightly better remission rates in favor for placebo. This difference almost disappeared for cut-off levels ≤ 1 and ≤ 2 and turned in favor for Sinusitis Hevert SL at a cut-off ≤ 3. The somewhat diverging results of the two primary endpoints in the adaptive interim analysis led to the decision to not continue the study with an adapted sample size and to completely report the results of 315 patients enrolled in 23 active centers.

The observed differences were in general from a statistically viewpoint not significant for analyses of the APTS, FAS and VCAS, but statistical trends to support the statements above were observed and in the group of valid completers the rate of the $MRSS_{pat}$ responders was significantly higher under treatment with Sinusitis Hevert SL.

Around 15% of the study participants had adverse events, which – apart from three severe adverse events – were mild or moderate in intensity. Across all System Organ Classes (SOCs) the safety events between Sinusitis Hevert SL and placebo were comparable; slight imbalances in the SOC 'Infections and infestations' were not suggestive of a negative Sinusitis Hevert SL effect. Overall tolerability and safety was excellent and no adverse drug reactions attributable to Sinusitis Hevert SL were identified.

In summary, this study – terminated after an adaptive interim analysis – suggests that Sinusitis Hevert SL exerts mild beneficial effects as compared to placebo and possesses an excellent tolerability and safety. These preliminary results, however, shall be confirmed by a confirmatory randomized clinical study utilizing the information obtained from this study and other studies conducted in ARS for study design optimization.