2 SYNOPSIS

Name of Sponsor/Company: Bionorica SE Name of Finished Product: - Name of Active Ingredient: BNO 1016	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)

EudraCT no.	2009-016682-28
Study code	ARhiSi-2
Title of study	A multi-centre, double-blind, placebo-controlled, randomised, parallel group study to assess the efficacy and safety of a herbal medicinal product (dry extract BNO 1016) in patients with acute rhinosinusitis
Study design	Multi-centre, double-blind, placebo-controlled, randomised, parallel group study
Phase of development	III
Co-ordinating investigator (LKP according to §40 German Drug Law)	[redacted]
Principal investigators	A total of 37 investigators were active: 16 specialists in otorhinolaryngology (including the co-ordinating investigator) and 21 specialists in internal medicine and general practitioners.
Study centres	Thirty-seven (37) out of 40 initiated study sites in Germany participated (medical practices)
Country	Germany
Publication (reference)	None
Studied period	Approx. 3 months (clinical part) Date of first enrolment (first patient first visit) 22 JAN 2010 Date of last completed (last patient last visit) 12 APR 2010
Objectives	• To assess the efficacy of a 15-day treatment with a herbal medicinal product (BNO 1016) for therapy of acute rhinosinusitis in adult patients compared to placebo on the basis of the Major Symptom Score (MSS) assessed by the investigator; • To assess the safety of BNO 1016 compared to placebo applied in patients with acute rhinosinusitis.
Study visits	Five visits plus one follow-up visit: Visit 1 Screening, randomisation, start of double-blind treatment (Day 0) Visit 2 – Visit 4 Control examinations 3 (±1), 7 (±1) and 10 (±1) days after Visit 1 Visit 5 End of treatment / study two weeks after Visit 1 (Day 14 ±1) Visit 6* Follow-up four weeks after Visit 1 (Day 28 ±2) or earlier in case of premature healing (14 days after Visit 2, 3 or 4 respectively). *The follow-up visit was not performed in patients with early study termination (drop outs) and patients who needed further treatment at Visit 5.

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Methodology	Male and female adult outpatients with acute rhinosinusitis (confirmed by ultrasonography) were screened for study participation from January to April 2010 (winter / spring). The individual study duration was 28 ±2 days, with a total of six visits. A diary was filled in by the patients during the treatment period. There was no run-in period. A follow-up examination was performed in all patients with no need for further treatment at study end / Visit 5 (control of the paranasal sinuses by ultrasonography 14 days after the end of treatment visit). At Visit 1 (Day 0) eligible patients who had given their written informed consent were randomised to one of the two parallel treatment groups. Treatment with the blinded study medication (480 mg BNO 1016 or placebo) started on Day 0 / Visit 1 in the investigator's office. Patients were instructed to continue taking the medication three times daily (tid) until Day 14, always at the same time of the day (2 tablets in the morning, at noon, and in the evening). The effect of study treatment on acute rhinosinusitis was evaluated by the change in MSS (sum of investigator's rating scores [office assessment] and sum of patient's rating scores [home assessment in a patient diary]) for the five main rhinosinusitis symptoms, namely rhinorrhea (anterior discharge), postnasal drip, nasal congestion, headache, and facial pain/pressure), and patient's response to treatment compared to baseline. The change in symptoms and emotional and social consequences of rhinosinusitis (health-related quality of life - HRQoL) was evaluated by a 20-item patient questionnaire (Sino-Nasal Outcome Test-20, German Adapted Version - SNOT-20, GAV), and a diary (patient's home assessment of interference of acute rhinosinusitis (ARS) with sleep, daily functioning and general well-being). The tolerability of study treatment was evaluated based on the intensity and course of adverse events, measurement of vital signs (blood pressure, pulse, body temperature), analyses of blood parameters (safety laboratory), and by patient's and investigator's global judgement of tolerability at study end. The following efficacy and safety measures were monitored during the study: Ultrasonography of paranasal sinuses (investigator)..... Visits 1, 5, 6 Main rhinosinusitis symptoms (investigator's 5-point verbal rating scale)..... Visits 1, 2, 3, 4, 5 Treatment response (investigator's 4-point verbal rating scale)..... Visits 2, 3, 4, 5 SNOT-20, GAV (patient questionnaire)..... Visits 1, 3, 5 Interference of ARS with sleep, daily functioning and general well-being (patient diary)..... Daily (Visit 1- 5) Adverse events ..... Visits 2, 3, 4, 5, 6 Vital signs (blood pressure, pulse, body temperature)..... Visits 1, 3, 5 Safety laboratory (and urine pregnancy test for females with childbearing potential)..... Visit 1, 5 Global judgement of tolerability by both the patient and the investigator (5-point verbal rating scale)..... Visit 5

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Number of patients	Planned: 380 patients (190 patients per treatment group) Analysed: (see table below)

Data Set	BNO 1016 480 mg		Placebo		Total	
	N	%	N	%	N	%
Randomised	194	*100.0*	192	*100.0*	386	*100.0*
SEP	194	*100.0*	191	*99.5*	385	*99.7*
FAS	190	*97.9*	190	*99.0*	380	*98.4*
PP	147	*75.8*	153	*79.7*	300	*77.7*

SEP= Safety population, FAS= Full analysis set, PP= Per protocol set

Inclusion diagnosis	Acute rhinosinusitis, for details see inclusion criterion no. 3 (ICD-10: J01.9)
Main criteria for inclusion	1. Signed informed consent including data protection declaration 2. Male and female outpatients aged ≥18 and ≤ 75 years 3. Diagnosis of acute rhinosinusitis – characterised by a major symptom score* (MSS) ≥ 8 points and ≤ 12 points (minimum 0, maximum 15 points) – individual score for facial pain / pressure ≥ 1 (mild) and ≤ 2 (moderate) – confirmed by ultrasonography of paranasal sinuses – with presence of symptoms ≤ 3 days prior to inclusion * Out of the five main rhinosinusitis symptoms at least 3 had to be present. Among these the presence of nasal congestion and facial pain / pressure was mandatory.
Investigational medicinal products (IMP) Test product - active ingredients: - mode of administration: - batch number: - expiry date:	 BNO 1016 coated tablets One coated tablet (CT) contained 80 mg BNO 1016 dry extract preparation of a fixed combination of five herbal drugs: *Gentianae radix* (gentian root), *Primula flos cum calycibus* (primrose flowers with calyx), *Rumicis herba* (common sorrel herb), *Sambuci flos* (elder flowers), and *Verbenae herba* (vervain herb), in the ratio 1:3:3:3:3.. peroral 0000030728 (blinded batch no. 0000037555) 06/2010
Reference - active ingredients: - mode of administration. - batch number: - expiry date:	Placebo tablets none peroral 0000023292 (blinded batch no. 0000037555) 06/2010
Dose regimen:	BNO 1016 (480 mg/day) was tested versus placebo from Day 0 to Day 14. Patients were randomly (1:1) assigned to the following two treatment groups: - BNO 1016: 3x160 mg / day (480 mg total daily dose) - Placebo Each patient had to take 3x2 (=6) tablets (either BNO 1016 or placebo) per day. First intake of study medication took place in the investigator's office at Visit 1 (Day 0).

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Duration of treatment:	15 (± 1) days
Criteria for evaluation - Efficacy	Primary efficacy endpoint (primary outcome measure) The primary efficacy endpoint was defined as the mean MSS assessed by the investigator at the end of treatment on Visit 5 (Day 14). Secondary efficacy endpoints 1. The course of the MSS calculated as AUC from baseline to Visit 5 (Day 14) [score points x days] 2. The mean MSS from Visit 3 (Day 7) to Visit 5 (Day 14) [score points] 3. The mean individual symptoms of the MSS at Visit 5 (Day 14) [score points] 4. The course of the individual symptoms of the MSS calculated as AUC from baseline to Visit 5 (Day 14) [score points x days] 5. SNOT-20 symptom scores (total score and subscores "primary nasal score", "primary rhinogen score" and "general quality of life score") at Visit 2 (Day 3), Visit 3 (Day 7), Visit 4 (Day 10) and at Visit 5 (Day 14) [score points] 6. Change in health related symptoms "sleep", "daily functioning" and "general well-being" calculated as AUC from Day 0 to Day 14 (Day -1 to Day 13, respectively) [score points x days] 7. The mean MSS_{pat} at Visit 5 (Day 14) [score points] 8. The course of the MSS_{pat} calculated as AUC from baseline to Visit 5 (Day 14) [score points x days] 9. The course of the MSS_{pat} during the first treatment week calculated as AUC from baseline to Visit 3 (Day 7) [score points x days] 10. The course of the MSS_{pat} during the second treatment week calculated as AUC from Visit 3 (Day 7) to Visit 5 (Day 14) [score points x days] 11. Percentage of patients classified as responders by the investigator on a 4-point rating scale at Visit 2 (Day 3), Visit 3 (Day 7), Visit 4 (Day 10) and Visit 5 (Day 14) [%] 12. Percentage of patients with permitted concomitant medication for treatment of acute rhinosinusitis [%] 13. Percentage of patients with premature termination due to antibiotic therapy for acute rhinosinusitis [%] 14. The mean MSS at Visit 5 (Day 14) for the subgroup of patients with or without intake of Paracetamol, respectively [score points] 15. The course of MSS calculated as AUC from baseline to Visit 5 (Day 14) for the subgroup of patients with or without intake of Paracetamol, respectively [score points x days] 16. Percentage of patients with signs of acute rhinosinusitis in ultrasonography of paranasal sinuses at Visit 5 (Day 14) and at Visit 6 (follow-up visit, Day 28) [%]
- Safety	1. Frequency and intensity of adverse events [N / %] 2. Investigator's and patient's global judgements on tolerability at Visit 5 (Day 14) based on a 5-point rating scale 3. Vital signs (blood pressure, pulse and body temperature) 4. Safety laboratory

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Statistical methods	Interim analysis In the week of April 5-9, 2010, a pre-planned blinded interim analysis was performed by the CRO (Pharmalog Institut für klinische Forschung GmbH, Munich / Germany) using the approach of Kieser and Friede. The objective of the interim analysis was to verify the assumptions of the sample size estimation performed for the study protocol and to re-calculate the sample size if required. Data of 267 (69.4%) patients with completed Visit 5 (of 385 treated patients) were available on 24 MAR 2010. Of these, 261 patients were included in the blinded interim analysis to re-estimate the standard deviation of the primary endpoint using the root Means Square Error (root-MSE) of the analysis of covariance (ANCOVA; treatment effect omitted from analysis). The analysis resulted in a root-MSE of 2.85 score points which was below the estimator of the standard deviation used for the sample size calculation (root-MSE: 3.0 score points). Therefore, a re-estimation of the sample size was not necessary. Final analysis The analyses of the primary and secondary endpoints were performed using the full analysis set (FAS) which included all randomised patients with acute rhinosinusitis and with at least one documented application of the investigational drug and post-baseline efficacy data. The analysis of the per-protocol set (PP) was performed additionally as a sensitivity analysis to determine the effects of the patients excluded from the PP cohort. All data were analysed exploratively by descriptive statistics. Categorical variables were described in contingency tables as absolute numbers and percentages. All secondary endpoints were tested for difference between treatment groups. These analyses were performed only for explorative purpose. Baseline values were compared between treatment groups and tested by Mann-Whitney-Wilcoxon test (numerical variables) or Chi-square test (categorical variables). Treatment effects regarding the primary endpoint were analysed by the ANCOVA with "Baseline" as covariate and "Treatment" as a fixed effect. The centre effect described by the variable "Medical Specialist" was included in the model as well as the interaction term "Medical Specialist x Treatment" as fixed effect.
Summary – Conclusions Efficacy results	480 mg BNO 1016 was superior to placebo for the treatment of ARS in patients with baseline symptoms MSS ≤ 12 and facial pain / pressure ≤ 2 score points present for maximum three days. In the second week of treatment, the severity of the five main symptoms of ARS markedly improved as demonstrated by the course of the MSS, the responder rate (healing and symptom improvement), and the 20-Item Sino-Nasal Outcome Test (SNOT-20). · Overall, the average MSS (investigator's ratings from Visit 1 to Visit 5 in the CRF) improved by 7.38 score points under 480 mg BNO 1016 compared to 6.32 score points under placebo (FAS). The group difference of 1.03 score points at Visit 5 (mean MSS: 2.38 vs. 3.41 score points; primary endpoint) was considered medically relevant and was highly statistically significant in favour of BNO 1016 (one-sided p-value of 0.0008 for the FAS calculated as the half of the ANCOVA two-sided p-value: p=0.0015), see Table 1. The results were confirmed by the ANCOVA in the PP set (p<0.0001).

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Summary – Conclusions Efficacy results (continued)

- The group differences between 480 mg BNO 1016 and placebo for the five individual rhinosinusitis symptoms at Visit 5 were statistically significant for the symptoms rhinorrhea, postnasal drip, headache and facial pain / pressure in the ANCOVA for the FAS and PP set (one-sided p-values <0.025) but not for the symptom nasal congestion (p-value=0.0987 and 0.0355, respectively).

- A similar statistically significant group difference (0.86 score points in mean values and 1.0 score point in median values) was calculated for the MSS_{pat} at Visit 5 using the patient's ratings of the evening before Visit 5 (diary data) for the five main rhinosinusitis symptoms (ANCOVA: one-sided p-value of 0.0117 for FAS).

Table 1: Evaluation of Major Symptom Score – MSS (FAS)

Variable		480 mg BNO 1016	Placebo	p-value (FAS)
Investigator ratings (CRF)	N	[190]	[190]	
MSS		[score points]	[score points]	
Visit 1	Mean ± SD	9.76 ± 1.39	9.73± 1.39	0.4244 A)
Visit 5 (primary endpoint)	Mean ± SD	2.38 ± 2.54	3.41 ± 3.36	**0.0008** B)*
Δ Visit 5 - Visit 1	Mean	7.38	6.32	
AUC in MSS (Visit 1 - Visit 5)	Mean ± SD	79.7 ± 27.1	87.2 ± 34.1	**0.0029** B)*
SUBSET ANALYSES:				
With concomitant Paracetamol	N	[39]	[47]	
MSS at Visit 5	Mean ± SD	3.0 ± 3.0	3.0 ± 3.7	0.4914 B)
AUC in MSS (Visit 1 - Visit 5)	Mean ± SD	81.8 ± 32.5	86.7 ± 36.9	0.1668 B)
Without concomitant Paracetamol	N	[151]	[143]	
MSS at Visit 5		2.2 ± 2.4	3.5 ± 3.2	**0.0001** B)*
AUC in MSS (Visit 1 - Visit 5)		79.1 ± 25.6	87.4 ± 33.3	**0.0031** B)*
Patient ratings (diary)	N	[180]	[183]	
MSS_{pat}		[score points]	[score points]	
Day -1 (retrospectively)	Mean ± SD	9.13 ± 2.37	8.93 ± 2.53	0.2715 A)
Visit 5C)	Mean ± SD	2.62 ± 2.76	3.48 ± 3.27	**0.0117** B) *
Δ Visit 5C)- Day-1	Mean	6.51	5.45	
AUC in MSS_{pat}				
1st week (Day -1 to Day 6)	Mean ± SD	51.5 ± 15.0	51.8 ± 16.2	0.1668 B)
2nd week (Day 6 to Day 13)	Mean ± SD	28.2 ± 17.4	32.0 ± 20.3	**0.0246** B)*
Overall (Day -1 to Day 13)	Mean ± SD	79.7 ± 29.4	83.8 ± 33.5	0.0445 B)

Δ = Difference; * = statistical significant group difference; SD =standard deviation; MSS_{pat} = MSS assessed by the patient; A) Wilcoxon 2-sample test, one-sided; B) ANCOVA, one-sided significance levels of alpha= 0.025 (two-sided ANCOVA p-values were halved and rounded to four decimal places); C) MSS_{pat} at Visit 5 was calculated using the diary data from Day -1 to the evening before Visit 5.

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Summary – Conclusions Efficacy results (continued)	· The better improvement in rhinosinusitis symptoms under 480 mg BNO 1016 was associated with a less frequent need to administer analgesics (Paracetamol) and antibiotics during the treatment period compared to placebo-treatment. The group differences regarding patients with concomitant use of Paracetamol (20.5% vs. 23.7%) and drop outs due to antibiotic use (2.1% vs. 3.7%) did not reach statistical significance. · The advantage of 480 mg BNO 1016 over placebo in reducing rhinosinusitis symptom severity was not seen in patients who concomitantly used Paracetamol for pain relief, as shown by the subset analyses of mean MSS at Visit 5 and mean AUC in MSS from Visit 1 to Visit 5 (ANCOVA: one-sided p-values of 0.4914 and 0.1668, respectively, for patients with Paracetamol, compared to one-sided p-values of 0.0001 and 0.0031, respectively, for patients without Paracetamol). Similar results were obtained in the additional FAS analysis that focussed on the administration of Paracetamol on the last treatment day (Visit 5 / EOT) or one day before Visit 5 / EOT accounting for the short half-life of Paracetamol which is about 2 hours in adults (ANCOVA: one-sided p-value of 0.2551 for patients with Paracetamol on Visit 5/EOT or one day before, compared to one-sided p-value of 0.0002 for patients without Paracetamol on Visit 5/EOT or one day before). The results of this additional analysis must be interpreted in light of the fact that patients with concomitant Paracetamol use on the last treatment day (and / or one day before) are a small and selected subset (9 out of 190 patients in the BNO 1016 group and 6 out of 190 patients in the placebo group: 4.7% versus 3.2%, respectively in the FAS). · 480 mg BNO 1016, as compared with placebo, was associated with higher responder rates at Visit 3 (Day 7: 85.8% vs. 80.5%), Visit 4 (Day 10: 91.6% vs. 82.1%) and Visit 5 (Day 14: 94.2% vs. 87.4%). The Chi-square test showed superiority of 480 mg BNO 1016 over placebo in responder rates at Visit 4 and Visit 5 for the FAS (two-sided p-values of 0.0063 and 0.0211, respectively) and at Visit 3, Visit 4 and Visit 5 for the PP set (two-sided p-values of 0.0107, 0.0003 and 0.0076, respectively). · The differences between 480 mg BNO 1016 and placebo regarding the improvement in the ratings of symptoms and social / emotional consequences of rhinosinusitis (SNOT-20 GAV questionnaire) were highly significant in the ANCOVA for the total SNOT-20 and the three subscales from Visit 2 to Visit 5 (one-sided p-values <0.025 for FAS and PP). · The better improvement under BNO 1016 480 mg, as compared to placebo, in the three evaluated health related symptoms 'daily functioning', general well-being' and 'sleep' (diary data) calculated as AUCs over 15 days did not reach statistical significance in the FAS whereas in the PP set, the group difference regarding sleep in favour of BNO 1016 was statistically significant with a one-sided p-value of 0.0092 in the ANCOVA. · The percentage of patients who had no ultrasonographic signs of ARS at Visit 5 was higher under 480 mg BNO 1016 compared to placebo (73.2% vs. 61.6%). The group difference in favour of 480 mg BNO 1016 was statistically significant for both the FAS (p=0.0262) and the PP set (p=0.0050) in the two-sided Cochran-Mantel-Haenszel test adjusting for centre. Also at Visit 6 (follow-up), more patients who had been treated with 480 mg BNO 1016, as compared to placebo, were free of ultrasonographic signs of acute rhinosinusitis, particularly in the small subset of 11 patients with a time interval <11 days between ultrasonography and last study visit (60.0% vs. 50.0% of patients without ultrasonographic signs of ARS). This group difference was not statistically significant.

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Summary – Conclusions Safety results

Adverse events

Throughout the whole study (Visit 2 to Visit 6 / follow-up), 53 AEs occurred in 46 (11.9%) of all 385 treated patients (SEP).
In the 480 mg BNO 1016 group, 19 (9.8%) patients reported 21 AEs; 14 (66.7%) of these AEs started during the treatment period.
In the placebo group, 27 (14.1%) patients reported 32 AEs; 22 (68.8%) of these AEs started during the treatment period.

The majority of AEs reported under 480 mg BNO 1016 and placebo was mild to moderate in intensity. Four (7.5%) out of 53 AEs were severe, all four were reported in the placebo group. Serious or fatal AEs were not reported.

The frequency of AEs with a probable or possible relationship to study medication (adverse reactions) according to the investigator's blinded assessment, was marginally less in the 480 mg BNO 1016 group (23.8% of 21 AEs) compared to placebo group (25.0% of 32 AEs).

AEs that were classified as possibly or probably related to treatment with 480 mg BNO 1016 (diarrhoea in two patients, flatulence in one patient, and both dizziness and nausea in one patient) showed no sign of an increased frequency of any expected or unexpected ARs observed under 480 mg BNO 1016.

Treatment (i.e., a change in concomitant medication) was required more frequently for AEs reported under 480 mg BNO 1016 (33.3% of 21 AEs) than for AEs reported under placebo (21.9% of 32 AEs).

Five patients prematurely discontinued study participation due to an AE, one (0.5%) out of 194 patients in the 480 mg BNO 1016 group due to dizziness, and four (2.1%) out of 191 patients in the placebo group due to a hypersensitivity reaction (two patients), abdominal pain and palpitations (one patient each).

Except for two (6.3%) AEs in the placebo group (toothache [recovering expected] and cholelithiasis [not recovered]), all AEs had resolved by study end.

Vital signs

Office measurements at Visit 3 and Visit 5 did not show any clinically relevant changes in average blood pressure, pulse or body temperature in any treatment group.

Safety laboratory

Safety laboratory parameters did not change relevantly in the majority of patients from Visit 1 to Visit 5. A change from within normal range at baseline (Visit 1) to significantly out of normal range at end of treatment (Visit 5) was not observed in any patient of the 480 mg BNO 1016 group compared to one patient in the placebo group.

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Summary – Conclusions Safety results (continued)	Global judgement of tolerability The frequencies of 'very good' or 'good' ratings were comparable between the 480 mg BNO 1016 group (96.4% by investigators / 94.8% by patients) and the placebo group (95.3% by investigators / 94.8% by patients). A total of four patients assessed the tolerability of investigational treatment as "very poor", one patient in the 480 mg BNO 1016 group (investigator's assessment "moderate") and three patients in the placebo group (investigators' assessments "moderate" for one patient and "very poor" for two patients).
Treatment compliance	The average treatment compliance was nearly 100% (according to pill count data in the CRF) with no relevant difference between the two treatment groups.
Conclusion	The results of the trial show that 480 mg BNO 1016 is more effective in relieving the symptoms of acute rhinosinusitis, as compared to placebo. Oral treatment with 480 mg BNO 1016 for about two weeks was safe, well tolerated and comparable to placebo treatment regarding the safety profile.
Date of the report	17 JAN 2013 (Final 2.0)