Clinical efficacy of a dry extract of five herbal drugs in acute viral rhinosinusitis*

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ABSTRACT

Objective: : A herbal drug combination (Dry Extract BNO 1016) has been assessed for efficacy and tolerability in patients with acute viral rhinosinusitis.

Methodology: In this randomised, controlled trial patients with symptom duration of ≤3 days, mild to moderate facial pain and a Major Symptom Score (MSS) of ≥ 8 and ≤ 12 were treated for 15 days with BNO 1016 or placebo (coated tablets administered orally). Primary efficacy endpoint was mean MSS at end of treatment. Secondary outcome measures included treatment response and changes in paranasal sinuses assessed by ultrasonography.

Results: Treatment resulted in clinically relevant, significant differences in mean MSS for BNO 1016 versus placebo. BNO 1016 provided symptom relief two days earlier than placebo. The number needed to treat for healing is 8. BNO 1016 was superior regarding responder rates at Day 10 and Day 14 and percentage of patients without signs of acute viral rhinosinusitis assessed by ultrasonography at end of treatment. BNO 1016 was well tolerated; no serious adverse events were reported.

Conclusion: The herbal dry extract BNO 1016 is efficacious and well tolerated in patients with acute viral rhinosinusitis.
Trial registration: ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT01146860; EudraCT: 2009-016682-28).

Key words: acute viral rhinosinusitis, herbal dry extract, major symptom score (MSS), Sino-Nasal Outcome Test (SNOT)-20, ultrasonography

Introduction

The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) [(1)] defines rhinosinusitis as an inflammatory process involving the mucosa of the nose and one or more paranasal sinuses. Acute rhinosinusitis (ARS) is characterised by sudden onset of two or more symptoms, such as nasal blockage/congestion, nasal discharge (anterior/post nasal drip), facial pain or pressure, and reduction/loss of smell. Additional symptoms such as headache, fever, fatigue, and sleep disturbance due to blocked nose may also occur. ARS is predominantly caused by rhino-, adeno-, or picorna-virus infection in adults, and often characterised by an increase in pro-inflammatory cytokines and neutrophilia similar to that seen for bacterial infections. ARS is thus frequently misunderstood as bacterial infection and treated with antibiotics [(1,2)]. Consequently, the use of antibiotics is discouraged in uncomplicated ARS. Acute rhinosinusitis can be differentiated into acute viral rhinosinusitis and acute post-viral rhinosinusitis [(1)]. Acute viral rhinosinusitis is characte-

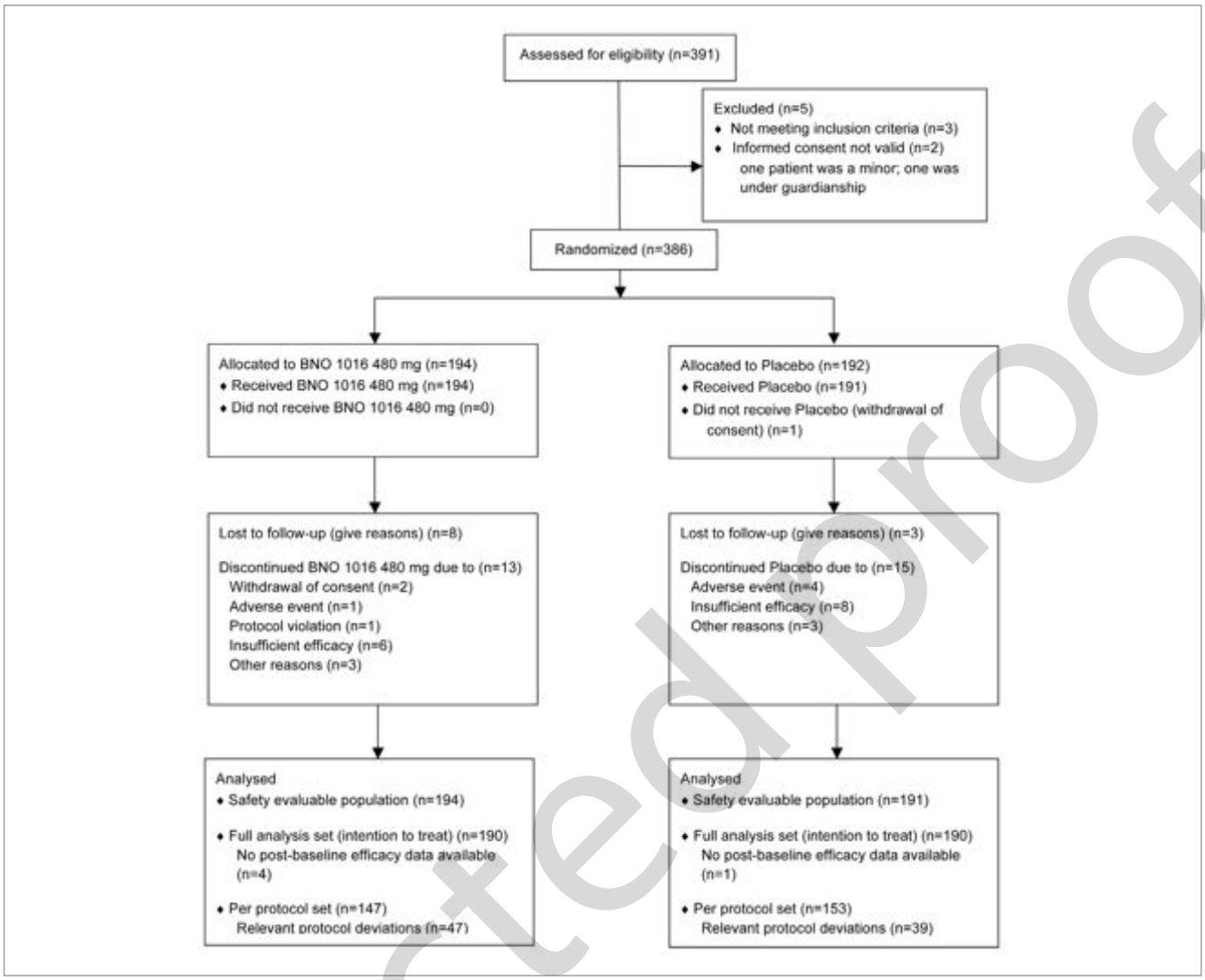

Figure 1. Patient disposition.

rized by duration of symptoms of less than 10 days, whereas in acute post-viral rhinosinusitis symptoms increase after 5 days or persist after 10 days.

Although the symptoms of ARS are mostly self-limiting and resolve completely, they adversely impact the quality of life of affected individuals and impose a substantial socio-economic burden on both the individual and society alike [1-4]. In view of the considerable morbidity and diminished quality of life of individuals affected with ARS, the main aims of treatment are to reduce the severity of symptoms and duration of the disease, and subsequently prevent the development of chronic disease and complications [2]. The use of intranasal corticosteroids alone or in combination with antibiotics is currently recommended as first-line treatment for ARS [1].

An increasing body of evidence suggests that phytotherapeutic agents may be useful in the treatment of ARS [5-7]. Dry Extract BNO 1016 (Bionorica SE, Neumarkt, Germany) is a novel extract of a fixed combination of five herbal drugs (comprising Gentian root *(Gentianae radix),* Primula flower *(Primulae flos*), Sorrel herb *(Rumicis herba*), Elder flower *(Sambuci flos*), and Verbena herb *(Verbenae herba*), in the ratio 1:3:3:3:3) that has been developed as a high-dosage product for the treatment of sinusitis. Pharmacological studies employing *in vitro* and animal models have demonstrated that BNO 1016 has antimicrobial and antiviral effects, as well as secretolytic and anti-inflammatory activity [8,9]. Findings from phase IIb/III studies have indicated that a dose of 160 mg three times a day (tid) was most effective (data available on file). In view of these findings, the aim of the present study was to investigate the efficacy and safety of a dose of BNO 1016 160 mg tid. for 15 days on symptoms of acute viral rhinosinusitis.

Materials and methods

Patients

Adult male and female outpatients aged ≥ 18 and ≤ 75 years

Table 1. Demographics and other baseline characteristics at Visit 1 (ITT).

Parameter	BNO 1016 (n = 190)	Placebo (n = 190)	Total (n = 380)
Age (years)			
Mean (SD)	41.0 (15.4)	40.4 (14.3)	40.7 (14.9)
Range	18 to 73	18 to 77	18 to 77
Weight (kg)			
Mean (SD)	75.1 (15.6)	75.1 (16.9)	75.1 (16.3)
Range	40.1 to 149.2	48.0 to 160.0	40.1 to 160.0
Height (cm)			
Mean (SD)	170.0 (8.9)	170.4 (8.9)	170.2 (8.9)
Range	143.0 to 198.0	150.0-194.0	143.0 to 198.0
Gender (n (%))			
Female	124 (65.3%)	121 (63.7%)	245 (64.5%)
Male	66 (34.7%)	69 (36.3%)	135 (35.5%)
Ethnicity (n (%))			
Caucasian	185 (97.4%)	186 (97.9%)	371 (97.6%)
Asian	3 (1.6%)	3 (1.6%)	6 (1.6%)
Other	2 (1.1%)	1 (0.5%)	3 (0.8%)
Mean MSS (SEM)	9.76 (0.10)	9.73 (0.10)	9.74 (0.10)

ARS: acute rhinosinusitis; MSS: major symptom score; SD: standard deviation; SEM: standard error of the mean.

with a clinical diagnosis of acute viral rhinosinusitis (ICD-10: J01.9), confirmed by ultrasonography of the maxillary sinuses for all patients, were recruited into the study. Acute viral rhinosinusitis was defined as sudden onset of at least three of five main ARS symptoms (rhinorrhoea/anterior discharge, postnasal drip, nasal congestion, headache and facial pain/ pressure). At enrolment duration of symptoms did not exceed 3 days. All patients were required to demonstrate an investigator-evaluated Major Symptom Score (MSS) of ≥ 8 and ≤ 12 (of maximum 15 score points) as well as the presence of nasal congestion and mild to moderate facial pain/pressure score of ≥ 1 and ≤ 2 to be eligible for inclusion in the study. Facial pain was limited to moderate intensity to ensure enrolment of patients presenting with symptoms of non-complicated acute viral rhinosinusitis.

Subjects treated with systemic or nasal antibiotics or corticosteroids within the last 4 weeks prior to inclusion were excluded as well as patients using medication for treatment of common cold like symptoms, or immunomodulating drugs within the last 7 days of study inclusion. Pregnant or lactating women and patients with severe diseases of liver or kidney or those with severe somatopathic, neurological and/or psychiatric diseases were not enrolled.

Study design

This was a prospective randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted from January 2010 to April 2010 in thirty-seven centres (16 specialists in otorhinolaryngology, 21 specialists in internal medicine and general practitioners) across Germany. At screening (Visit 1/ Day 0) outpatients suffering from acute viral rhinosinusitis were evaluated for eligibility. Selected patients providing written informed consent were randomized to treatment with either two 80 mg coated tablets of BNO 1016 tid or matched placebo for 15 days. The study medication was administered orally. Randomization was done according to a computer-generated randomisation code for a parallel group model using a ratio of 1:1 with neither the subjects nor the investigator knowing the identity of the medication to allow treatment in double-blind manner. Diary cards were provided to each subject to record the severity of each of the five symptoms of the disease, as well as intake of study medication and concomitant treatment. The patients were asked to return to the site on Days 3, 7, 10, and 14 (Visits 2, 3, 4 and 5, respectively) and for a follow-up visit (Visit 6), four weeks after Visit 1 or earlier in case of premature remission of symptoms. At each visit the patients were evaluated by the investigator for the five symptoms of the MSS, response to treatment, health-related quality of life using the Sino-Nasal Outcome Test-20 German Adapted Version (SNOT-20 GAV) questionnaire [10], AEs experienced and compliance to treatment according to the number of tablets taken/remaining. Ultrasonography of paranasal sinuses was performed at end of treatment (Visit 5) and at the follow-up visit (Visit 6, Day 28).

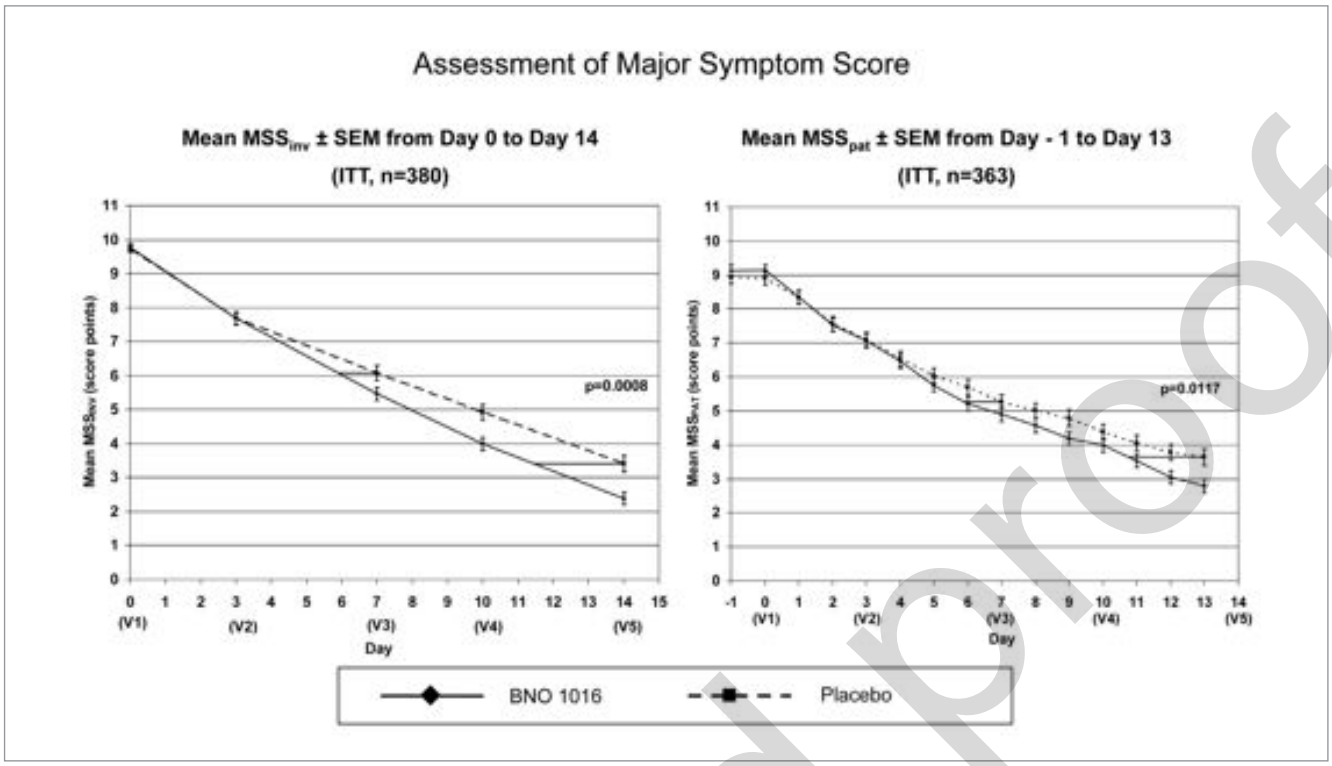

Figure 2. Left: Time course of Major Symptom Score (MSS$_{inv}$) from Visit 1/Day 0 to Visit 5/Day 14 (ITT). Right: Time course of Major Symptom Score assessed by the patient (MSS$_{pat}$) at home from Day -1 (retrospectively) to evening before Visit 5 (ITT). Horizontal lines indicate earlier course of remission of ARS symptoms in BNO 1016-treated groups.

The study was conducted in accordance with the Declaration of Helsinki [11] and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) [12]. Before enrolment of the first patient, the trial was approved by the German competent authority and received a favourable opinion by the ethics committee competent for the coordinating investigator ('Leiter der klinischen Prüfung', LKP). Written informed consent was obtained from all patients prior to any study related measures.

Efficacy measurements

Primary and secondary endpoints. The primary efficacy endpoint was the mean MSS assessed by the investigator at the end of treatment (MSS$_{inv}$; Visit 5; Day 14). Additionally, the differences between treatment groups for the rate of patients considered to be healed (MSS ≤ 1) at Visit 5 and for patients without distinct treatment effect (MSS at Visit 5 > 50% of MSS at baseline) were analysed. The results for the rate of patients with MSS ≤ 1 at end of treatment were used to calculate the number needed to treat to achieve healing.

The secondary efficacy endpoints were i) mean patient-assessed MSS (MSS$_{pat}$) for the evening before Visit 5 (Day 14), ii) patients' total and subscale scores of the SNOT-20 GAV questionnaire at each visit, iii) percent responders, iv) percent patients with premature termination due to antibiotic therapy, and v) percent patients with signs of acute viral rhinosinusitis detectable by ultrasonography of paranasal sinuses at the end of treatment and at follow up.

Major symptom score (MSS). The MSS combines the five most relevant symptoms of rhinosinusitis based on expert clinician recommendations (rhinorrhoea/ anterior discharge, postnasal drip, nasal congestion, headache and facial pain/ pressure) and has been employed as primary efficacy criterion in several clinical trials [5,13-14].

Assessment of Major Symptom Score (MSS). Investigators rated the severity of each of the five symptoms of the MSS at each visit using a 4-point rating scale of increasing severity (0 = none/ not present, 1 = mild, 2 = moderate, 3 = severe). Pain parameters and postnasal drip were rated according to the description of the patients. The MSS was calculated as the sum of the five individual symptom scores. Additionally, patients recorded their scoring (0-3) of MSS symptoms daily in the evening in a diary card from Day -1 to Day 13 (MSS$_{pat}$).

Assessment of responders and non-responders to treatment. Overall response to treatment was assessed by the investigator at each visit using a 4-point rating scale (0 = symptoms healed/cured; 1 = symptoms improved compared to Visit 1; 2 = symptoms unchanged compared to Visit 1; 3 = symptoms deteriorated compared to Visit 1). Patients who were cured or

Table 2. Effect of treatment on mean MSS_{inv} ± SEM (Visit 5) and mean MSS_{pat} ± SEM (evening before Visit 5).

	BNO 1016		Placebo		Mean group difference V5 $MSS_{placebo}$ - $MSS_{BNO\ 1016}$ ± SEM	p-value[A]
	Baseline	Visit 5	Baseline	Visit 5		
MSS_{inv} (ITT)	9.76 ± 0.10	2.38 ± 0.18	9.73 ± 0.10	3.41 ± 0.24	1.03 ± 0.24	0.0008*
MSS_{inv} (PP)	9.64 ± 0.11	2.07 ± 0.18	9.59 ± 0.10	3.47 ± 0.28	1.40 ± 0.28	< 0.0001*
[B]MSS_{pat} (ITT)	9.13 ± 0.18	2.62 ± 0.21	8.93 ± 0.19	3.48 ± 0.24	0.86 ± 0.24	0.0117*
[B]MSS_{pat} (PP)	8.90 ± 0.20	2.25 ± 0.20	8.83 ± 0.21	3.55 ± 0.28	1.30 ± 0.28	0.0010*

[A]ANCOVA; *statistically significant difference between treatment groups on a one-sided type-I-error rate level of α=0.025; [B]MSS_{pat}: patient assessed MSS on the evening before Visit 5; MSS_{inv}: investigator assessed MSS at Visit 5; SEM: standard error of the mean.

had improved symptoms (0 and 1 rated score) were classified as responders, whereas patients with unchanged or deteriorated symptoms (2 and 3 rated score) were classified as non-responders.

Ultrasonography. Ultrasonography was performed by well trained investigators or referring ENT specialists. Observation of a back-wall echo is considered to be due to fluid retention and indicative of an inflamed maxillary sinus.

Assessment of tolerability. AEs were recorded at each visit including follow up and evaluated by the investigators for severity, duration, outcome, actions taken, pattern of occurrence and the causal relationship to treatment. Additionally, changes in vital signs (blood pressure, heart rate, body temperature) were recorded at each study visit as well as temperature at Visits 1, 3 and 5. Tolerability was judged by investigator and patient at the end of treatment (Visit 5) using a verbal 5-point rating scale ranging from 0 (very good) to 4 (very poor).

Statistical analyses

Sample size. The sample size was calculated based on a MSS of 2.6 and 3.6 (± adjusted standard deviation of 2.92) following treatment for 15 days with BNO 1016 and placebo. To demonstrate a treatment group difference of at least one score point in MSS at 2.5% significance level and with a power of 90%, a total of 380 patients would be required including a 5% drop-out rate.

Analysis sets and handling of missing data. Efficacy analyses were performed primarily on the intention to treat population (ITT), which comprised data for all randomised patients who had received at least one dose of the study medication and at least one evaluation of efficacy. P-values ≤ 0.025 indicate statistical significance. Tolerability analyses were performed on the Safety Evaluable Population (SEP), which comprised all randomised patients who had received at least one dose of the study medication and had documented safety data. The Per-Protocol population (PP) comprised all randomized patients inform the ITT excluding those with major protocol violations.

No imputation of missing values was performed when only baseline data were available; otherwise missing values were replaced according to the "last observation carried forward (LOCF)" principle except for SNOT-20. Missing score ratings in the SNOT-20 patient questionnaire were replaced by the worst category.

Statistical methods

All data were analyzed using the SAS Version 9 statistical software. If not indicated otherwise, deviations are indicated as standard error of the mean (SEM).
The primary efficacy endpoint was analysed using analysis of covariance (ANCOVA). A difference of one score point in MSS between the treatment groups was prospectively judged to be clinically relevant.

All secondary endpoints were analysed exploratively. Categorical variables were tested by the Chi-square test. Continuous data were analysed by the ANCOVA similar to the primary endpoint or by the Cochran-Mantel-Haenszel test. Baseline values were compared between treatment groups and tested by Mann-Whitney-Wilcoxon test (continuous variables) or Chi-Square test (categorical variables).

AEs were summarised descriptively according to individual/total numbers and percent patients reporting any AE. The t-test was used to compare the group means for vital signs and Mann-Whitney-Wilcoxon test for investigators' and patients' tolerability ratings.

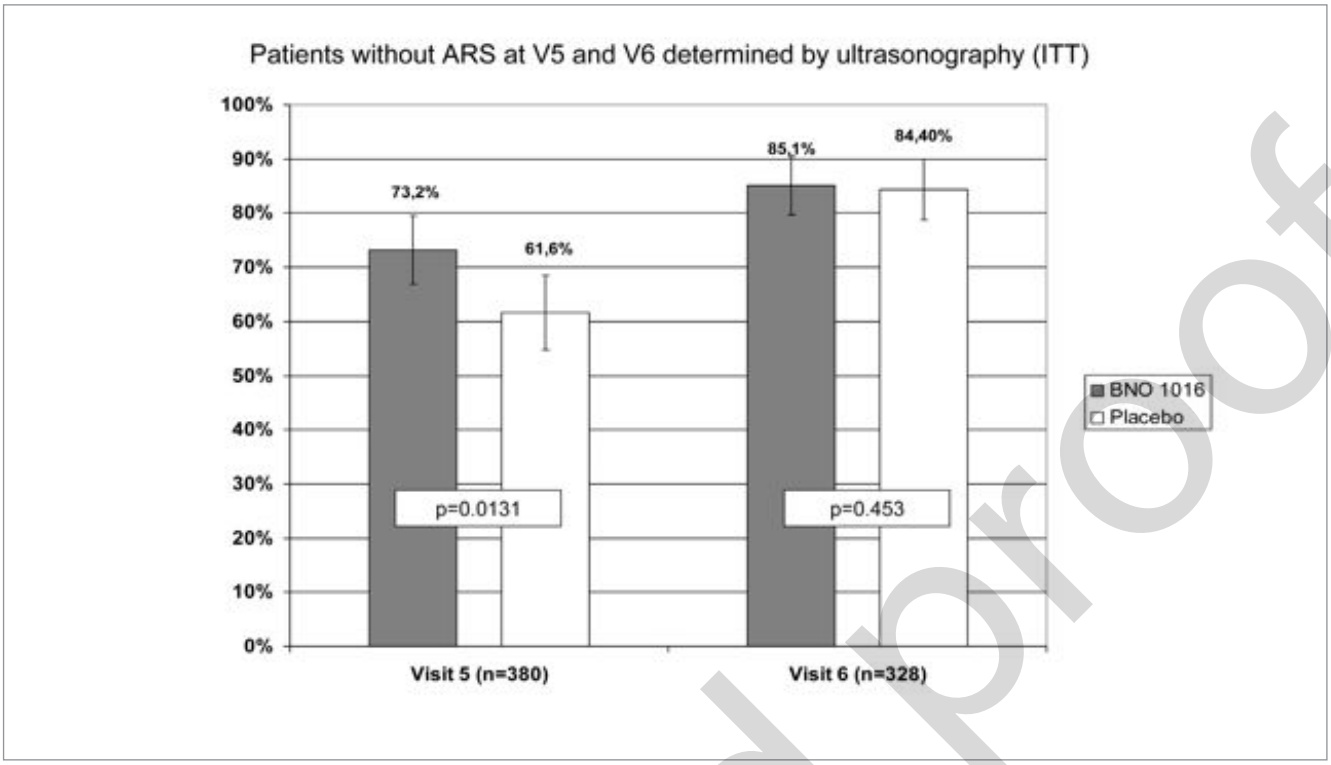

Figure 3. Percentage of patients without signs of acute rhinosinusitis, assessed by ultrasonography of maxillary sinuses at Visit 5 for ITT and for all patients who performed Visit 6 (n = 328). 95% confidence intervals are indicated.

Table 3. Responder rates BNO 1016 and placebo by visit (ITT and per protocol).

	Responder rates for ITT			Responder rates for per protocol		
	BNO 1016	Placebo	p-value[A]	BNO 1016	Placebo	p-value[A]
Visit 2 (Day 3)	56.8%	58.4%	0.3778	60.5%	58.8%	0.3807
Visit 3 (Day 7)	85.5%	80.5%	0.0853	89.8%	79.1%	0.0054*
Visit 4 (Day 10)	91.6%	82.1%	0.0032*	95.9%	83.0%	0.0002*
Visit 5 (Day 14)	94.2%	87.4%	0.0106*	95.2%	86.3%	0.0038*

[A]Chi-square test, one-sided; *statistically significant difference between treatment groups on a one-sided type-I-error rate level of α=0.025

Results

Patient disposition

Figure 1 shows the disposition of patients. A total of 386 patients were randomised to treatment (n = 194 BNO 1016 group; n = 192 placebo group). One patient in the placebo group did not take any study medication. The safety population therefore comprised 385 patients.

Four patients in BNO 1016 group and one patient in placebo group lacked post-baseline efficacy data (lost to follow-up). Thus, the ITT comprised 380 patients.

Overall, 21 patients in the BNO 1016- and 18 patients in the placebo-treated group discontinued the study prematurely. Most patients discontinued due to lack of efficacy of study treatment (14 patients: 6 in BNO 1016 group and 8 in placebo group) or were lost to follow-up (11 patients: 8 in BNO 1016 group and 3 in placebo group). Overall, 2.1% (n = 4) of patients in the BNO 1016-treated group and 3.7% (n = 7) in the placebo-treated group terminated the study prematurely because they required antibiotic therapy.

For a total of 86 patients relevant protocol deviations (47 in the BNO 1016 group and 39 in the placebo group) were detected;

Table 4. Effect of BNO 1016 or placebo treatment on SNOT-20 GAV scores over the course of treatment for ITT.

SNOT-20 GAV scores for (Mean ± SD)	BNO 1016 (n = 190)	Placebo (n = 190)	p-value[A]
Total SNOT-20[B]			
Visit 2	33.05 ± 14.15	34.71 ± 14.66	
Visit 3	23.04 ± 14.21	26.73 ± 15.16	0.0019*
Visit 4	16.28 ± 12.38	21.18 ± 15.04	
Visit 5	11.02 ± 12.72	15.76 ± 16.26	
Primary nasal subscale – PNS[C]			
Visit 2	10.77 ± 4.25	10.83 ± 4.12	
Visit 3	7.84 ± 3.98	8.42 ± 4.26	0.0113*
Visit 4	5.86 ± 3.66	6.94 ± 4.44	
Visit 5	3.78 ± 3.87	4.90 ± 4.70	
Primary rhinogen subscale – PRS[D]			
Visit 2	10.55 ± 4.95	10.81 ± 4.96	
Visit 3	7.44 ± 5.22	8.57 ± 5.25	0.0078*
Visit 4	5.15 ± 4.55	6.68 ± 5.19	
Visit 5	3.40 ± 4.59	4.95 ± 5.38	
General quality of life subscale - ALQ[E]			
Visit 2	11.73 ± 7.06	13.17 ± 7.58	
Visit 3	7.76 ± 6.62	9.68 ± 7.54	0.0012*
Visit 4	5.27 ± 5.67	7.57 ± 7.11	
Visit 5	3.87 ± 5.65	5.88 ± 7.32	

[A] p-values for treatment differences from Visit 2 to Visit 5 analyzed by repeated measures ANCOVA; [B]Total SNOT-20: Sum-score of items 1-20; [C]PNS: Sum-score of items 1, 2, 3, 5, 10; [D]PRS: Sum-score of items 4, 6, 7, 8, 9, 12; [E]ALQ: Sum-score of items 11, 13, 14, 15, 16, 17, 18, 19, 20

* statistically significant difference between treatment groups on a one-sided type-I-error rate level of α=0.025 for each individual test

thus the PPS comprised 300 patients (n = 147 patients for BNO 1016 and n = 153 for placebo).

Assessment of the patients' demographic and baseline clinical characteristics indicated that both treatment groups were comparable (Table 1).

Efficacy results

Study duration and treatment compliance. The median duration of participation of the patients was 29 days for both treatment groups with a range of 4 - 40 days with BNO 1016 and 3 - 48 days with placebo. Compliance with treatment, based on the tablet count, was 100.0 % in the BNO 1016 group and 100.2 % in the placebo group.

Major symptom score (MSS). No significant differences could be detected at baseline for the investigator-assessed mean MSS between the treatment groups (p = 0.4244) (Table 2). MSS improved progressively over the course of the 15-day treatment in both groups by a mean of 7.38 ± 0.21 to 2.38 ± 0.18 with BNO 1016 and by a mean of 6.32 ± 0.26 to 3.41 ± 0.24 with placebo (Figure 2). The group difference of 1.03 ± 0.24 at the end of treatment was statistically significant in favour of BNO 1016 product (p=0.0008). Results for the per protocol set are displayed in Table 2.

Assessment of MSS_{pat} resulted in a significant improvement for BNO 1016 compared with placebo (mean difference in MSS: 0.86 ± 0.24; p = 0.0117).

At the end of treatment the number of patients considered to be healed (MSS ≤ 1) was significantly higher in the BNO 1016-treated group compared with the placebo-treated group (ITT: 48.4% vs. 35.8%; p = 0.0063). In line with these results, the number of patients without distinct treatment effect (MSS > 50% of baseline) was significantly lower in the BNO 1016-treated group compared to the placebo-treated group (14.7% vs. 24.2%; p = 0.0099. The number needed to treat for patients to be cured (MSS ≤ 1 at end of therapy) was eight for the ITT and seven for the per protocol set.

Both MSS_{inv} and MSS_{pat} indicated BNO 1016 to initiate a faster recovery of patients, starting from Day 3 (Visit 2). Evaluation of MSS_{inv} at Day 7 and Day 14 indicated that recovery of the group treated with BNO 1016 was 1 day and 2.5 days ahead, respectively, compared to the group treated with placebo (ITT, Figure 2).

Table 5. Adverse Events (SEP).

		BNO 1016			Placebo	
Patients with AEs		19	9.8%		27	14.1%
Total number of AEs		21	100.0%		32	100.0%
Number of AEs after end of treatment		7	33.3%		10	31.3%
Intensity						
	mild AE	13	61.9%		19	59.4%
	moderate AE	8	38.1%		9	28.1%
	severe AE	0	0.0%		4	12,5%
System Organ Class						
	Infections + infestations	5	22.7%	Gastrointestinal disorders	8	25.0%
	Gastrointestinal disorders	4	18.2%	Infections + infestations	4	12.5%
	Ear + labyrinth disorders	4	18.2%	Respiratory + mediastinal disorders	4	12.5%
	Other	8	38.1%	Other	16	50.0%

Evaluation of MSS_{pat} at Day 6 and Day 13 also showed that recovery of the BNO 1016-treated group was 1 and 2 days ahead of placebo, respectively (ITT, Figure 2).

Overall response to treatment. The responder rates increased progressively in both BNO 1016-treated group and the placebo-treated group from Visit 3 onwards; however, the increase was more pronounced in the BNO 1016-treated group and significantly different at Day 10 (Visit 4: $p = 0.0032$) and Day 14 (Visit 5: $p = 0.0106$), compared to the placebo-treated group (Table 3). Responder rates for the per protocol set are displayed in Table 3.

Quality of life (QOL) measures. The mean total and subscale scores for SNOT-20 GAV were progressively improved in both the BNO 1016- and placebo-treated groups over the course of treatment. However, the improvements were significantly greater at all visits for the BNO 1016-treated patients than for the placebo-treated patients (Table 4).

Ultrasonography assessment. At enrolment acute viral rhinosinusitis was confirmed by ultrasonography for all patients. The percentage of patients without signs of acute viral rhinosinusitis at the end of treatment (Visit 5), as assessed by ultrasonography, was significantly higher in BNO 1016-treated group (73.2%, $[66.86\text{-}79.46\%]_{CI\ 95\%}$) compared to placebo-treated group (61.6% $[54.26\text{-}68.53\%]_{CI\ 95\%}$; $p = 0.0131$) for ITT (Figure 3). Overall, 328 patients were followed-up on Day 28 (Visit 6). Ultrasonography at Visit 6 showed no signs of acute viral rhinosinusitis in the majority of patients in both treatment groups (85.1% $[79.74\text{-}90.50\%]_{CI\ 95\%}$ in the BNO 1016-treated and 84.4% $[78.75\text{-}90.00\%]_{CI\ 95\%}$ in the placebo-treated groups).

Safety results. A total of 53 AEs were reported by 46 (11.9%) patients over the course of the study from Visit 2 to Visit 6; serious AEs were not reported. Characteristics of AEs and their incidence in the treatment groups are displayed in Table 5. Tolerability to BNO 1016 was also comparable to placebo; as indicated by 96.4% of investigators' and 94.8% of patients' rating BNO 1016 as 'very good' or 'good', and 95.3% of investigators' and 94.8% of patients' rating placebo as 'very good' or 'good'.

Discussion

This study has demonstrated that treatment with an oral dose of 160 mg BNO 1016 (fixed dose combination of 5-herbs Dry Extract comprising Gentian root *(Gentianae radix),* Primula flower *(Primula flos*), Sorrel herb *(Rumicis herba*), Elder flower *(Sambuci flos*), and Verbena herb *(Verbenae herba*), in the ratio 1:3:3:3:3) three times daily for 15 days, led to significant and clinically relevant improvements in symptoms of acute viral rhinosinusitis by end of treatment (primary efficacy end point) compared to placebo. Symptoms were assessed by means of the MSS. The MSS combines the five most relevant symptoms of rhinosinusitis based on expert clinician recommendations and has been employed as primary efficacy criterion in several clinical trials [5,13-14]. The study further demonstrated that BNO 1016 led to a faster recovery from symptoms of acute viral rhinosinusitis and higher rate of complete recovery compared with placebo. In particular, the remission of symptoms was found to occur on average two days earlier in BNO 1016-treated group of patients, compared to placebo-treated group, and the number needed to treat for patients considered to be cured (MSS ≤ 1) at end of therapy was calculated to be eight, clearly visualizing the effect size of the observed MSS reduction at end of treatment. Moreover, the improvement of rhinosinusitis symptoms at end of therapy was confirmed by ultrasonography of the sinuses; with the differences between treatments disappearing over the course of the following two weeks without the study medication reflecting the self-limiting course of the disease. Nevertheless, at follow-up

15% of the patients still showed signs of acute viral rhinosinusitis in ultrasonography, indicating that healing of the maxillary mucosa lags behind remission of clinical signs. Treatment with BNO 1016 improved the mean total and subscale scores for SNOT-20 GAV progressively and to a significantly greater extent from Day 3 onwards compared to placebo. Safety assessments further demonstrated that BNO 1016 had a comparable AE profile, with no reports of severe or serious AEs. Similarly, tolerability of BNO 1016 was high and comparable to placebo, as indicated by ≥ 95% of both investigators and patients rating tolerability to both BNO 1016 and placebo being 'very good' or 'good'

To our knowledge, this is the first well-controlled study to investigate the effect of a fixed dose combination of herbs in the treatment of acute viral rhinosinusitis meeting all the current quality standards of a double blind, randomized, placebo-controlled trial. Inclusion and exclusion criteria, symptoms assessment and the system of grading symptom severity are in line with EPOS 2012 and also in accordance with the recommendations of the German regulatory authority (BfArM). Indeed, the low percentage of patients who terminated the study prematurely because they required an antibiotic therapy (2.1% under verum and 3.7% under placebo, ITT) confirms that the inclusion criteria ensured the selection of the right target population suffering from acute viral rhinosinusitis. Although patients with acute viral rhinosinusitis were included, we noticed that 84.5% in the BNO 1016 group and 86.5% in the placebo group (ITT) still suffered from symptoms at day 10, fulfilling the criteria of post-viral rhinosinusitis according to EPOS 2012. Despite these positive attributes, the present study is somewhat limited in other aspects. In particular, although rhinosinusitis symptoms such as headache and facial pain were rated by the investigator based on the description given by the patients, to ensure a uniform rating of symptom severity across the investigational sites, this was nevertheless subjective and open to error.

Evidence for beneficial effects of herbal medicines in the treatment of acute viral rhinosinusitis is limited. The findings of the present study, nevertheless, are in accordance with the findings of recent studies in patients with ARS. In one double-blind, randomised, placebo-controlled, parallel-group, multicenter trial, Bachert and colleagues [5] evaluated the efficacy and safety of a single herbal drug preparation from the roots of Pelargonium sidoides (EPs 7630), in symptomatic patients with radiographically and clinically confirmed ARS. The authors demonstrated that treatment with EPs 7630 for 22 days decreased the six symptom Sinusitis Severity Score (SSS) to a significantly greater degree (5.5 points) compared to placebo (2.5 points; $p < 0.00001$). Baseline SSS was 14.3 ± 1.8 for the EP 7630 group and 13.8 ± 1.5 for the placebo group. Moreover, EPs 7630 also improved all secondary endpoints to a greater extent than placebo and led to faster recovery. However, unlike the present study, the patients investigated by Bachert and colleagues [5] were suffering from ARS of presumably bacterial origin; with the therapeutic intervention interfering later in the course of disease.

Despite the recommendation of intranasal corticosteroids alone or in combination with antibiotics as first-line treatment for rhinosinusitis data for corticosteroid monotherapy in adults with non-complicated ARS is limited, with one study demonstrating twice-daily topical steroid administration to be more effective than therapy with oral antibiotics and producing a minor, albeit significant, reduction of symptoms of rhinosinusitis. The difference in mean MSS between steroid twice-daily versus placebo over the treatment period (days 2 to 15) was 0.81 score points ($p < 0.001$). The difference between placebo and the oral antibiotic administered once daily did not reach statistical significance. However, besides patients suffering from rhinosinusitis due to viral infection also patients with a mild to moderate bacterial infection were investigated in this study [13].

Overall, the findings of the present study have clear economic and clinical implications in the management of patients with acute viral rhinosinusitis. Despite being a self-limiting disease, the symptoms of acute viral rhinosinusitis lead to substantial direct and indirect costs due to additional requirements for healthcare resources and indirect costs due to loss of productivity resulting from absenteeism. Moreover, acute viral and post-viral rhinosinusitis is often misdiagnosed and incorrectly treated with antibiotics, adding to the healthcare burden and leading to side-effects of antibiotic therapy as well increased bacterial resistance to the antibiotics. Indeed, a meta-analysis of randomized clinical trials in which patients with ARS were treated with antibiotics has recently demonstrated that the number needed to treat with an antibiotic is 15 before one additional patient is cured [15], which is in marked contrast to the eight patients needed to treat with BNO 1016. Similarly, another meta-analysis of trials investigating the efficacy of intranasal corticosteroids in the treatment of acute sinusitis demonstrated that the number needed to treat with intranasal mometasone (200 µg BID) was 11 for symptoms having resolved or improved [16], suggesting that BNO 1016 may also be equally or more effective than some corticosteroids for the management of patients with acute viral rhinosinusitis.

In conclusion, this study has clearly demonstrated that 160 mg BNO 1016 t.i.d for two weeks is an efficacious and safe treatment option for the management of patients with acute viral rhinosinusitis; providing a faster and clinically relevant remission of symptoms and improved quality of life, compared with placebo.

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Authorship contribution

RJ, Specialist in Otorhinolaryngology, was the coordinating investigator and scientific consultant ('Leiter der klinischen Prüfung' according to § 40 German Drug Law) of this multicentre study, and provided scientific advice for writing of the trial protocol and the publication manuscript. MM was responsible for the design of the trial protocol and the operational aspects of the trial. HS and HS were responsible for biometrical aspects of trial planning and statistical analysis. PS and CB were responsible for the trial design and interpretation of results and commented on the publication.

Conflict of interest

MM and HS are employed by Bionorica SE. The other authors have no conflict of interests.

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