Supplementary Materials

Efficacy and effectiveness of the herbal medicinal product BNO 1016 in the management of acute rhinosinusitis in the context of antibiotic stewardship

Contents: Detailed methods

Appendix A: Detailed Methods

1. Meta-analysis of ARhiSi-1 and ARhiSi-2

1.1. Clinical methods

Trial design

ARhiSi-1 and ARhiSi-2 were independent, prospective, randomised, double-blind clinical trials of similar design that included patients with acute rhinosinusitis (ARS) receiving BNO 1016. Both studies were conducted in Germany and in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles of the Declaration of Helsinki. Trial protocols and all amendments were reviewed by Independent Ethics Committees for each participating site. All patients provided written informed consent.

Clinical assessments

Efficacy assessments analysed in this meta-analysis included the Major Symptom Score (MSS) and the 20-Item Sino-Nasal Outcome Test (SNOT-20). With regards to safety results, adverse event rates were evaluated. Short introductions to the clinical assessments are given below.

The MSS is the sum of the investigator´s assessment of the 5 main symptoms of acute rhinosinusitis, namely:

- Rhinorrhoea (anterior discharge),
- Postnasal drip,
- Nasal congestion,
- Headache and
- Facial pain/pressure.

The investigator evaluated each of the 5 symptoms of the MSS using a 4-point rating scale of increasing severity (0 = absent [none/not present], 1 = mild, 2 = moderate, 3 = severe). The MSS total score was calculated as the sum of the five symptoms and thus ranges from 0 to 15, i.e., higher values indicate worse ARS symptoms.

The SNOT-20 questionnaire is a disease-specific, health-related quality-of-life measure for rhinosinusitis. It contains 20 items related to the symptoms and social/emotional

consequences of rhinosinusitis. The test describes patient's health burden and is sensitive to clinical changes. As the trials were performed in Germany only, the German adapted version (GAV) of the test was used, which is a translated and marginally changed version of the SNOT-20. The patient was asked to rate the severity of the 20 questionnaire items retrospectively for the last 24 hours using a 6-point verbal rating scale of increasing severity (0 = not present/no problem, 1 = very mild problem, 2 = mild or slight problem, 3 = moderate problem, 4 = severe problem, 5 = problem as bad as it can be). The SNOT-20 total score was calculated as the sum of the 20 items and thus ranges from 0 to 100, i.e., higher values indicate worse quality of life.

1.2. Statistical Methods

General methods

The statistical output for the meta-analysis was produced using the Statistical Analysis System (SAS®). SAS-Version was 9.4M3 with SAS/STAT 14.1 and SAS/IML 14.1 package (SAS Institute Inc., Cary, NC, USA). Efficacy and safety endpoints as well as general definitions, if not mentioned otherwise, were identical to the Statistical Analysis Plan (SAP) of trial ARhiSi-2. Also, the used methods of analyses followed the ones described in the SAPs of the individual studies. If there was a difference in handling and generating data in the SAP of ARhiSi-1 and ARhiSi-2, then the newer SAP (ARhiSi-2) was used. The only deviations from the approach mentioned above were:

- MSS based on combined data was analysed using the same model as for ARhiSi-2, except that pooled site instead of medical specialist was used to account for the centre effect.
- The SNOT-20 analysis was changed from the one originally defined in the ARhiSi-2 SAP, i.e., instead of a repeated measures ANCOVA, a linear mixed effect model for repeated measures with the fixed categorical effect of treatment, pooled site, visit and treatment-by-visit interaction as well as fixed continuous effect of baseline was used. Within-subject variation was modelled as random effect with unstructured covariance structure. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Visit 5 (day 14) data of both studies were used in the model.

Treatment groups

The treatment groups BNO 1016 480 mg and placebo were used for this meta-analysis. The treatment group BNO 1016 240 mg from the ARhiSi-1 trial was not included.

Analysis sets

The analysis set definitions from the original trials were used for this meta-analysis. These were the Safety Evaluable Population (SEP), the Full Analysis Set (FAS) and the Per Protocol Evaluable Population (PP). The SEP included all patients randomised with at least one

documented application of the investigational drug and post-baseline safety data. This tolerability analysis was done in order to gain information on potential side effects of the study medication in comparison to spontaneous health-related issues observed under the reference medication (i.e., placebo).

The FAS for the efficacy analyses included all randomised patients with acute rhinosinusitis (as per inclusion criterion) and with at least one documented application of the investigational drug and post-baseline efficacy data. As with the statistical analyses of the individual trials, the FAS population was the analysis set of primary interest for the efficacy meta-analyses. The results presented in the manuscript are therefore results for the FAS.

The PP population for the efficacy analyses included all FAS patients who did not show protocol deviations which could have a relevant influence on the assessment of the primary endpoint. The relevance of protocol deviations was assessed at the respective blinded review meetings before unblinding the treatment code. The following criteria were defined as relevant protocol deviations and patients violating these criteria were excluded from the safety and/or efficacy analyses:

Exclusion from SEP, FAS and PP in case of:
- Premature study discontinuation without documented intake of study medication

Exclusion from FAS and PP in case of:
- Premature study discontinuation with documented intake of study medication but efficacy data regarding primary endpoint not documented
- Violation of inclusion criteria "diagnosis of acute rhinosinusitis" (diagnosis not confirmed) (ARhiSi-1 only)

Exclusion from PP in case of:
- Not allowed previous/concomitant medication
- Violation of visit schedule (ARhiSi-1: More than ± 2 days at visit 5. ARhiSi-2: visit 5 not 13 – 15 days after visit 1)
- Last intake of study medication more than 2 days before last visit
- Compliance unknown or <80%
- Violation of inclusion/exclusion criteria

Patients who prematurely discontinued the study (e.g., due to lack of efficacy, premature healing or occurrence of AEs) were also allocated to the PP population if relevant protocol violations did not occur. The PP set was used for the sensitivity analysis of the FAS to analyse the effect of patients deviating from the protocol.

Pooling of sites to virtual sites

To consider the influence of trial site on efficacy endpoints, site-ID was included as effect in the models. If a site's number of subjects was too low, the model cannot be calculated correctly. So, subjects of sites with less than five subjects in an actual model were pooled together to virtual sites. This pooling had to be done separately for each subgroup in the different populations (FAS or PP).

Statistical hypotheses

There was no formal hypothesis set for this meta-analysis.

Endpoints

Endpoint	Data from trials
1. Major Symptom Score (MSS) at visit 5 (day 14)	ARhiSi-1 + ARhiSi-2
2. SNOT-20 at visit 5 (day 14)	ARhiSi-1 + ARhiSi-2
3. Frequency of adverse events by SOC/PT	ARhiSi-1 + ARhiSi-2

SOC: system organ class; PT: preferred term

Subgroups

The following subgroups were defined:

- Subgroup moderate/severe: Patients with assessment "moderate" (count: 2) or "severe" (count: 3) for each of the five MSS symptoms (always resulting in MSS ≥ 10)
- Subgroup none/mild: All patients without assessment "moderate" or "severe" for each of the five MSS symptoms (complementary group to subgroup moderate/severe)

Repetition of the primary endpoint analyses of ARhiSi-2

The analysis of the primary endpoint of ARhiSi-2 was a repetition of the primary endpoint analysis of the clinical trial ARhiSi-2. This was performed as a quality assurance measure, to confirm that independent statisticians could reproduce analyses of the individual trial with the provided data sets. This analysis was not performed by subgroup.

Imputation of missing values

Missing values were handled as follows:

<u>MSS</u>
If premature discontinuation had occurred it was checked whether the prior visit was doubled at visit 5. Any doubled entry at visit 5 was erased. If premature discontinuation had occurred it was checked whether the day of visit 5 was nearer to a prior visit and then shifted backwards, if so. If not, only baseline was done, the missing visit was imputed value by value of last done visit (last observation carried forward [LOCF]) for all visits until next non-missing visit, according to trial protocol. If a visit was imputed, the scheduled day was used as visit day for fill up.

SNOT-20

Imputation in a subscore was done by using worst case for missing questions with a maximum of one missing question. Imputation in total SNOT-20 score was done by using worst case for missing questions with a maximum of two missing questions. No imputation of whole missing visits was done, except in case of premature termination caused by insufficient efficacy, where LOCF was applied. LOCF was also allowed for single (sub)scores. LOCF was not applied when only baseline was available, but if baseline was missing and a visit post baseline was available LOCF was applied. If there were doubled entries for a visit, worst case per question was used if there were discrepancies. It was checked whether there were double entries for a visit date for different visits (the date of prior visits was sometimes documented in the original scheduled visit and in visit 5 too, in case of premature termination). If there was as premature termination documented at visit 5, the last visit was shifted back to the nearest scheduled visit.

2. Retrospective cohort study on the effectiveness of BNO 1016

2.1. Study design

This study was a retrospective database analysis (IMS®DA) that was conducted as a cohort study in patients diagnosed with acute rhinosinusitis in an outpatient care setting in Germany[(1)].

Study Population

The study was designed to include data of all patients with the diagnosis of ARS (ICD-10: J01) from January 2012 to December 2020, provided by nearly 3,000 office-based physicians. Patients diagnosed by general practitioners (GPs) and ear, nose and throat specialists (ENT) were considered. The focus therapy was BNO 1016 (reference therapy), which was compared with the following therapies, which comprise the most frequently prescribed therapies in ARS:

A. Antibiotics
B. Topical intranasal corticosteroids (INCS)
C. Nasal spray without corticosteroid (contains more than 100 products; the most frequent are Nasenspray AL, Nasenspray-ratiopharm, Nasic, Olynth) (= inverse of group B. above)
D. Antibiotics plus BNO 1016
E. Antibiotics plus INCS
F. Antibiotics plus nasal spray without corticosteroid
G. Antibiotics plus analgesics (nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol)
H. Nasal spray without corticosteroid plus analgesic (NSAIDs or paracetamol)
I. BNO 1016 plus nasal spray without corticosteroid

Data Source(s)

This analysis was based on the IMS®DA database, which contains case-based information provided by office-based physicians (both GPs and specialists) in Germany. Information is available on patient demographics, drug prescriptions, concomitant medication, comorbid conditions, sick leave, and referrals. Data analyses only considered data from those sites that had continuously delivered data to the IMS®DA panel in the past. IMS®DA contains data from more than 13 million patients in the time period between 2012 and 2020. Information is provided by nearly 3,000 office-based physicians, representing approximately 3.5% of all German practices (IMS®DA status date: March 2019). Practices can be categorized into ten classes according to the physician's medical specialty (GPs and various specialists). The sample of practices included is geographically representative for Germany, covering eight major German regions.

The table below specifies the relevant patient data longitudinally collected in the IMS®DA database:

Patient Characteristics	Age
	Sex
	Charlson Comorbidity Index (CCI)
Diagnosis	International Classification of Diseases, 10th Revision (ICD-10) codes (three digits)
	Date of visit
Therapy	Date of prescription
	Prescribed daily dosage (in approximately 50% of prescriptions)
	Number of prescribed refills
	Product (form, strength, package size)
	Molecule
	Therapy classes (European Pharmaceutical Marketing Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) codes, five digits)
	Price of prescribed medication
Actions	Referrals to hospital (emergency admissions are not included)
	Referrals to specialists
	Days of medical leave

Data Quality

Analyses carried out in comparison with reference statistics did not indicate any lack of representativeness or validity with respect to the IMS®DA database. The database appears to be suitable for pharmaco-epidemiological and pharmaco-economic studies[(1)]. IQVIA ensured the accuracy, consistency, and completeness of the data.

Inclusion Criteria

For this study, patients who met the following inclusion criteria were considered:

- Patients with the first diagnosis of an acute (rhino-)sinusitis (ICD-10: J01) in the period between January 2012 and December 2020
- Patients who have prescriptions of the therapies mentioned above in the section "Study Population" on the day of diagnosis or within three days afterwards.

Exclusion Criteria

- Patients with a diagnosis of acute or chronic acute (rhino-)sinusitis prior to the index date
- Patients with prescriptions of at least one of the study therapies within 90 days prior to the index date including Sinupret®, antibiotics, topical INCS, nasal spray without corticosteroid, analgesics (NSAIDs or paracetamol).

Study Period

This analysis evaluated data from January 2012 to December 2020. The first diagnosis of ARS documented during this period was considered the index date and each patient was subject to follow-up for up to 365 days after the index date.

Covariates

The following covariates were used in multivariable regression analyses:

- Age of the patient
- Sex: male, female
- CCI
- Month of the year

The CCI is a method for categorizing comorbidities of patients based on the ICD diagnosis codes found in administrative data, such as hospital abstracts. It contains 19 comorbidities, including diabetes with diabetic complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukaemia, lymphoma, metastatic tumour, and acquired immunodeficiency syndrome. Each comorbidity category has an associated value from 1 to 6, based on the adjusted risk of mortality or resource use, and the sum of all the values results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use[(2)].

2.2. Statistical Analysis

During this study, the following analyses were conducted:

1. Percentage of patients with antibiotics prescription due to ARS from 4 to 30 days and from 31 to 365 days after the index date
2. Percentage of patients with sick leave ≥7 days associated with ARS diagnosis within the first 30 days after the index date.
3. Number of medical appointments due to ARS between 4-30 days after the index date
4. Incidence of epistaxis (ICD-10 code: R04.0) within 4 to 365 days after the index date

Analysis Details

To compare the therapy groups with the reference therapy (BNO 1016), several statistical methods were used. The table below specifies statistical methods used in this study, sorted by outcome.

Outcome	**Method**	**Variables adjusted for**
Percentage of patients with antibiotic prescription due to ARS from 4-30 days and from 31-365 days after the index date	Multivariable logistic regression models	Sex, age, month, and Charlson Comorbidity Index (CCI)*
Proportion of patients with sick leave associated with ARS diagnosis within the first 30 days after the index date (at least 7 sick leave days)	Multivariable logistic regression models	Sex, age, month, and Charlson Comorbidity Index (CCI)*
Number of medical appointments due to AS between 4-30 days after the index date (patients with at least one visit)	Multivariable logistic regression models	Sex, age, month, and Charlson Comorbidity Index (CCI)*
Incidence of epistaxis within 4-365 days after the index date	Multivariable Cox proportional hazard regression models	Sex, agemonth, and Charlson Comorbidity Index (CCI)*

Further details for the statistical analysis can be found below, sorted by outcome.

1. Percentage of patients with antibiotics prescription due to ARS from 4 to 30 days and from 31 to 365 days after the index date

Multivariable logistic regression models were computed to compare new antibiotic prescriptions between the therapy groups. ORs and respective 95% CI were computed.

2. Proportion of patients with sick leave associated with ARS diagnosis within the first 30 days after the index date

The proportion of patients who have a documentation of sick leave ≥7 days within one month following the diagnosis of ARS was compared across therapy groups using Chi-square test or Fisher's exact test, as appropriate. Multivariable logistic regression models, as well as ORs and 95% CIs were computed.

3. Number of medical appointments due to ARS between 4-30 after the index date

The number of medical appointments due to ARS between 4-30 days after the index date were taken and compared across therapy groups using analysis of variance or Kruskal-Wallis test, as appropriate. Negative binomial regression models were performed, and adjusted risk differences (Odds ratios (ORs)) were calculated.

4. Incidence of epistaxis within 4 to 365 days after the index date

New cases of epistaxis between 4 and 365 days after the ARS diagnosis were considered. Multivariable Cox proportional hazard regression models were computed to compare the incidence of epistaxis between the therapy groups. HRs and respective 95% CI were calculated.

Descriptive Analyses

Descriptive statistics are provided for variables considered in the analyses. Continuous variables are summarized as total number of patients (N), mean and standard deviation (SD), median and 25th and 75th percentiles, and range – minimum and maximum. Categorical variables are presented as total number of patients (N), as well as absolute (n) and relative frequencies (%).
Percentages are always quoted using number of 'known' values in the denominator and are specified to one decimal place. The following variables are used to describe the patient characteristics:

Variable	**Value**
Age	Years (mean, SD)
Sex	Female (number, %)
CCI	Score (mean, SD)
Month	Months (number, %)

CCI: Charlson Comorbidity Index; SD: standard deviation

Analysis of Safety Endpoint(s)/Outcome(s)

The reporting of adverse events is not applicable because the data sources utilized in this study did not contain information on adverse events (or did not contain physician attribution of causality of adverse events to any medicinal products).

References

1. Rathmann W, Bongaerts B, Carius H-J, Kruppert S and Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. Int Journal of Clinical Pharmacology and Therapeutics 2018; 56(10): 459-466.

2. Quan H, Sundararajan V, Halfon P et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data. Medical Care 2005; 43(11): 1130-1139.