

# Treatment of acute rhinosinusitis with the preparation from *Pelargonium sidoides* EPs 7630: A randomized, double-blind, placebo-controlled trial\*

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## SUMMARY

**Objective:** To evaluate the efficacy and safety of the herbal drug preparation from the roots of *Pelargonium sidoides* (EPs 7630) compared to placebo.

**Design:** Double-blind, randomized, placebo-controlled, parallel-group, multicenter trial with a group-sequential adaptive design.

**Subjects:** Patients with sinonasal symptoms of at least 7 days duration, and radiographically and clinically confirmed acute rhinosinusitis of presumably bacterial origin with a Sinusitis Severity Score (SSS) of at least 12 out of 24 points at inclusion.

**Interventions:** EPs 7630, a herbal drug preparation from the roots of *Pelargonium sidoides* (1 : 8-10; extraction solvent: ethanol 11% (w/w)), or matching placebo at a dose of 60 drops three times daily for maximum 22 days.

**Main outcome measures:** Change in the SSS after 7 days.

**Results:** 103 patients were recruited until the planned interim analysis. The mean decrease in the SSS was 5.5 points in the EPs 7630 group compared to 2.5 points in the placebo group, a difference of 3.0 points (95% confidence interval 2.0 to 3.9,  $p < 0.00001$ ). This result was confirmed by all secondary parameters indicating a more favourable course of the disease and a faster recovery in the EPs 7630 group. According to the pre-specified decision rule, the study was stopped after obtaining proof of efficacy for EPs 7630.

**Conclusions:** EPs 7630 was well tolerated and superior in efficacy compared to placebo in the treatment of acute rhinosinusitis of presumably bacterial origin.

**Key words:** acute rhinosinusitis, EPs<sup>®</sup> 7630, *Pelargonium sidoides*, randomized controlled trial

## INTRODUCTION

Acute rhinosinusitis (ARS) is one of the most common infections of the upper respiratory tract. It affects a significant proportion of the population<sup>(1)</sup>. In the US alone, people with sinus disorders spend more than \$2 billion annually on over-the-counter medication, and make 16 million physician visits each year in pursuit of symptomatic relief<sup>(2)</sup>. For adults seeking care in ambulatory medical practices, sinusitis is the most common diagnosis treated with antibiotics. However, the efficacy of antibiotics is limited<sup>(3)</sup> or controversial<sup>(4,5)</sup>, and although often considered to be of bacterial origin, ARS mostly is a viral disease<sup>(1)</sup>. There is a significant overuse of antibiotics in general practice due to uncertainty to differentiate bacterial from viral rhinosinusitis on the basis of clinical judgement alone. In a recent meta-analysis of randomised trials in adults with clinically diagnosed acute rhinosinusitis, the authors conclude that antibiotics are not justified even if a

patient reports symptoms for longer than 7-10 days<sup>(6)</sup>. Even in cases of bacterial ARS, the moderate benefits of antibiotics should be weighed against associated risks such as gastrointestinal disorders, allergic reactions and the development of resistant germs<sup>(3)</sup>. Therefore, a search for effective and safe alternative treatments for viral and bacterial ARS is justified.

Traditionally, herbal medicines have been used for generations to treat bacterial ARS, and there has been an increasing interest in herbal medicine both in the USA<sup>(7)</sup> and in Europe<sup>(8)</sup>. There is a need to further align herbal medicine with the requirements of evidence based medicine, and thus the National Center for Complementary and Alternative Medicine (NCCAM; <http://nccam.nih.gov/>) has made a major effort in the last decade to further stimulate the conduct of pharmacological and clinical studies on herbs.

A herbal drug preparation from the roots of *Pelargonium sidoides* (1 : 8-10; extraction solvent: ethanol 11% (w/w)), referred to as EPs 7630, is widely used in Germany, the Commonwealth of Independent States, the Baltic states and in Mexico for the treatment of ENT- and respiratory tract infections. For EPs 7630 and its isolated constituents, pharmacological activities including moderate direct antibacterial potencies and notable immune modulatory capabilities could be demonstrated *in vitro*. The immunomodulatory activities are mediated mainly by the release of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and nitric oxides, the stimulation of interferon- $\beta$ , and the increase in natural killer cell activity<sup>(9-12)</sup>. Further biological activities *in vitro* are improved phagocytosis, oxidative burst and intracellular killing of human peripheral blood phagocytes, and an inhibition of the interaction of group A streptococci and host epithelia<sup>(13,14)</sup>. Observational and anecdotal data suggest that *Pelargonium sidoides* is effective in the treatment of sinusitis. We therefore set out to evaluate the efficacy and safety of EPs 7630 compared to placebo.

## MATERIAL AND METHODS

### Design

We conducted a multi-centre, prospective, randomized, double-blind, parallel group, placebo-controlled clinical trial, using a group-sequential adaptive design. All patients with ARS of presumably bacterial origin were further screened for eligibility during a screening phase of up to 3 days. Eligible patients who provided informed consent were randomized to receive either EPs 7630 or placebo drops for up to 22 days, which is considered to be an appropriate treatment period for bacterial ARS<sup>(15)</sup>. Assessments took place by the same investigator during the screening visit, at day 0, day 7, day 14 and day 21. The trial was conducted in accordance with ICH guidelines for Good Clinical Practice.

### Setting and participants

The study took place in 11 ENT clinics and outpatient departments in Kiev, Ukraine, following approval by the State Pharmacological Committee and Ethics Committee in Kiev. The setting was chosen because of the specific health care structure in Ukraine, with sinusitis patients directly approaching "ambulatoria" in specific clinics.

Patients were enrolled between November 2003 and April 2004. Patients with an age ranging from 18 to 60 years with radiographically confirmed ARS and a Sinus Severity Score of 12 points or greater were eligible. The Sinusitis Severity Score (SSS) is based on 6 symptoms and signs associated with bacterial ARS<sup>(16,17)</sup>: 1) headache; 2) maxillary pain; 3) maxillary pain worsening on bending forward, percussion or pressure; 4) nasal obstruction; 5) purulent nasal secretion; 6) purulent nasal discharge visualised in the middle meatus, or purulent postnasal discharge. The SSS was calculated as the sum of the 6 symptom scores as assessed on a 5 point verbal rating scale ranging from "0" (not present) to "4" (very severe). The investigator

determined the most ARS affected side during the initial visit, based on the patient's complaints, a physical examination and rhinoscopy. This side was consistently used in subsequent assessments. The diagnosis ARS was confirmed by sinus radiography (using the occipitomeatal view) of the most affected side, when one of the following criteria was present: mucosal thickening  $\leq$  6mm measured at the upper lateral border of the maxillary sinus; complete opacification; air fluid level. Assessment was made according to a modified version of the score used by van Buchem and co-workers<sup>(4)</sup>: NA = not assessable, 1 = normal, 2 = mucosal thickening  $\leq$  6mm at the upper lateral border, 3 = mucosal thickening  $>$  6mm at the upper lateral border, 4 = complete opacification, 5 = air-fluid level. Patients were excluded if one or more of the following criteria applied: obstructive anatomical lesions in the nasopharynx; previous surgery or need for surgery of the nose or paranasal sinuses; sphenoid sinusitis, odontological infection, allergic rhinitis, acute or chronic lung diseases; recurrent sinusitis ( $>$  3 episodes) during the past 12 months prior to enrolment or chronic sinusitis (symptoms lasting a month or more). Patients were also excluded from the enrolment into the trial if one of the following applied: treatment with antibiotics, steroids or antihistamines during the 4 weeks prior to enrolment, or anti-inflammatories, secretolytics or any other medication or treatment during the 7 days prior to enrolment, or the need for treatment with any of the above medications during the trial; known or suspected hypersensitivity to the investigational drug; existing severe cardiovascular disease, unstable diabetes mellitus, severe renal or hepatic dysfunction, malignant disease or suspicion of malignancies; heavy smoking  $\geq$  25 cigarettes a day; alcohol intake  $\geq$  10 ml ethanol per day; intake  $\geq$  500 mg caffeine per day; pregnancy or breastfeeding.

Use was made of EPs 7630-solution<sup>1)</sup>, which is a herbal drug preparation from the roots of *Pelargonium sidoides* (1 : 8-10), extraction solvent: ethanol 11% (w/w), or matched placebo. Patients were instructed to take 60 drops of the investigational medication orally 3 times daily in the morning, at noon, and in the evening, at least 30 minutes before or after meals (in total 9 ml per day). Study medication was taken during a maximum period of 22 days; consumption was documented in the patient diary and checked by the investigator at each follow up contact. Saline inhalations were allowed as an adjunctive measure, if necessary.

### Objective, outcome assessment and sample size calculation

The primary objective was to evaluate the efficacy and safety of EPs 7630 compared to placebo in patients with ARS of presumably bacterial origin.

The primary outcome measure was prospectively defined as the change in the Sinusitis Severity Score (SSS; investigator's

<sup>1)</sup> Footnote: EPs 7630 is the active ingredient in the product Umckaloabo<sup>®</sup> (ISO-Arzneimittel, Ettlingen, Germany)

assessment) at day 7 of treatment compared to baseline. Secondary outcome criteria were: response defined as A) an SSS < 10 points on day 7, B) a reduction of at least 4 points on day 7, or C) both of the above; occurrence of complete remission (SSS = 0 on day 21) or substantial improvement of signs and symptoms (SSS ≤ 1 point for each of the 6 symptoms on day 21); the occurrence of complete remission or substantial improvement of individual signs/symptoms as defined above; radiographic cure ('normal') or substantial improvement ('mucosal thickening at the lower border' or 'mucosal thickening ≤ 6 mm at the upper border') at day 21; SNOT-20 and SNOT-MI description and evaluation of health related quality of life as assessed on the 100mm EQ-VAS<sup>(18, 19)</sup> on day 7 (0 = worst state of health, 100 = best state of health); activity level (% of normal level); ability to work or engage in usual activities (yes/no) on day 7; general well-being<sup>(20)</sup> (% "in good spirits mainly" or "in very good spirits") on day 7; treatment outcome as assessed by the patient and the investigator on the 'Integrated Medicine Outcomes Scale' (IMOS), a five point verbal rating scale with the categories 'complete recovery', 'major improvement', 'slight to moderate improvement', 'no change' and 'deterioration'.

The safety assessment was based on vital signs, laboratory safety parameters, and the occurrence of adverse events and included an assessment of the likelihood of a causal relationship with the investigational medication.

Sample size calculation was based on a four-stage, group-sequential design. Assuming a common standard deviation of 3 points, N = 50 patients per treatment group for each stage (i.e., maximum total sample size N = 400) resulted in a power of 90% to detect clinically relevant difference of 1 point on the SSS with an overall two-sided type I error rate  $\alpha$  of 5%. The adaptive design allowed an adjustment of the sample size based on the results of the interim analyses<sup>(21)</sup>. The stopping rules for the interim analyses were pre-defined in the study protocol. For the first interim analysis, a  $p < 0.000026$  for the comparison of EPs 7630 and placebo regarding the primary outcome measure<sup>(22)</sup> lead to the stop of the clinical trial with proof of efficacy.

#### Data collection, randomisation, allocation concealment and blinding

All data collected were entered by the investigators into notebook computers, using an electronic case report form (eCRF) with inbuilt logical and consistency checks, and transmitted via the internet to the data collection centre at the contract research organisation in Cologne, Germany, where further checks on completeness and plausibility took place.

A computer generated randomisation list was prepared with a balanced block randomisation using the program R-Coste, validated EDP-random number generator. The block length was not known to the investigators. Each investigator received a set of blocks with correspondingly numbered study medication.

Eligible patients were sequentially allocated to a patient number in ascending order on entry in the trial. Placebo was indistinguishable from active treatment in colour, smell and taste as well as viscosity. Persons who packed the study medication were not involved in the further course of the trial. Blinding was maintained for both the patients and investigator throughout the trial. The investigators received sealed emergency envelopes for individual patients, all of which were returned unopened after completion of the trial.

#### Statistical methods

The confirmatory statistical analysis of the primary outcome variable was based on the intention-to-treat (ITT) principle. Additionally, a per-protocol analysis was performed including the patients without major protocol violations. The last observation carry forward (LOCF) procedure was applied in case of premature withdrawal from the trial. The confirmatory comparison was predefined and carried out as a two-factorial analysis of covariance with 'treatment group' and 'investigational site' as factors and the baseline value of the SSS as a covariate. The statistical analysis plan that includes the definition of relevant protocol deviations was finalised after database lock and before unblinding. Statistical analyses were conducted using SAS (version 8.2) by ClinResearch GmbH in Cologne, Germany.

#### RESULTS

In accordance with the protocol, the first interim analysis was conducted when the data of at least 100 patients that had completed the study were available. The first interim analysis was

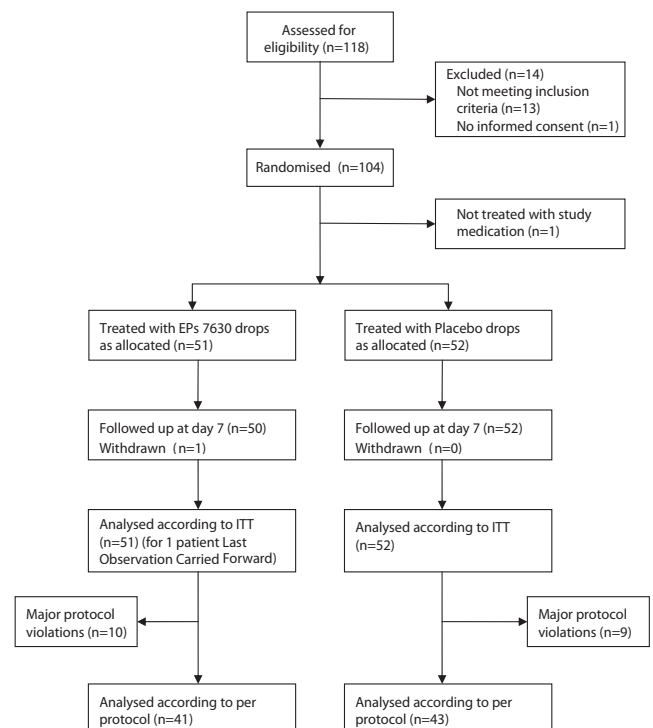


Figure 1. Flow of patients and dataset for analysis.

Table 1. Demographic, clinical and other relevant baseline characteristics (ITT analysis).

Characteristics	EPs 7630 (n = 51)	Placebo (n = 52)
Age: Mean (SD)	34.3 (10.3)	35.6 (12.8)
Sex (men / women): n (%)	19 (37)/32 (63)	17 (33)/35 (63)
Body Mass Index in kg/m <sup>2</sup> : Mean (SD)	23.9 (3.4)	24.1 (4.4)
Smoking (smoker/ex-smoker/ non-smoker): n (%)	11 (22)/2 (4)/38 (74)	8 (15)/0 (0)/44 (85)
Headache: n (%)	51 (100)	52 (100)
Maxillary pain: n (%)	48 (94)	50 (96)
Nasal obstruction: n (%)	51 (100)	52 (100)
Purulent nasal secretion or discharge: n (%)	51 (100)	52 (100)
Sinusitis Severity Score (SD)	14.3 (1.8)	13.8 (1.5)
Activity level 75% or 100% of normal level: n (%)	11 (22)	10 (19)
General Wellbeing: “in good spirits mainly” or “in very good spirits”: n (%)	0 (0)	1 (2)
EQ-VAS in mm: Mean (SD)	43.2 (18.4)	44.9 (16.0)
Able to work or engage in usual activities: n (%)	13 (26)	13 (25)

conducted in September 2004, and included in total 103 patients (ITT) enrolled and treated at 11 investigational sites between January and May 2004. See Figure 1 for the flow and follow-up of patients in the trial. The per-protocol analysis was performed on the basis of 84 patients.

Baseline demographic and clinical characteristics of patients were similar in both treatment groups (Table 1).

#### Outcome assessment

The mean decrease in the primary outcome measure (SSS day 0 minus SSS day 7) in the ITT analysis was 5.5 points in the EPs 7630 and 2.5 points in the placebo group, resulting in a between group difference of 3.0 points (95% confidence interval (2.0 to 3.9)). The time course of the SSS throughout the study is shown in Figure 2. The per-protocol analysis of the patients without major protocol deviations confirmed the results of the ITT analysis (data not shown).

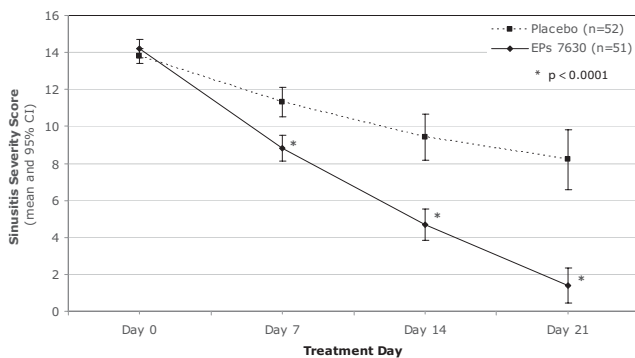


Figure 2. Time course of the Sinusitis Severity Score (SSS) for the two treatment groups (mean  $\pm$  95% CI) (ITT analysis).

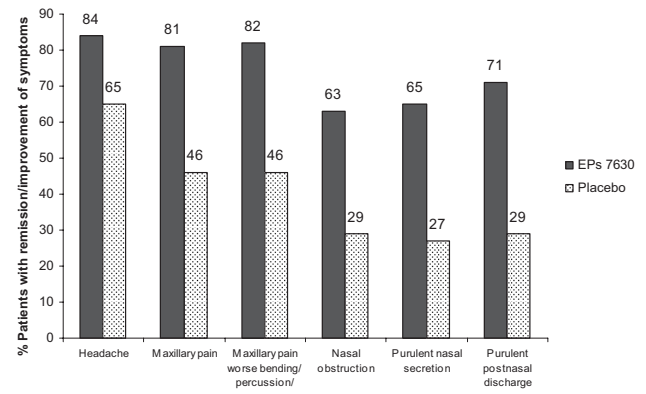


Figure 3. Assessment of individual symptoms of the Sinusitis Severity Score at day 7, ITT analysis (% of patients with improvement or remission; improvement = any decrease in symptom intensity from day 0 to day 7 except remission, remission = symptom rated mild, moderate, severe or very severe on day 0 and not present on day 7).

The confirmatory comparison of EPs 7630 versus placebo resulted in a one-sided  $p < 0.00001$ . This was lower than the pre-specified threshold of 0.000026 defined as stopping rule in the protocol. Therefore, the study could be stopped with the proof of efficacy of EPs 7630.

Analysis of the secondary outcome measures (Table 2 and Figure 3) was consistent with the confirmatory comparison of the primary variable: EPs 7630 was statistically and clinically superior to placebo on all the secondary outcome parameters assessed.

In Table 3 the rate of radiographic cure is given, stratified by the paranasal sinuses affected. Results indicated a statistically significant superiority in the EPs 7630 group for the maxillary sinus, with clear tendencies to superiority for the frontal and ethmoid sinuses.

The difference in total SNOT-20 (EPs 7630 0.6; placebo 0.2;  $p < 0.0001$ ) and SNOT-MI (EPs 7630 0.8; placebo 0.3;  $p = 0.0001$ ) between day 0 and 7 were significantly higher in the EPs 7630 group. The majority of patients did not show fever on day 0 and on day 7 (EPs 7630: 32 out of 51 patients (63%); placebo: 35 out of 52 patients (67%)). Nineteen patients in the EPs 7630 group did show fever on day 0 compared to 17 patients in the placebo group. On day 7, no patient showed fever in the EPs 7630 group compared to 6 patients in the placebo group. The rate of remission or improvement of general symptoms was higher in the EPs 7630 group compared to the placebo group across all symptoms assessed, but did not reach significance (data not shown).

The investigator assessed the treatment outcome as a ‘major improvement’ in 15 (30%) in the EPs 7630 group, compared to 3 (5.8%) patients in the placebo group ( $p < 0.0001$ ) and treatment outcome assessment by the patients yielded to a similar pattern in favour of the EPs 7630 group (Table 4).

Table 2. Secondary outcome measures (ITT analysis).

Outcome measure <sup>†</sup>	EPs 7630 (n = 51)	Placebo (n = 52)	p-value (two-sided)
Response defined as			
A) SSS < 10 points on day 7	34 (67)	14 (27)	<0.0001
B) Reduction SSS ≥ 4 points on day 7	45 (88)	15 (29)	<0.001
A) and B)	34 (67)	13 (25)	<0.001
Complete remission (SSS = 0 on day 21)	31 (61)	5 (10)	<0.001
Substantial improvement (SSS ≤ 1 for each symptom)	44 (86)	19 (37)	<0.001
Radiographic cure on day 21	24 (47)	6 (12)	
Radiographic improvement on day 21	37 (73)	20 (39)	
Improvements in activity level on day 7	33 (65)	16 (31)	<0.001
General well-being			
‘In good spirits mainly’ or ‘in very good spirits’ on day 7	16 (31)	5 (10)	
Mean improvement EQ-VAS in mm on day 7 (SD)	18.1 (14.1)	5.1 (11.0)	< 0.0001
Able to work or engage in usual activities on day 7	32 (63)	19 (37)	
Mean duration of inability to work in days (SD)	8.7 (6.4)	15.9 (11.8)	0.0018
Improvement or remission of sleepiness/alertness in the morning on day 7	33 (66)	23 (49)	0.0394
Improvement or remission of sleepiness/alertness in the evening on day 7	37 (74)	27 (55)	0.0202
Remission or improvement of sleep disorders at day 7	40 (82)	27 (54)	0.0033
Major improvement Integrative Medicine Outcome Scale on day 7	15 (30)	3 (6)	
Satisfaction with treatment: very satisfied / satisfied / undecided / dissatisfied / very dissatisfied	16 (34)/25 (53) 4 (9)/1 (2) 1 (2)	1 (2)/16 (37) 16 (37) 10 (23)/1 (2)	< 0.0001

<sup>†</sup> number and (%) are given unless stated otherwise.

Table 3. Radiographic assessment of the most affected side of various sinuses at final assessment compared to baseline (ITT analysis).

	Maxillary sinuses		Frontal sinuses		Ethmoid sinuses	
	EPs 7630 (n = 49)	Placebo (n = 50)	EPs 7630 (n = 49)	Placebo (n = 50)	EPs 7630 (n = 49)	Placebo (n = 50)
<b>No pathological finding: n (%)</b>						
Yes	24 (49)	6 (12)	47 (96)	44 (88)	49 (100)	41 (82)
No	25 (51)	44 (88)	2 (4)	6 (12)	0 (0)	9 (18)
Comparison*	p < 0.0001		p = 0.1484		p = 0.0018	
<b>Substantial improvement A<sup>1</sup></b>						
Yes	37 (76)	20 (40)	49 (100)	47 (94)	49 (100)	47 (94)
No	12 (25)	30 (60)	0 (0)	3 (6)	0 (0)	3 (6)
Comparison*	p = 0.0004		p = 0.0816		p = 0.0816	
<b>Substantial improvement B<sup>2</sup></b>						
Yes	34 (69)	22 (44)	4 (8)	3 (6)	3 (6)	2 (4)
No	15 (31)	28 (56)	45 (92)	47 (94)	46 (94)	48 (96)
Comparison*	p = 0.0108		p = 0.6746		p = 0.6297	
<b>Substantial improvement C<sup>3</sup></b>						
Yes	24 (69)	22 (44)	4 (8)	3 (6)	3 (6)	2 (4)
No	15 (31)	31 (62)	45 (92)	47 (94)	46 (94)	48 (96)
Comparison*	p = 0.0017		p = 0.6746		p = 0.6297	

\* Chi-square test, two-sided

<sup>1</sup> Assessment = ‘normal’, ‘mucosal thickening at the lower border’ or ‘mucosal thickening ≤ 6mm at the upper border’

<sup>2</sup> Improvement in the rating scale at least 2 points

<sup>3</sup> Combination of 1) and 2)

Table 4. Treatment outcome (IMOS) as defined by the patient and the investigator (absolute (and relative) frequency) (ITT analysis).

	Assessment by the investigator (Day 7)		Assessment by the patient (Day 7)	
	EPs 7630 (n = 50)	Placebo (n = 52)	EPs 7630 (n = 50)	Placebo (n = 52)
Major improvement	15 (30.0%)	3 (5.8%)	17 (34.0%)	2 (3.8%)
Slight to moderate improvement	32 (64.0%)	26 (50.0%)	29 (58.0%)	25 (48.1%)
No change	3 (6.0%)	22 (42.3%)	4 (8.0%)	24 (46.2%)
Deterioration		1 (1.9%)		1 (1.9%)

The mean improvement of health related quality of life as assessed on the EQ-VAS was 13mm higher for EPs 7630 than on placebo at day 7. This corresponds to a significant gain in clinical utility within a relatively short timeframe.

Another useful way to reflect on the clinical significance of the study findings is the ‘number needed to treat’, which is the estimated number of patients who need to be treated with EPs 7630 (rather than placebo) for one additional patient to benefit (the lower the number needed to treat, the better). For instance, the number needed to treat (NNT) to achieve complete remission of the bacterial ARS by day 21 is approximately 2 (100 / (61-10) with a 95% confidence interval<sup>(23)</sup> of 1.6 to 2.4). This means that treatment with EPs 7630 will lead to one extra complete remission by day 21 for every 2 patients treated. The NNT ranges from 2 to 5 patients for the binary outcome measures in Table 2.

#### Safety assessment

There was no clinically relevant change in any laboratory safety parameter and no clinically relevant individual deviations occurred in both treatment groups. Vital signs parameters remained unchanged in both treatment groups.

A total of 8/103 patients (7.8%) reported at least one adverse event (AE) during the trial, 6/51 (11.8%) in the EPs 7630 group and 2/52 patients (3.8%) in the placebo group. All AEs were assessed as non-serious. In four cases that occurred in the EPs 7630 group the causal relationship with the study drug could not be excluded (gastrointestinal complaints (3x), allergic skin reaction (1x)), all of them are known very rare side effects of EPs 7630. Overall, the AEs were mostly classified as mild, and the results indicate that EPs 7630 is a safe and well-tolerated treatment for ABMS.

#### DISCUSSION

The most common cause of ARS is a viral infection. Sometimes this viral infection is complicated by a bacterial infection. Bacterial and viral rhinosinusitis are difficult to differentiate on clinical grounds<sup>(24)</sup>. Radiography has a limited role in the evaluation of patients with suspected bacterial ori-

gin. Several trials on the diagnostic accuracy of sinus X-rays have been published: however, air-fluid level and total opacification are the most specific findings<sup>(25)</sup>. The design and setting of the study was adapted to the fact that an accurate diagnosis of a bacterial sinusitis is difficult in ambulatory practice<sup>(26)</sup>. In the present study, patients were not included before day 7 of upper respiratory tract infection symptoms in order to exclude viral rhinitis. As no sinus puncture was performed to prove bacterial growth, we refer to the disease included here as “ARS of presumably bacterial origin”.

Despite the consensus on the evaluation and management of bacterial ARS published as the EPOS paper by Fokkens and colleagues<sup>(27)</sup>, there is a considerable variation in clinical practice<sup>(28)</sup>. Due to the possibility of secondary bacterial infection, a lack of precise diagnosis based on symptoms only and the inappropriateness of applying imaging procedures in routine clinical practice, many patients receive unnecessary prescriptions for an antibiotic. These prescribing habits have a major impact on health care cost, both directly<sup>(29)</sup> and indirectly through contributing to the increasing prevalence of drug-resistant strains of common respiratory pathogens.

In the absence of an accurate diagnosis of bacterial ARS, it is therefore currently recommended to employ antibiotics only if certain clinical signs and symptoms do not improve or worsen after 7-10 days<sup>(27-30)</sup>. Moreover, results of a recent meta-analysis in adults with clinically diagnosed acute rhinosinusitis indicate that antibiotics are even not justified if a patient reports symptoms for longer than 7-10 days<sup>(6)</sup>.

The aim of this trial was the evaluation of EPs 7630 as a treatment option in cases of rhinosinusitis due to viral or even bacterial infection. Therefore, all patients with URTI symptoms for at least 7 days, also patients with fever or unilaterally prominent sinus pain, and a maxillary sinus X-ray suggestive of bacterial ARS were included.

There is already an increasing amount of evidence from randomized controlled trials on the efficacy of EPs 7630 in inflammations of the lower respiratory tract<sup>(31-33)</sup>. Since both lower and upper respiratory tract infections initially present with an infection of the nasopharynx - moving down into the bronchial-system in the case of bronchitis or moving up into the sinuses in case of rhinosinusitis - it is worthwhile to determine whether EPs 7630 is a suitable therapeutic option also for the treatment of bacterial ARS.

In this study we demonstrated a highly statistically significant and clinically relevant superiority of EPs 7630 over placebo with respect to the primary and secondary outcome variables and confirmed that EPs 7630 is well tolerated. As sinusitis is one of the 10 most costly physical health conditions, in which absence and disability losses constitute a considerable part of the total health and productivity related expenditures<sup>(34)</sup>, the improvements shown in the patients’ health-related quality of life, activity level, and general well-being as well as the

observed decrease in duration of inability to work need to be highlighted. Taken together, these parameters indicate a more favourable course of the disease and a faster recovery from ARS of presumably bacterial origin in the EPs 7630 group compared to placebo, which may result in pharmaco-economic benefit. As there is a lack in standardized criteria and internationally recognized scores for ARS, the results of these parameters also underline that the statistically significant difference of 3 points between EPs 7630 and placebo in the SSS detected in this prospective trial has to be considered as clinically relevant.

The study was randomized, and care was taken to ensure the concealment of random allocation and blinding. Using an electronic CRF aided consistency and quality of data entry. Patients were carefully selected on the basis of symptom duration to exclude viral rhinitis, following recent international guidelines<sup>(27)</sup>, and the presumably bacterial nature of the infection was made highly probable by radiographic confirmation<sup>(35)</sup>. The main outcome assessment was based on subjective criteria. However, a follow up radiographic assessment, which confirmed the principal finding, was used as a secondary outcome measure, evaluated by a radiologist and randomly checked by the responsible ENT-physician.

At a first sight, the low rate of spontaneous resolution with placebo treatment observed in this study (35%) may be surprising. The degree of spontaneous remission rates in clinical studies, however, apparently depends on the number and severity of symptoms the patients suffer from at baseline<sup>(36)</sup>. In the present trial, patients had suffered from ARS symptoms for at least 8 days prior to study inclusion with patients in the placebo group showing rhinosinusitis symptoms with a mean total severity score of 13.8 points. This would mean that these patients suffered from at least four of the six rhinosinusitis symptoms. The high rate of patients being unable to work after a 3-week-treatment phase can therefore be explained by the fact that, in the present trial, truly ill patients were included.

With regard to safety, the risk of experiencing an adverse event was slightly higher on EPs 7630 compared to placebo. However, the intensity of most AEs in the EPs 7630 group was only mild. The absence of serious side effects of EPs 7630 in this trial has already been confirmed in the other EPs 7630 trials referred to in this paper. The daily dosage of EPs 7630-solution in this trial (3 times 60 drops) exceeded the recommended dosage (3 times 30 drops) in the manufacturer's 'Summary of Product Characteristics'. This higher dose was chosen on the basis of clinical experience in bacterial ARS and other promising preliminary observational data. Several pre-clinical trials demonstrated that no dose-dependent risks were to be expected<sup>(37-39)</sup>, and this trial confirmed these findings.

In this controlled randomized study, we found EPs 7630 to be well tolerated and superior in efficacy compared to placebo in

the treatment of ARS of presumably bacterial origin. Significant and clinically relevant benefits of treatment with EPs 7630 were already evident after 7 days of treatment. EPs 7630 should be considered as a possible first line treatment even in patients suffering from an acute rhinosinusitis of presumably bacterial origin.

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