sciendo

DOI: 10.2478/rjr-2023-0025

Romanian Journal of Rhinology, Volume 13, No. 52, October - December 2023

ORIGINAL STUDY

Treatment with Cinnabsin in patients with acute and exacerbated chronic rhinosinusitis

Rumen Benchev[1], Dilyana Vicheva[2]

[1]ENT Department, Hill Clinic, Sofia, Bulgaria
[2]ENT Department, Kaspela University General Hospital, Plovdiv, Bulgaria

ABSTRACT

BACKGROUND. Patients with rhinosinusitis account for about 30% of the total amount of otolaryngologic patients and their number is constantly growing. Currently, there is no ideal treatment for acute and especially chronic rhinosinusitis and various therapeutic approaches are still under debate.
OBJECTIVES. To evaluate the effectiveness and the safety of Cinnabsin® in acute and exacerbated chronic rhinosinusitis treatment.
MATERIAL AND METHODS. We included in our non-interventional, multicenter, prospective study 200 patients with acute and exacerbated chronic rhinosinusitis in order to evaluate the effectiveness and the safety of treatment with Cinnabsin® (while 20 out of 200 patients received additional therapy, only patients who did not receive additional therapy were taken into account in the statistical analysis; 180 patients have been treated with Cinnabsin® only and this is the basis of the statistical assessments performed). Changes in the total score of the typical symptoms of rhinosinusitis were assessed, and changes in edema, hyperemia and secretion were assessed by rhinoscopy.
RESULTS. The total score of the typical symptoms of rhinosinusitis showed a statistically significant difference between the first and final visits – v4 vs. v1 according to Pearson Chi-square (p = 0.0000) as well as in accordance with Risk Difference (RD), Relative Risk (RR), Odds Ratio (OR) ratios at the beginning and end of the treatment. The healthy status of the patients (major improvement, improvement, no complaints) was rated as 93.9% at the final visit. The efficacy of treatment (major improvement, improvement, no complaints) was rated as 93.9% at the final visit. Treatment tolerance was rated as very good in almost all patients (99.4%).
CONCLUSION. Cinnabsin® could be considered efficient in reducing the symptoms of acute rhinosinusitis, shows a very good safety profile, and could be recommended for outpatient treatment of patients with acute or exacerbated chronic rhinosinusitis, no matter the additional therapy.
KEYWORDS: acute rhinosinusitis (ARS), chronic rhinosinusitis (CRS), treatment of acute rhinosinusitis, treatment of exacerbated chronic rhinosinusitis, Non-individualised Homeopathic Treatment (NIHT), Cinnabsin®.

INTRODUCTION

Patients with rhinosinusitis account for about 30% of the total amount of otolaryngologic patients. Their number is constantly growing due to the weakening of local and systemic immune response, increasing cases of allergic reactions, and resistant strains of microorganisms. The main clinical signs of the disease are compromised nasal breathing, nasal discharge and headache, which significantly decrease the quality of life of these patients. Rhinosinusitis can determine the development of orbital or intracranial complications. The inflammatory process in paranasal sinuses impairs the function of the lower respiratory tract and negatively affects the cardiovascular system.

As the mucous membranes of the nose and sinuses are continuous, a certain degree of inflammation of the sinuses also occurs with every case of rhinitis.

Acute rhinosinusitis (ARS) as well as chronic rhinosinusitis (CRS) are common diseases: the prevalence of ARS in the general population is variably noted to be 6-15%[1].

In a recent study in Germany, the incidence was found to be 18.8 episodes per 1000 inhabitants per year[2]. Chronic rhinosinusitis (CRS) is one of the most common chronic medical conditions worldwide, affecting all age groups. Its estimated incidence is 12.3% in the USA, 10.9% in Europe, and 13% in China[3]. In North American and European countries, the CRS rates range 4.5-12%[4]. According to other data, 12.5% of the world's population suffers from chronic rhino-

Corresponding author: Dilyana Vicheva, Prof., MD, PhD, University General Hospital, Plovdiv, Bulgaria
Address: Kaspela Hospital, 64 Sofia Street, Plovdiv, 4001, Bulgaria.
ORCID: https://orcid.org/0000-0002-6805-3825
e-mail: vdilyana@gmail.com
Received for publication: April 24, 2023 / **Accepted:** August 23, 2023

sinusitis[5]. The total cost per ARS episode in Europe is over €1000[1]. It was estimated that in the USA, the direct costs associated with CRS are approximately USD 10-13 billion per year[3]. Therefore, because of its high prevalence, sinusitis represents a considerable socio-economic problem.

Potential complications of sinus infections involve the spread of pathogens along the venous vessels to intracranial structures, the eye, the brain, meninges, and the cranial bones in particular, or the formation of abscesses. These occur extremely rarely but can be serious and life-threatening even today[6].

Rhinogenous rhinosinusitis has a polyetiological origin and wide diversity of clinical manifestations. In the majority of cases, they evoke as a result of acute respiratory viral infections accompanied by compromised local and systemic immune response, alteration of rheological properties of nasal secretion and mucociliary clearance, and nasal mucosa edema. These changes worsen the drainage properties of the paranasal sinuses.

Administration of a wide range of medicinal agents in the majority of cases does not favour the effectiveness of rhinosinusitis treatment and sometimes is accompanied by polypragmasia and adverse reactions, especially in cases of prolonged administration. Recently, investigators observed a change in etiologic factors of rhinosinusitis and revealed new pathogens causing the disease, which are strongly resistant to antibiotics. The correlation between acute and chronic rhinosinusitis is 5:1, though an increasing tendency for chronic forms is observed[7-9].

Rhinosinusitis treatment usually aims to clear the secretory congestion in the sinuses and restore mucociliary clearance. If necessary, topical corticoids are primarily used in combination with concomitant measures such as heat treatment, inhalations, etc. Various phytotherapeutic extracts have also been shown to be effective[10,11]. However, according to the recommendations of the European Academy of Allergology and Clinical Immunology (EAACI), they should only be prescribed after a 5-day period of illness or for severe symptoms[12]. The development of resistance in the bacterial pathogen represents an increasing problem in the antibiotic treatment of chronic sinusitis and nasal polyposis[13].

To date, Non-individualised Homeopathic Treatment (NIHT) is considered an adjuvant therapeutic concept that activates the self-regulatory mechanisms and, thus, the self-healing power of the organism. It is effective and well-tolerated in various acute and chronic diseases. The effectiveness of NIHT for ENT infections has been shown many times in clinical studies, including randomised, double-blind, placebo-controlled trials, controlled post-marketing surveillance studies of acute otitis media in children[14]. The meta-analysis includes 12 studies of upper respiratory tract diseases, 11 of which demonstrated the superiority of NIHT[13]. A placebo-controlled study, which shows the effectiveness of a homeopathic combination product in chronic sinusitis, is also included[14]. Forty-eight different clinical conditions were represented in 75 eligible RCTs. Fifty-four trials had qualitative data: pooled SMD was -0.33 (95% confidence interval (CI) -0.44, -0.21), which was attenuated to -0.16 (95% CI -0.31, -0.02) after adjustment for publication bias. The three trials with reliable evidence yielded a non-significant pooled SMD: -0.18 (95% CI -0.46, 0.09)[15]. The generalisability of findings is restricted by the limited external validity identified overall. The highest intrinsic quality was observed in the equivalence and non-inferiority trials of NIHT[15].

Treatment of rhinosinusitis can be successful and effective only on condition of providing a therapeutic effect to all the components of the pathologic process. As a rule, a combination of etiotropic, pathogenic and symptomatic therapy is used, involving medicines of different types. However, most of them cannot affect the whole range of signs and symptoms, and particular components of rhinosinusitis pathogenesis are left untouched, therefore providing only a partial effect of that kind of treatment.

OBJECTIVE

The objective of our research was to study the parameters of the treatment of rhinosinusitis when Cinnabsin® is used in routine clinical practice, by documenting the effects of Cinnabsin® on patients with acute or exacerbation of chronic rhinosinusitis, evaluating rhinosinusitis symptoms assessed by the patient and by the physician.

MATERIAL AND METHODS

Study design. A non-interventional, multicenter, prospective study.

Ethics. Before the start of this study, written approval from the Independent Ethics Committee (IEC) – Ethics Committee for Clinical Research at the Minister of Health and the Medicines Executive Agency was obtained. Documents submitted to the IEC included the final study protocol, patient information and informed consent sheet, and the Summary of Product Characteristics (SPC), containing information on the study drug, as well other documents requested according to the local regulations.

Patients profile. The study included 204 patients with acute rhinosinusitis (ARS) and exacerbation of chronic rhinosinusitis (ECRS), with 4 patients excluded according to the exclusion criteria, and 20 out of 200 patients receiving additional therapy to Cinnabsin® (corticosteroids, proton pump inhibitor, fluoroquinolones, topical antibiotics, antihistamines, hyaluronic acid), were excluded from the evaluation of the results of the study. Thus, only 180 patients with ARS and ECRS who received Cinnabsin®, of both sexes and different ages, were randomly selected, taken into account in the statistical analysis, and are the basis of the statistical estimates performed.

Patients' disposition. The study was conducted in three sites in Bulgaria. All participating investigators provided a

written commitment to comply with GCP, Helsinki Declaration and the study protocol. For each patient, patient data were collected in paper Case Report Form (CRF). The period of the study was 30.10.2019 – 13.02.2020. Patients allocated to Research Clinical Centres: Site 1 (Diagnostic Consulting Centre III – Sofia, Ear, Nose, Throat (ENT) office, Principal investigator (PI) V. Hristova) – 73 patients (36.5%), Site 2 (Diagnostic Consulting Centre III – Sofia, ENT office, PI V. Georgieva) – 22 patients (11.0%), and Site 3 (Diagnostic Consulting Centre III – Sofia, ENT office, PI E. Yordanova) – 105 patients (52.5%).

Inclusion and exclusion criteria. *Inclusion Criteria:* patients having been prescribed Cinnabsin® in accordance with the terms of the marketing authorization; a written consent form has been obtained; male or female patients from 6 to 65 years with the diagnosis of acute rhinosinusitis or exacerbation of chronic rhinosinusitis (ARS or ECRS). *Exclusion Criteria:* patients with significant morphological abnormalities in the nasal cavity; patients with purulent secretions and severe spontaneous headache; patients with odontogenic maxillary sinusitis, cystic or polypus forms of the disease requiring surgery; patients with severe concomitant diseases or oncologic history; treatment with other homeopathic agents or phytotherapeutic agents; known allergy to Cinnabsin® ingredients; progressive systemic diseases (e.g. tuberculosis, sarcoidosis), systemic diseases of leucocytes (e.g., leukemia and leucosis), autoimmune diseases (e.g., collagenoses, multiple sclerosis), immune deficiency (AIDS, HIV infections) immunosuppression (e.g., after organ or bone marrow transplantation, chemotherapy), chronic viral diseases; pregnancy and lactation.

Product. Cinnabsin® is a homeopathic combination product that includes Cinnabaris D3 25.0 mg, Hydrastis D3 - 25.0 mg, Kalium bichromicum D3 - 25.0 mg and Echinacea D1 - 25.0 mg. Cinnabaris, Hydrastis and Kalium bichromicum contribute to the reduction of swelling of the mucous membranes and facilitate nasal breathing, reduce the secretion of mucus and secretions, and also lead to a reduction of the feeling of pressure in the entire head area. Echinacea contributes to the overall strengthening of the body's defences.

The collection and evaluation of data on treatment with Cinnabsin® were carried out in the current routine clinical practice. Cinnabsin® was prescribed at visit 1 (day 0) and the start of the intake was on day 1 in the morning. Dosing (sublingually): in the acute period (3 days): children 6-12 years – 1 tablet every 1-2 hours, 6 tablets per day, children over 12 years and adults – 1 tablet every 1 hour, 12 tablets per day. After acute period, 3 x 1-2 tablets per day till day 14.

Treatment. Non-individualised Homeopathic Treatment (NIHT) with Cinnabsin® homeopathic combination product. The study consisted of 4 visits: Visit 1 (v1) – the subjects' eligibility for the study was checked for patients who desired to be treated with Cinnabsin®; Visit 2 (v2) – follow-up visit during which the symptoms of rhinosinusitis were checked; Visit 3 (v3) – follow-up visit on day 7 that was done as a phone call to check the patient's condition; Visit 4 (v4) – follow-up visit on day 14 that was done as a site visit to check patient's condition. Phone call visits could have been switched to medical examinations if there was such a need or if the patient preferred that. A study visit on day 14 could have been performed as a follow-up call if the patient was not able to visit the study site within 3 days of the scheduled visit on day 14.

Assessment of the rhinosinusitis symptoms. During each visit, all changes in the total score of five typical symptoms of rhinosinusitis – headache, facial pain or pressure (pain when pressed on the maxillary sinus), nasal congestion (difficulty of nasal breathing), anterior nasal secretions (nasal secretion from the nose), pharyngeal flow of mucus (postnasal drip) – were assessed by the patients on VAS for each symptom.

The completion of a questionnaire for the health status has been done after a detailed explanation by the physician on how the questionnaire should be completed, but without influencing how the patients would be assessing his/her health status regarding the disease. The patients have reported the status and the physician has recorded the value in the CRF. The patients should have completed a questionnaire for the five typical rhinosinusitis symptoms (headache, facial pain or pressure, impairment of nasal breathing, anterior nasal secretions and pharyngeal flow of mucus) on each visit. The patients should have assessed the symptoms on VAS. After the completion of the questionnaire, the physician measured the VAS score and recorded the value in the CRF. The total score has been calculated as a sum of the score for each symptom. On each visit, the patients have been asked if there are any concomitant diseases related to rhinosinusitis and have been asked if any medication has been taken for the treatment of the symptoms. All concomitant medications related to the treatment of the symptoms have been recorded in the CRF. Patients have been asked also for any adverse event/s that have occurred till the current moment at v2 (day 3), at v3 (day 7), and at v4 (day 14). A questionnaire for the health status has been completed by the patients to assess the effects of the treatment ("major improvement", "improvement", "no complaints", "no change in the condition", "worsening").

The final effect of the treatment was in total assessed by the patients (no complaints, significant improvement, improvement, no change in condition, deterioration) and data were obtained on the safety of using Cinnabsin® in routine clinical practice.

For the purpose of the study, the physicians checked the anamnesis and diagnoses of rhinosinusitis (ARS or ECRS). The diagnosis of rhinosinusitis was confirmed by rhinoscopy in all cases. Rhinoscopy was performed to test inclusion and exclusion criteria at v1 (Day 0), as well as changes in edema, flushing, and secretion at the second visit (Day 3) and at v4 (Day 14). During each visit, all changes in edema, hyperaemia and secretion assessed by rhinoscopy were assessed by the physicians as absent, slight, moderate and severe (positive outcomes were rated absent, slight, moderate, and the negative outcome was rated severe). If it was impossible to perform rhinoscopy (the patient did not visit the clinic), the doctor asked the patient for changes in edema, hyperaemia

and secretion to assess the patient's safety, and rhinoscopy was not performed.

After filling out a questionnaire for typical symptoms of rhinosinusitis, the physicians measured the VAS score and recorded the value in the CRF. The total score was calculated as the sum of the scores for each symptom.

Effectiveness and safety analysis. To assess defined effectiveness and safety objectives, a statistical descriptive analysis was planned. Each measure is reported in tables and appropriate figures using absolute and relative representation as appropriate. The change of planned effectiveness variables was assessed through a Repeated Measures ANOVA analysis. If the statistical assumptions of the Repeated Measures ANOVA were not met, then the assessment of the significance of the change was done through non-parametric analogues.

Primary effectiveness endpoints: an overall assessment of the five typical rhinosinusitis symptoms, the assessment of edema, hyperaemia and secretion severity reduction; and the *secondary effectiveness endpoints:* the dynamic of the assessment of the typical rhinosinusitis symptoms.

The planned statistical significance level was set to 5%, based on which also the appropriate 95% two-sided confidence interval (CI) was reported for each measure. The significance of each planned comparison (statistical effect) was judged based on this level too.

For the assessment of statistical significance and relevance of the data obtained, the Pearson Chi-square p-values of multiple comparison changes versus the previous measurements were used. It is also known that scores such as Risk Difference (RD), Relative Risk (RR) and Odds Ratio (OR) together measure the relationship between exposure and treatment outcome[16]. In order to study the relationship between exposure and treatment outcome, we assessed the dynamics of the reduction of symptoms of Edema, Hyperaemia and Secretion, as well as Healthy status, and Effect from treatment at the beginning of v1 and at the end of v4 treatment (v4 vs. v1). Positive outcomes were rated absent, slight, moderate, and the negative outcome was rated severe. The result of missing data was excluded from the statistical assessment. We calculate RD (Risk Difference), RR (Relative Risk) and OR (Odds Ratio) according to Kim HY[17]. Interpretation: RD is the difference between the risk of an adverse outcome at the end of treatment v4 and the risk of an adverse outcome at the start of treatment v1; a negative RD value means reduced risk when exposed to treatment; RR < 1 means reduced risk of the adverse outcome when exposed to treatment; OR is a quantitative characteristic of the density of the relationship between trait A (result) and trait B (treatment) in the statistical sample; OR < 1 indicates an increase in the chances of a favourable outcome with treatment (respectively, a decrease in the chances of an unfavourable outcome). RR and OR differ in interpretation: RR indicates the significance of differences in the probability of a certain outcome depending on the treatment, and OR indicates the difference in the probabilities of the presence of a risk factor (respectively, no chance) under different conditions (at the beginning of v1 and at the end of v4 of treatment).

RESULTS

Baseline characteristics. The majority of the study patients were women – 127 (63.5%), and men – 73 (36.5%). The average age for women and men was very close – around 36 years and varies from 7 to 65 years for women and from 8 to 64 years for men.

Effectiveness results. The score of typical symptoms assessed during rhinoscopy on day 1, day 3, and day 14 was used for effectiveness assessment (positive outcomes were rated absent, slight, moderate, and the negative outcome was rated severe); the score from patient questionnaires – typical rhinosinusitis symptoms and health status also was used for effectiveness assessment (positive outcomes were rated absent, slight, moderate, and the negative outcome was rated severe).

Primary effectiveness endpoints. Results for the overall assessment of the five typical rhinosinusitis symptoms (Table 1). The development of this score was measured for statistical significance through a parametric t-test over arithmetic averages (Table 1, p-values of multiple comparison, t-test, given in the table).

Table 1. Overall assessment of the five typical symptoms of rhinosinusitis.

Total patients	Valid N	Mean	Median	Minimum	Maximum	Std. Dev.	Std. Error
Visit 1	180	25.32	25	9	47	7.55	0.56
Visit 2	180	22.91	22.5	6	42	7.27	0.54
Visit 3	180	16.64	16	5	30	6.24	0.46
Visit 4	180	10.58	9	5	31	4.96	0.37
p-values of multiple comparison	**v1**	**v2**	**v3**	**v4**			
v1	1	0.0000	0.0000	0.0000			
v2	0.0000	1	0.0000	0.0000			
v3	0.0000	0.0000	1	0.0000			
v4	0.0000	0.0000	0.0000	1			

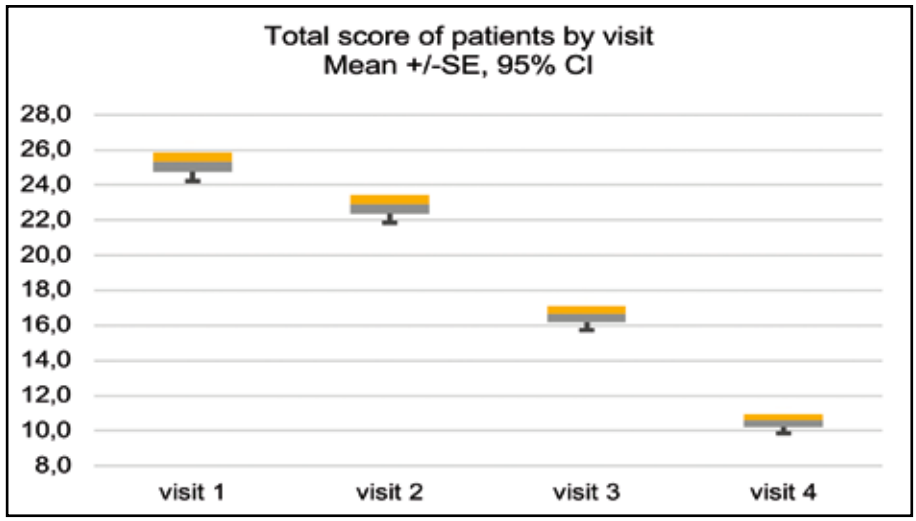

Figure 1. Overall assessment of the five typical symptoms of rhinosinusitis.

The overall assessment of the five typical symptoms of rhinosinusitis (headache, facial pain or pressure, impairment of nasal breathing, anterior nasal secretions, pharyngeal flow of mucus) indicates a positive trend of treatment 4.96±0.37 (v4) vs. 7.55±0.56 (v1); dynamics are shown in Figure 1.

The change in the overall assessment of the five typical symptoms of rhinosinusitis showed a significant decrease in values for each subsequent study visit. There is a visible improvement with increasing duration of treatment, i.e., the third assessment compared to the second has a higher percentage of improvement compared to the difference between the second and the first assessment.

Assessment of edema severity during v1, v2 and v4 are presented in Table 2 and Figure 2. Missing values are given, and the percentages are calculated when those are excluded, i.e., only using the valid data as a base for each period. Different levels are sorted in 'worsening' order and the difference by the visit was checked versus the previous one (Pearson Chi-square p-values given). In all cases, a significant change in the distribution pattern was confirmed. Observed improvements in the assessment during visits v1, v2, and v4 were statistically significant. Another observation is the big increase in the absent category share in v4 vs. v2.

The relationship between exposure and treatment outcome for edema as a typical symptom of rhinosinusitis (v4 vs. v1) is: RD -0.17 (95%CI -0.22– -0.11), RR 0.83 (95%CI 0.78-0.89). A negative RD value means reduced risk of edema when exposed to Cinnabsin® treatment; RR 0.83 (< 1) means reduced risk of the adverse outcome of edema when exposed to Cinnabsin® treatment. According to Pearson Chi-square p-value changes vs. the previous measurement, RD and RR, the given data of the edema severity in dynamics are reliable and relevant from the point of view of the study.

The assessment of edema severity (positive outcomes were rated absent, slight, and moderate, and the negative outcome was rated severe) was 83.3% during v1, 89.9% at v2, and 100.0% at v4, the ratio being shown in Figure 2.

According to investigators, the data in Table 2 and Figure 2 (the edema severity in dynamics) indicate a positive effect of Cinnabsin® treatment on the reduction of edema as one of the typical symptoms of rhinosinusitis.

Assessment of hyperaemia severity during v1, v2 and v4 are presented in Table 3 and Figure 3. Missing values are given, and the percentages are calculated when those are excluded, i.e., only using the valid data as a base for each period. Different levels are sorted in 'worsening' order and the difference

Table 2. The assessment of edema severity reduction.

Edema	Visit 1			Visit 2			Visit 3		
	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %
Absent	2	1.1%	1.1%	3	1.7%	1.7%	73	47.4%	47.4%
Slight	39	21.7%	22.8%	39	21.8%	23.5%	64	41.6%	89.0%
Moderate	109	60.6%	83.3%	119	66.5%	89.9%	17	11.0%	100.0%
Severe	30	16.7%	100.0%	18	10.1%	100.0%	0	0.0%	100.0%
Missing data	0	-	-	1	-	-	26	-	-
Pearson Chi-square p-value change vs. the previous measurement			-			0.000			0.000

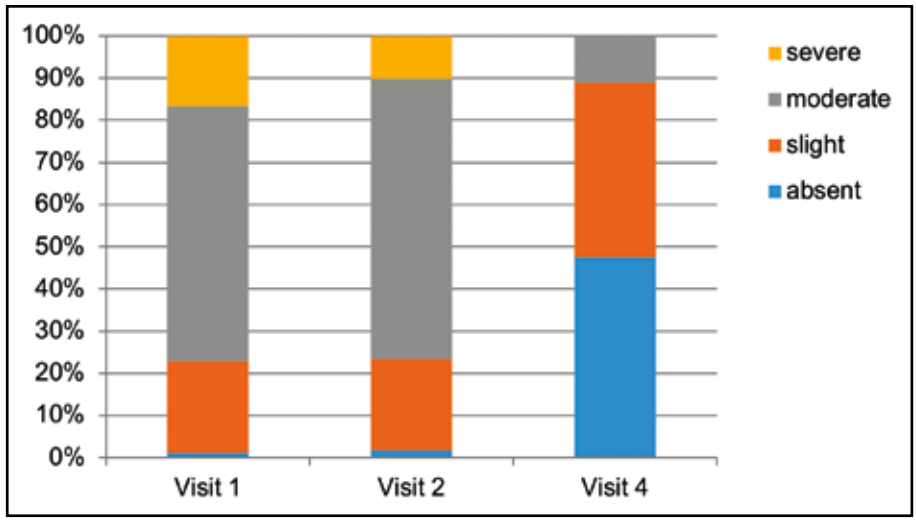

Figure 2. The assessment of edema severity ratio.

by the visit was checked versus the previous one (Pearson Chi-square p-values given). In all cases, a significant change in the distribution pattern was confirmed. Observed improvements in the assessment during visits v1, v2 and v4 were statistically significant. Another observation is the big increase in the absent category share in v4 vs. v2.

The relationship between exposure and treatment outcome for hyperaemia as a typical symptom of rhinosinusitis

Table 3. The assessment of hyperaemia severity reduction.

Hyperaemia	Visit 1			Visit 2			Visit 3		
	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %
Absent	2	1.1%	1.1%	3	1.7%	1.7%	90	58.4%	58.4%
Slight	48	26.7%	27.8%	55	30.7%	32.4%	55	35.7%	94.2%
Moderate	102	56.7%	84.4%	109	60.9%	93.3%	8	5.2%	99.4%
Severe	28	15.6%	100.0%	12	6.7%	100.0%	1	0.6%	100.0%
Missing data	0	-		1			26		
Pearson Chi-square p-value change vs. the previous measurement			-			0.000			0.000

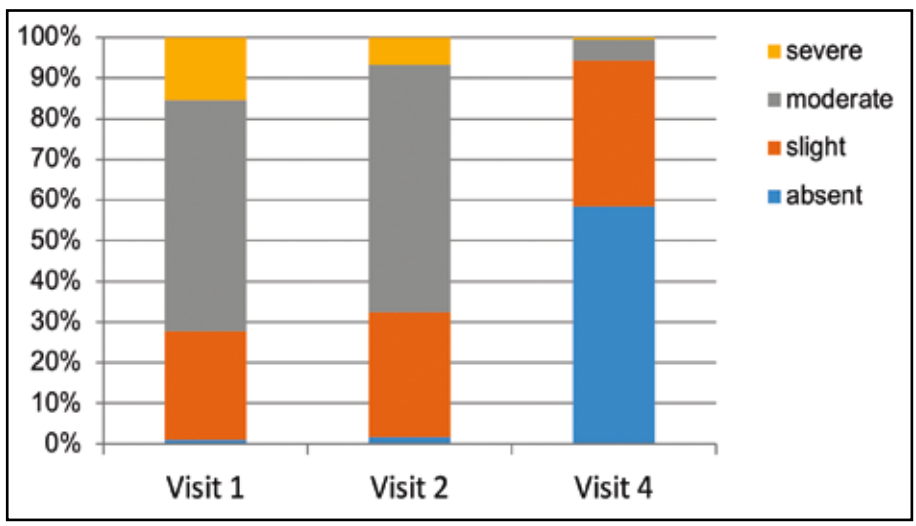

Figure 3. The assessment of hyperaemia severity ratio.

Table 4. The assessment of secretion severity reduction.

Secretion	Visit 1			Visit 2			Visit 3		
	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %
Absent	2	1.1%	1.1%	1	0.6%	0.6%	31	20.1%	20.1%
Slight	27	15.0%	16.1%	34	19.0%	19.6%	92	59.7%	79.9%
Moderate	96	53.3%	69.4%	115	64.2%	83.8%	30	19.5%	99.4%
Severe	55	30.6%	100.0%	29	16.2%	100.0%	1	0.6%	100.0%
Missing data	0	-		1	-		26	-	
Pearson Chi-square p-value change vs. the previous measurement			-			0.000			0.000

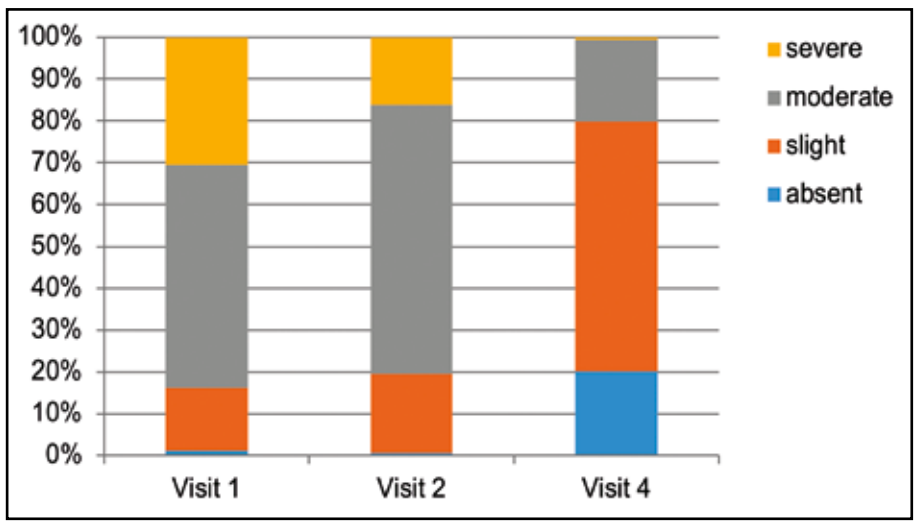

Figure 4. The assessment of secretion severity ratio.

(v4 vs. v1) was: RD -0.15 (95%CI -0,20– -0,09), RR 0.85 (95%CI 0.80-0.91), OR 0.04 (95%CI 0.01-0.26). A negative RD value means reduced risk of hyperaemia when exposed to Cinnabsin® treatment; RR 0.85 (< 1) means reduced risk of the adverse outcome of hyperaemia when exposed to Cinnabsin® treatment, and OR 0.04 (< 1) indicates an increase in the chances of a favourable outcome with Cinnabsin® treatment (respectively, a decrease in the chances of an unfavourable outcome). According to Pearson Chi-square p-value changes vs. the previous measurement, RD, RR and OR, the given data of the hyperaemia severity in dynamics are reliable and relevant from the point of view of the study.

The assessment of hyperaemia severity (positive outcomes were rated absent, slight and moderate, and the negative outcome was rated severe) was 84.4% during v1, 93.3% at v2, and 99.4% at v4, the ratio being shown in Figure 3.

According to investigators, the data in Table 3 and Figure 3 (the hyperaemia severity in dynamics) indicate a positive effect of Cinnabsin® treatment on the reduction of hyperaemia as one of the typical symptoms of rhinosinusitis.

Assessment of secretion severity during v1, v2 and v4 are presented in Table 4 and Figure 4. Missing values are given, and the percentages are calculated when those are excluded, i.e., only using the valid data as a base for each period. Different levels are sorted in 'worsening' order and the difference by the visit was checked versus the previous one (Pearson Chi-square p-values given). In all cases, a significant change in the distribution pattern was confirmed. Observed improvements in the assessment during visits v1, v2 and v4 were statistically significant. Another observation is the big increase in the absent category share in v4 vs. v2.

The relationship between exposure and treatment outcome for secretion as a typical symptom of rhinosinusitis (v4 vs. v1) was: RD -0.30 (95%CI -0.37– -0.23), RR 0.70 (95%CI 0.63-0.77), OR 0.02 (95%CI 0.00-0.11). A negative RD value means reduced risk of secretion when exposed to Cinnabsin® treatment; RR 0.70 (< 1) means reduced risk of the adverse outcome of secretion when exposed to Cinnabsin® treatment, and OR 0.02 (< 1) indicates an increase in the chances of a favourable outcome with Cinnabsin® treatment (respectively, a decrease in the chances of an unfavourable outcome). According to Pearson Chi-square p-value changes vs. the previous measurement, RD, RR and OR, the given data of the secretion severity in dynamics are reliable and relevant from the point of view of the study.

The assessment of secretion severity (positive outcomes

Table 5. The assessment of headache reduction (the score by VAS).

Headache	Valid N	Mean	Median	Minimum	Maximum	Std. Dev.	Std. Error
visit 1	180	3.39	3	1	10	2.52	0.19
visit 2	180	2.94	2	1	9	2.26	0.17
visit 3	180	2.02	1	1	9	1.55	0.12
visit 4	180	1.42	1	1	9	1.05	0.08
p-values of multiple comparison	**v1**	**v2**	**v3**	**v4**			
v1	1	0.0000	0.0000	0.0000			
v2	0.0000	1	0.0000	0.0000			
v3	0.0000	0.0000	1	0.0000			
v4	0.0000	0.0000	0.0000	1			

were rated absent, slight and moderate, and the negative outcome was rated severe) was 69.4% during v1, 83.8% at v2 and 99.4% at v4, the ratio being shown in Figure 4.

According to investigators, the data in Table 4 and Figure 4 (the secretion severity in dynamics) indicate a positive effect of Cinnabsin® treatment on the reduction of secretion as one of the typical symptoms of rhinosinusitis.

Secondary effectiveness endpoints. The dynamic of the individual assessment of the physicians on each of the five typical rhinosinusitis symptoms (headache, facial pain or pain with pressure (pain when pressed on maxillary sinus), nasal congestion (difficulty of nasal breathing), nasal secretion (nasal secretion from the nose), pharyngeal flow of mucus (postnasal drip)) were assessed by VAS for each symptom. In each case, a statistically significant reduction was confirmed (Tables 5–9, Figures 5–9).

The assessment of headache reduction (the score by VAS), t-test for dependent means comparison, were confirmed with non-parametric analogues (Table 5, Figure 5; p-values of multiple comparison, t-test, given in the table).

The score for headache was 1.05±0.08 at visit 4 versus 2.52±0.19 at visit 1. According to p-values (all of them = 0.0000) of multiple comparison, this study point of view is relevant (and statistically significant). The dynamics of headache reduction is shown in Figure 5.

Figure 5 shows positive evolution of headache reduction from each visit to the previous visits (t-test for dependent means comparison, all results confirmed with non-parametric analogs, and v4 vs. v1 changes are statistically significant ($p<0.05$)). The investigators rate this as a relevant positive effect on one of the five typical symptoms of rhinosinusitis.

The assessment of facial pain or pain with pressure reduction (the score by VAS), t-test for dependent means comparison, were confirmed with non-parametric analogues (Table 6, Figure 6; p-values of multiple comparison, t-test, given in the table).

The assessment for facial pain or pain with pressure reduction was 1.16±0.09 at visit 4 versus 2.77±0.21 at visit 1. According to p-values of multiple comparison (all p-values <0.05), this study point of view is relevant (and statistically signifi-

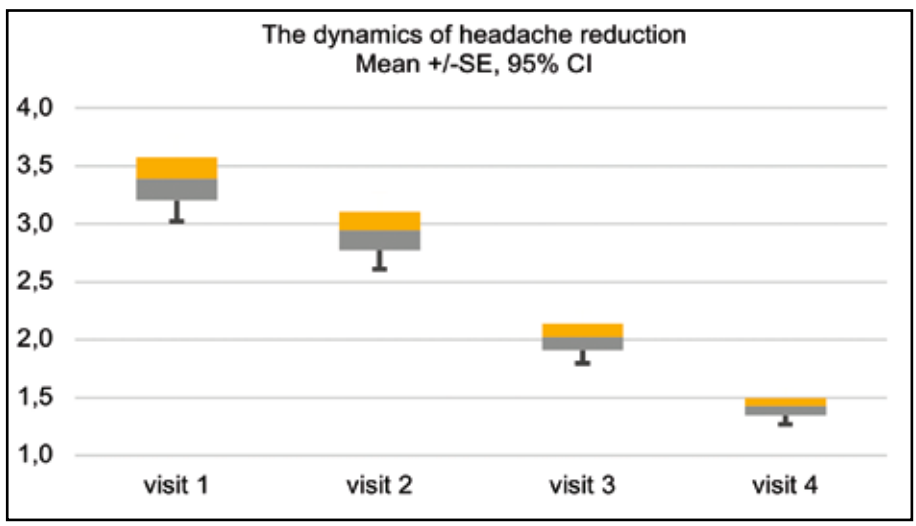

Figure 5. The dynamics of headache reduction (the score by VAS).

Table 6. The assessment of facial pain or pain with pressure reduction (the score by VAS).

Facial pain or pressure	Valid N	Mean	Median	Minimum	Maximum	Std. Dev.	Std. Error
visit 1	180	3.89	3	1	9	2.77	0.21
visit 2	180	3.54	3	1	9	2.65	0.20
visit 3	180	2.39	2	1	9	1.82	0.14
visit 4	180	1.56	1	1	9	1.16	0.09
p-values of multiple comparison	**v1**	**v2**	**v3**	**v4**			
v1	1	0.0000	0.0000	0.0000			
v2	0.0000	1	0.0000	0.0000			
v3	0.0000	0.0000	1	0.0000			
v4	0.0000	0.0000	0.0000	1			

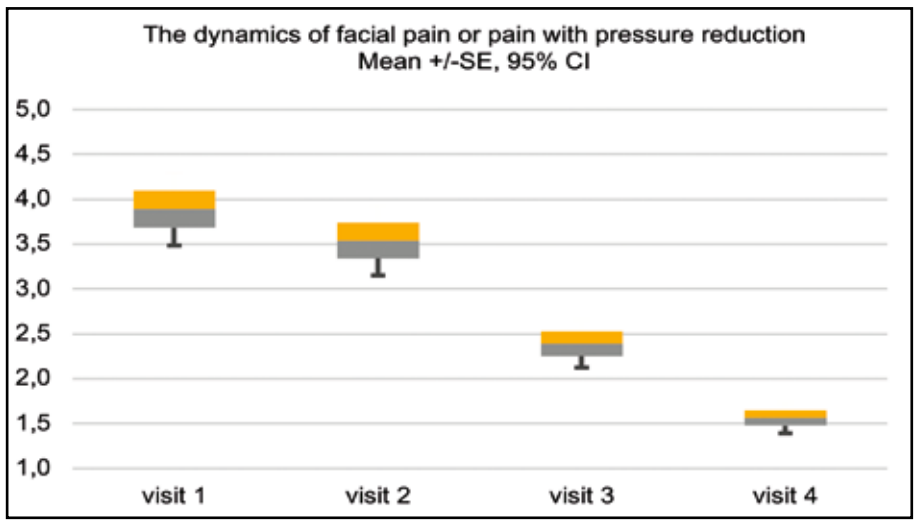

Figure 6. The dynamics of facial pain or pain with pressure reduction (the score by VAS).

cant). The dynamics of facial pain or pain with pressure reduction being shown in Figure 6.

Figure 6 shows positive evolution of facial pain or pain with pressure reduction from each visit to the previous visits (t-test for dependent means comparison, p-values in Table 6 above, all results confirmed with non-parametric analogs, and v4 vs. v1 changes are statistically significant). The investigators rate this as a relevant positive effect on one of the five typical symptoms of rhinosinusitis.

The assessment of nasal congestion (the score by VAS), t-

Table 7. The assessment of nasal congestion (the score by VAS).

Nasal congestion	Valid N	Mean	Median	Minimum	Maximum	Std. Dev.	Std. Error
visit 1	180	6.47	6	1	10	2.03	0.15
visit 2	180	5.85	6	1	10	2.08	0.16
visit 3	180	4.11	4	1	9	1.78	0.13
visit 4	180	2.62	2	1	9	1.57	0.12
p-values of multiple comparison	**v1**	**v2**	**v3**	**v4**			
v1	1	0.0000	0.0000	0.0000			
v2	0.0000	1	0.0000	0.0000			
v3	0.0000	0.0000	1	0.0000			
v4	0.0000	0.0000	0.0000	1			

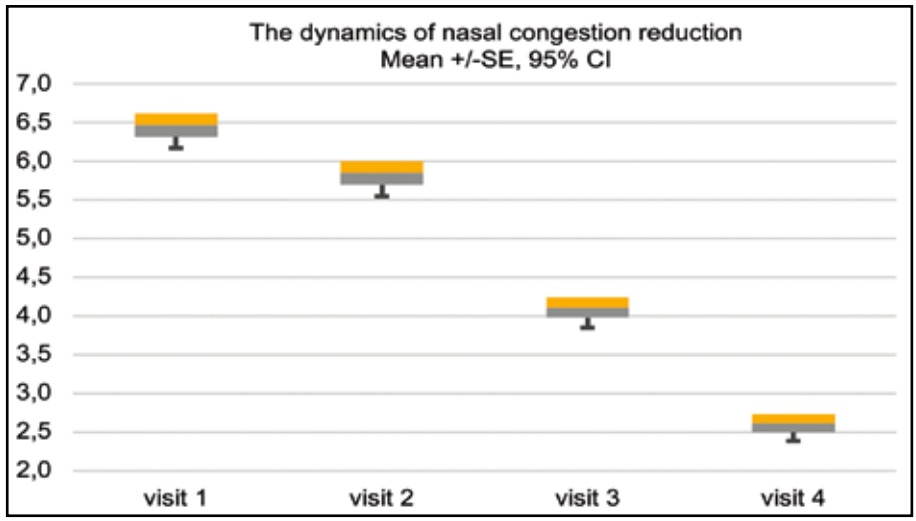

Figure 7. The dynamics of nasal congestion reduction (the score by VAS).

test for dependent means comparison, were confirmed with non-parametric analogues (Table 7, Figure 7; p-values of multiple comparison, t-test, given in the table).

The assessment of nasal congestion was 1.57±0.12 at visit 4 versus 2.03±0.15 at visit 1. According to p-values of multiple comparison (all < 0.05, Table 7), this study point of view is relevant. The dynamics of nasal congestion reduction is shown in Figure 7.

Figure 7 shows positive evolution of nasal congestion reduction from each visit to the previous visits (t-test for dependent means comparison, all results confirmed with non-parametric analogs, and v4 vs. v1 changes are statistically significant (each p-value < 0.05, Table 7)). The investigators rate this as a relevant positive effect on one of the five typical symptoms of rhinosinusitis.

The assessment of nasal secretion (the score by VAS), t-test for dependent means comparison, were confirmed with non-parametric analogues (Table 8, Figure 8; p-values of multiple comparison, t-test, given in the table).

The assessment of nasal congestion was 1.63±0.12 at visit 4 versus 2.20±0.16 at visit 1. According to p-values of multiple comparison (all < 0.05, Table 8), this study point of view is relevant (and statistically significant). The dynamics of nasal congestion reduction is shown in Figure 8.

Figure 8 shows positive evolution of nasal secretion reduction from each visit to the previous visits (t-test for dependent means comparison, all results confirmed with non-parametric analogs, and v4 vs. v1 changes are statistically significant (each p-value < 0.05, Table 8)). The investigators rate this as a relevant positive effect on one of the five typical symptoms of rhinosinusitis.

The assessment of pharyngeal flow of mucus (the score by VAS), t-test for dependent means comparison, were confirmed with non-parametric analogues (Table 9, Figure 9; p-values of multiple comparison, t-test, given in the table).

The assessment of pharyngeal flow of mucus was 1.49±0.11 at visit 4 versus 2.77±0.21 at visit 1. According to p-values of multiple comparison (all < 0.05), this study point of view is relevant (and statistically significant). The dynamics of nasal congestion reduction is shown in Figure 9.

Figure 9 shows positive evolution of pharyngeal flow of mucus reduction from each visit to the previous visits (t-test

Table 8. The assessment of nasal secretion (the score by VAS).

Nasal secretion	Valid N	Mean	Median	Minimum	Maximum	Std. Dev.	Std. Error
visit 1	180	6.38	6	1	10	2.20	0.16
visit 2	180	5.92	6	1	10	1.97	0.15
visit 3	180	4.50	4	1	9	1.85	0.14
visit 4	180	2.79	2	1	9	1.63	0.12
p-values of multiple comparison	**v1**	**v2**	**v3**	**v4**			
v1	1	0.0000	0.0000	0.0000			
v2	0.0000	1	0.0000	0.0000			
v3	0.0000	0.0000	1	0.0000			
v4	0.0000	0.0000	0.0000	1			

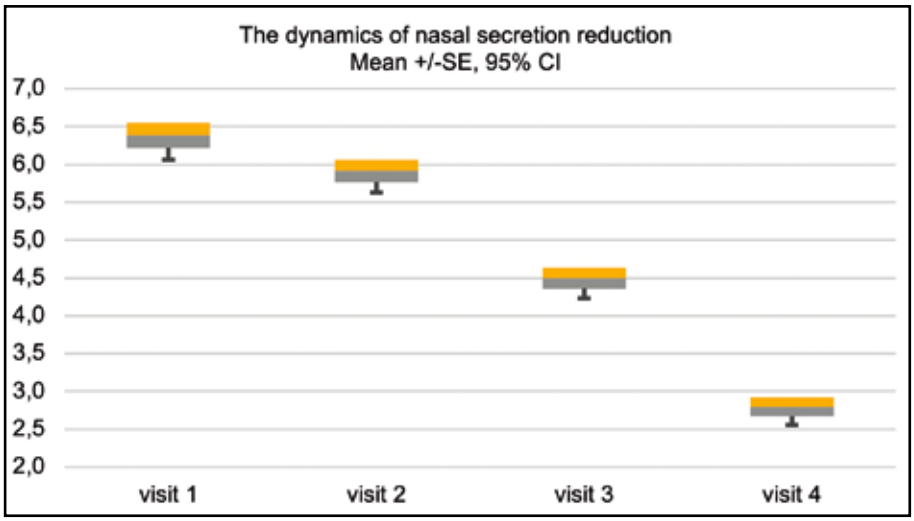

Figure 8. The dynamics of nasal secretion reduction (the score by VAS).

Table 9. The assessment of pharyngeal flow of mucus (the score by VAS).

Pharyngeal flow	Valid N	Mean	Median	Minimum	Maximum	Std. Dev.	Std. Error
visit 1	180	5.19	5	1	10	2.77	0.21
visit 2	180	4.67	4	1	9	2.44	0.18
visit 3	180	3.62	3	1	9	2.10	0.16
visit 4	180	2.19	2	1	9	1.49	0.11
p-values of multiple comparison	**v1**	**v2**	**v3**	**v4**			
v1	1	0.0000	0.0000	0.0000			
v2	0.0000	1	0.0000	0.0000			
v3	0.0000	0.0000	1	0.0000			
v4	0.0000	0.0000	0.0000	1			

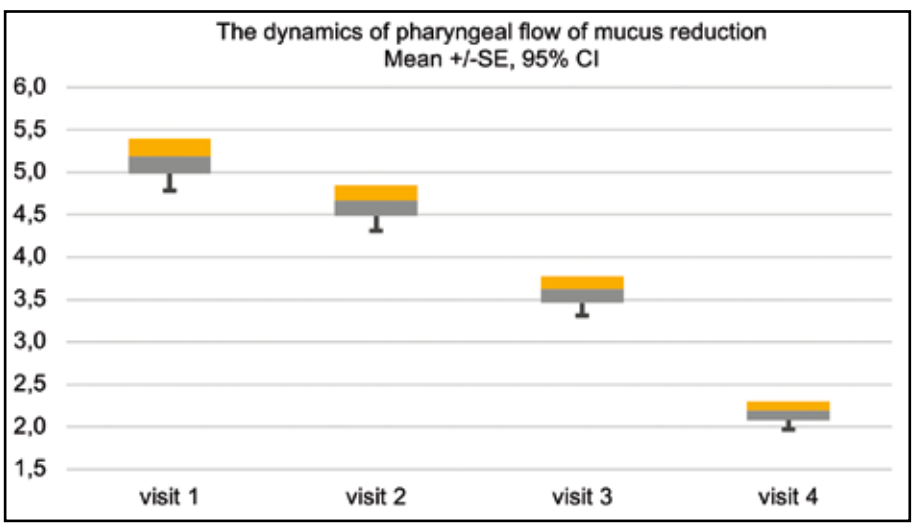

Figure 9. The dynamics of pharyngeal flow of mucus reduction (the score by VAS).

Table 10. The speed and degree of five typical symptoms of rhinosinusitis reduction.

Symptoms	v2 - v1 * (mean score)	v4 - v1 ** (mean score)
Headache	-1.97	-1.97
Facial pain or pain with pressure	-0.35	-2.33
Nasal congestion	-0.47	-3.85
Nasal secretion	-0.62	-3.59
Nasal secretion	-0.52	-3.00
Valid N	180	180

* Significant difference between facial pain and nasal congestion ($p<0.05$)

** 3 statistically significant groups formed: 1 (headache & facial pain or pain with pressure), 2 (nasal congestion & nasal secretion) and 3 (pharyngeal flow of mucus). Difference between the groups proven statistically significant ($p<0.05$), no significant difference within group 1 and 2 ($p>0.05$).

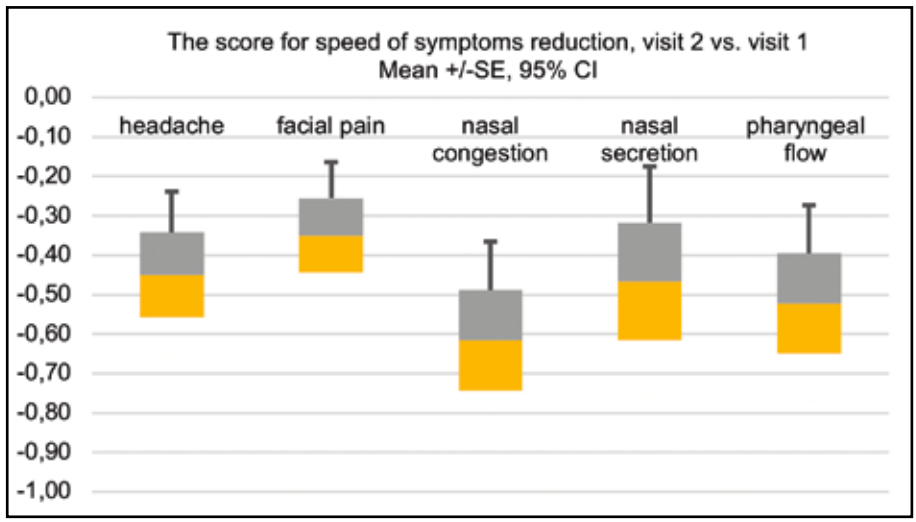

Figure 10. The score for speed of symptoms reduction (v2 vs. v1).

for dependent means comparison, all results confirmed with non-parametric analogs, and v4 vs. v1 changes are statistically significant (each p-value < 0.05, Table 9)). The investigators rate this as a relevant positive effect on one of the five typical symptoms of rhinosinusitis.

The assessment done by the patients in their questionnaires was statistically the same as the assessment done by investigators in the CRF, no matter that there were several cases in which they were not assessed in the same way by the patients and by the investigators.

The five typical symptoms of rhinosinusitis – headache, facial pain or pain with pressure (pain when pressed on maxillary sinus), nasal congestion (difficulty of nasal breathing), nasal secretion (nasal secretion from the nose), pharyngeal flow of mucus (postnasal drip) – were also assessed for their speed and degree of symptom reduction, using the following criteria (Table 10):

- the difference in score between visit 2 and visit 1 was used to estimate the rate of reduction of symptoms – the maximum difference indicates the fastest decreasing symptom (Figure 10);
- the difference in score between visit 4 and visit 1 was used to assess the overall rate of reduction – the maximum difference indicates the most severe decreasing symptom (Figure 11).

Table 10 and Figures 10 and 11 summarise the results of this assessment:

- there is no statistically significant difference between the established parameter for speed of reduction (v2–v1 score), i.e., each symptom was reduced with a similar amount ($p > 0.05$); the only exception is the significant result for facial pain and nasal congestion (p-value < 0.05);
- the degree of reduction (v4-v1), though, is showing statistically significant results ($p < 0.05$): the greatest reduction was observed for nasal congestion and nasal secretion ($p < 0.05$); the second was measured the pharyngeal flow of mucus ($p < 0.05$); the least reduction was recorded in the group of headache and facial pain or pain with pressure ($p < 0.05$).

The data in Table 10 indicate a different rate and degree of reduction of symptoms in patients with rhinosinusitis. We also found a significant difference between facial pain and nasal congestion (v2 - v1), and symptoms such as nasal con-

Table 11. The healthy status of the patients.

Healthy status	Visit 1			Visit 2			Visit 3		
	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %
major improvement	13	7.2%	7.2%	49	27.2%	27.2%	78	43.3%	43.3%
improvement	39	21.7%	28.9%	94	52.2%	79.4%	35	19.4%	62.8%
no complaints	1	0.6%	29.4%	5	2.8%	82.2%	56	31.1%	93.9%
no change	102	56.7%	86.1%	31	17.2%	99.4%	11	6.1%	100.0%
worsening	25	13.9%	100.0%	1	0.6%	100.0%	0	0.0%	100.0%
Pearson Chi-square p-value change vs. the previous measurement			-			0.000			0.000

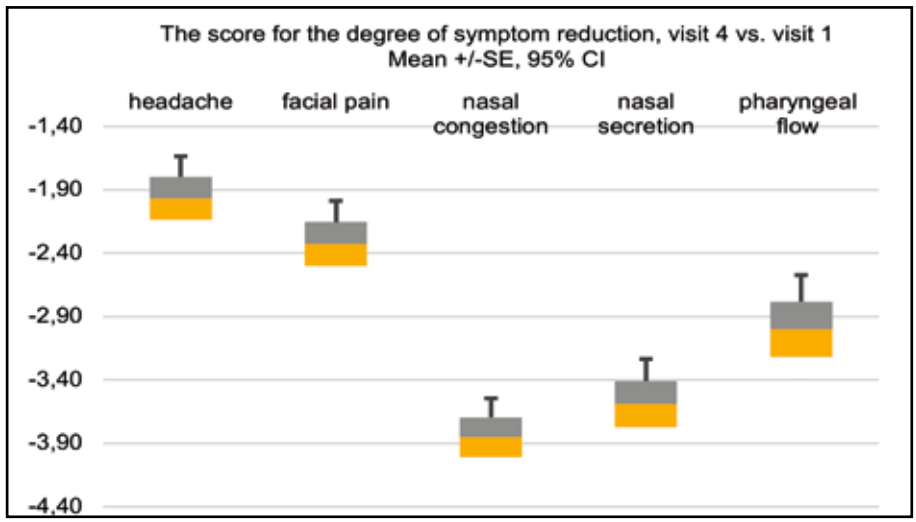

Figure 11. The score for the degree of symptom reduction (v4 vs. v1).

gestion, nasal secretion, pharyngeal flow of mucus, and less for facial pain or pain with pressure (v2 – v1, based on individual comparisons t-test p-values).

The five typical rhinosinusitis symptoms assessed by patients presented an important improvement from one visit to other (Figure 10, Figure 11). Figure 10 shows different rates of score for speed of symptoms reduction, more for symptoms such as nasal congestion, pharyngeal flow of mucus, nasal secretion, and less for facial pain or pain with pressure and headache when comparing visit 2 with visit 1 (v2 - v1, based on individual comparisons t-test p-values). figure 11 shows different rates of score for the degree of symptom reduction, more for symptoms such as nasal congestion, nasal secretion, pharyngeal flow of mucus, and less for facial pain or pain with pressure and headache when comparing Visit 4 with Visit 1 (v4 - v1, based on individual comparisons t-test p-values).

The healthy status of the patients was determined according to the following criteria: major improvement, improvement, no complaints, no change, worsening (Table 11).

The good health status of the patients ("major improvement", "improvement" and "no complaints") was rated as 29.4% during visit 2, 82.2% during visit 3, and 93.9% during visit 4. According to Pearson Chi-square p-values changes vs. the previous measurements, this study point of view is relevant. The investigators rate the positive effect of healthy status changes of the patients. The ratio of healthy status of the patients is shown in Figure 12.

Figure 12 shows a different ratio of healthy status of the patients with an increase in the share of indicators "major improvement" and "improvement" for the v3 and v4.

Assessment of the effectiveness of treatment was determined according to the following criteria: major improvement, improvement, no complaints, no change, worsening (Table 12).

The effectiveness of treatment ("major improvement", "improvement" and "no complaints") was rated as 30.0% during visit 2, 81.7% at visit 3 and 93.9% at visit 4.

There were 17.8% of patients with "no changes" at v3, but only 6.1% remained at v4, "worse" was observed in 1 patient at v3, but not at v4. However, at visit 4, the treatment was not assessed as effective in 6.1% of patients. According to the researchers' opinion, this is a common result, since in routine practice there are no products or combinations of them with

Table 12. Assessment of the effectiveness of treatment.

Effect of treatment	Visit 1			Visit 2			Visit 3		
	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %	Count	Valid %	Cumulative %
major improvement	13	7.2%	7.2%	49	27.2%	27.2%	79	43.9%	43.9%
improvement	40	22.2%	29.4%	93	51.7%	78.9%	35	19.4%	63.3%
no complaints	1	0.6%	30.0%	5	2.8%	81.7%	55	30.6%	93.9%
no change	101	56.1%	86.1%	32	17.8%	99.4%	11	6.1%	100.0%
worsening	25	13.9%	100.0%	1	0.6%	100.0%	0	0.0%	100.0%
Pearson Chi-square p-value change vs. the previous measurement			-			0.000			0.000

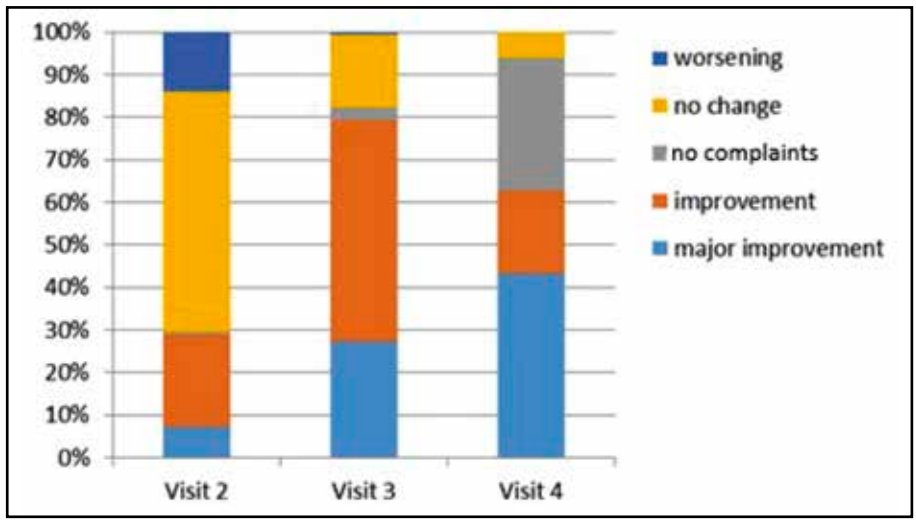

Figure 12. The ratio of healthy status of the patients.

ideal effectiveness. In such cases, approaches to the treatment of patients change in routine practice. According to Pearson Chi-square p-values changes vs. the previous measurements, this study point of view is relevant and statistically significant (p-values < 0.05). The investigators rate the high effectiveness of the treatment of the patients.

The ratio of the effectiveness of treatment is shown in Figure 13.

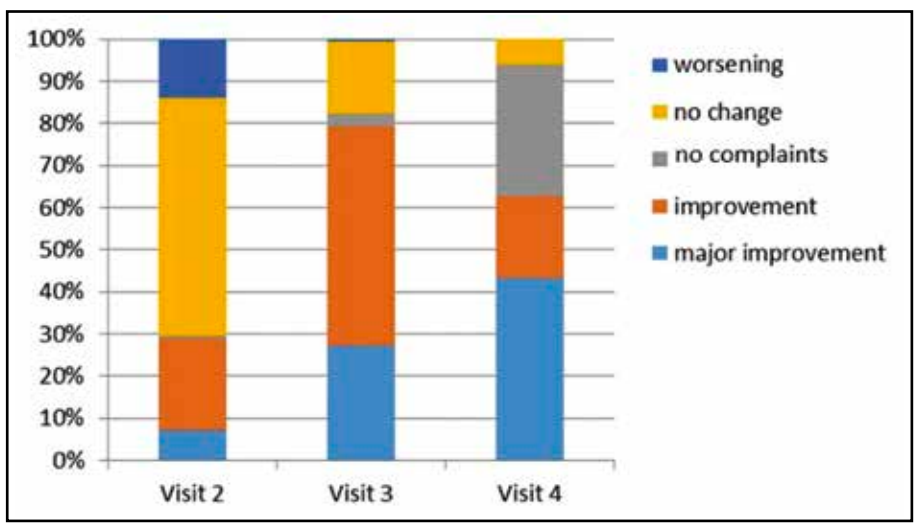

Figure 13. The effectiveness of treatment ratio.

Figure 13 shows a different ratio of the effectiveness of treatment with an increase in the share of indicators "major improvement" and "improvement" for the v3 and v4.

Safety results. Treatment tolerance was rated as "very good" (99.4%) in almost all patients included in the study (n=180). One of the patients reported an adverse event (AE) during visit 2 – a body temperature of 38°C, which was not presented on the next visit and was assessed as not related to the study drug by the investigator. This single AE represents 0.6% of the total safety population under study.

DISCUSSIONS

The results of the study of primary endpoints, in particular the results of the overall assessment of the five typical symptoms of rhinosinusitis in patients evaluated by physicians, showed a statistically significant decrease in values, which was confirmed at each subsequent visit. It is important to note that all identified primary and secondary variables show a statistically significant trend toward improvement. This is especially noticeable with an increase in the duration of treatment (i.e., the third score compared to the second with a higher rate of improvement compared to the difference between the second and first scores). That being said, the results are fairly even for each endpoint.

The overall assessment of the five typical symptoms of rhinosinusitis (headache, facial pain or pressure, nasal congestion, anterior nasal secretions, pharyngeal flow of mucus) assessed by the patient indicates a positive dynamic of treatment (4.96±0.37 v4 vs. 7.55±0.56 v1, Figure 1), which indicates a positive effect of the study drug on all typical symptoms of rhinosinusitis.

The five typical rhinosinusitis symptoms assessed by the patient are shown positive dynamics of speed and the degree of symptom reduction (Figure 10, Figure 11). Objective evaluation: changes in edema, hyperaemia and secretion assessed by rhinoscopy by the physicians as absent, slight, moderate and severe – statistically confirmed the effectiveness of treatment with Cinnabsin in all cases ($p < 0.05$). The assessment of secondary efficacy endpoints for each of the five typical symptoms of rhinosinusitis in patients is consistent with the dynamics of the total score. In each case, a statistically significant reduction in the severity of symptoms is confirmed, such as headache and facial pain or pain with pressure ($p < 0.05$), nasal congestion and nasal secretion ($p < 0.05$), and pharyngeal flow of mucus ($p < 0.05$).

There is no statistically significant difference between the established parameter for speed of reduction (v2–v1 score) ($p > 0.05$) (i.e., each symptom is reduced with a similar amount (the only exception is the significant result for facial pain and nasal congestion (p-value < 0.05)). However, the degree of reduction (v4-v1) is showing statistically significant results ($p < 0.05$): the greatest reduction is observed for nasal congestion and nasal secretion ($p < 0.05$); the second comes the pharyngeal flow of mucus ($p < 0.05$); the least reduction is observed for the group of headache and facial pain ($p < 0.05$). It is important that the subjective assessment made by the patients in their questionnaires is in almost all cases statistically consistent with the objective assessment made by the investigators in the CRF.

The effectiveness of treatment with Cinnabsin® was determined according to the criteria "major improvement", "improvement" and "no complaints" (in total), and it was rated as 81.7% at visit 3 and 93.9% at visit 4, which is a positive result. The tolerance of treatment with Cinnabsin® was rated as "very good" (99.4%; there is only one AE, and it was assessed as not related to the treatment with Cinnabsin®). In addition, the patients' compliance to study drug intake is reported as 100%.

Cinnabsin® is a fairly well-studied drug and our data are generally consistent with data from other studies. In the randomized, double-blind study[18] the efficacy and tolerability of a homeopathic combination remedy for the treatment of acute rhinosinusitis were investigated. A total of 144 patients with acute rhinosinusitis were treated with Cinnabsin® (n=72) or placebo (n=72). At the control examinations after 7, 14 and 21 days, five sinusitis-typical symptoms were measured with scores from 0 (absent) to 4 (very strong). The change of sum score of the sinusitis-typical symptoms (max. 20 points) during the treatment served as the primary efficacy criterion. In the Cinnabsin® treatment group, the average sum score dropped from initially 12.1±1.6 to 5.9±2.0 points after 7 days, and in the placebo group, it decreased from 11.7±1.6 to 11.0±2.9 points ($p<0.0001$). The homeopathic treatment resulted in freedom from complaints in 90.3% of the patients and improvement in a further 8.3%, whereas in the placebo group, the complaints remained unchanged or became worse in 88.9% of the patients. Only one adverse event occurred in one patient from the placebo group[18]. This study has a 1b level of evidence ("Individual randomized controlled trials") according to "OCEBM Levels of Evidence"[19]. It should be noted that the European Position Paper on Rhinosinusitis and Nasal Polyps – EPOS 2020 recommendations include a compositionally similar combination of homeopathic remedy with a comparable level of evidence[20]. Similar positive results on the high efficacy (in RCT) and effectiveness (in routine practice) as well as good tolerance of Cinnabsin® have been obtained in other clinical studies[8,9,21-26]. One of those few agents effecting all the

components of rhinosinusitis pathogenesis and covering the whole symptom complex of nasal and paranasal sinuses mucosa inflammation is Cinnabsin® (DHU, Germany)[7]. Also, of practical perspective are studies on the effectiveness of Cinnabsin® in adenoiditis treatment[27,28]. In addition to clinical studies, Cinnabsin® was investigated in an experimental study, which showed its modulating effect on various parts of the immune system[29]. The data obtained in this study cannot be explained by the "placebo effect", which is sometimes attempted to explain the effectiveness of combined homeopathic remedies.

CONCLUSIONS

In the study about the therapeutic efficacy, tolerance and safety of Cinnabsin® in the treatment of acute or exacerbation of chronic rhinosinusitis, all defined primary and secondary variables are showing a statistically significant trend toward improvements. The total score of the five typical rhinosinusitis symptoms shows a statistically significant reduction of the values for each subsequent study visit from both patient and physician's point of view.

This is rational for us that, if Cinnabsin® is taken as per the specified requirements in out-patient conditions, it shows high effectiveness.

Cinnabsin® is efficient in reducing the symptoms of acute rhinosinusitis, shows a very good safety profile, and could be recommended for outpatient treatment of patients with acute or exacerbated chronic rhinosinusitis, no matter the additional therapy (no matter no statistical measurement).

Conflict of interest: The authors have no conflict of interest to declare because the study was performed in the course of routine clinical practice.

Contribution of authors: All the authors have equally contributed to this work.

Financial discloser: Alpen Pharma OOD supported the organization and implementation of the study.

Acknowledgements: We are grateful to the principal investigators Valentina Hristova, Valentina Georgieva, and Emiliya Yordanova for the study management at the sites, and Alpen Pharma OOD for the organizational support of the study.

Authors' information:

Rumen Benchev, Professor MD, PhD, Board member of the Bulgarian Society of ORL. ENT Department, Hill Clinic, Sofia, Bulgaria. E-mail: marbenchev@gmail.com

Dilyana Vicheva, Professor, MD, PhD, Board member of the Bulgarian Society of ORL, President of the Bulgarian Rhinologic Society, President of the Bulgarian Pediatric ORL Society, Member of the Advisory Board of the European Rhinologic Society. ENT Department, Kaspela University General Hospital, Plovdiv, Bulgaria. E-mail: vdilyana@gmail.com. ORCID: https://orcid.org/0000-0002-6805-3825.

REFERENCES

1. Jaume F, Valls-Mateus M, Mullol J. Common cold and acute rhinosinusitis: up-to-date management in 2020. Curr Allergy Asthma Rep. 2020;20(7):28. DOI: 10.1007/s11882-020-00917-5.
2. Hoffmans R, Wagemakers A, van Drunen C, Hellings P, Fokkens W. Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment. PLoS One. 2018;13(2):e0192330. DOI: 10.1371/journal.pone.0192330.
3. Albu S. Chronic rhinosinusitis-an update on epidemiology, pathogenesis and management. J Clin Med. 2020;9(7):2285. DOI: 10.3390/jcm9072285.
4. DeConde AS, Soler ZM. Chronic rhinosinusitis: epidemiology and burden of disease. Am J Rhinol Allergy. 2016;30(2):134-9. DOI: 10.2500/ajra.2016.30.4297.
5. Hamilos DL Chronic rhinosinusitis: epidemiology and medical management. J Allergy Clin Immunol. 2011;128(4):693-707. DOI: 10.1016/j.jaci.2011.08.004.
6. Iro H, Wurm J, Zenk J. Komplikationen bei entzündlichen Erkrankungen der Nasennebenhöhlen. HNO. 2004;52:395-408.
7. Garashchenko TI. Complex homeopathic preparations in the treatment of diseases of the ENT organs. RMZh. 2002;20:935. (In Russ.).
8. Gladush Y, Tyshko FA, Skitsyuk SV. Sinusitis. Clinical guide in tables and charts. Kiev:B/i; 2000, p.56. (In Russ.).
9. Piskunov G, Timen G, Kheger M. Homeopathic treatment of acute rhinosinusitis. Report on multicenter prospective uncontrolled outcomes-study. Preprint; 2003, p.13. (In Russ.).
10. Guo R, Canter PH, Ernst E. Herbal medicines for the treatment of rhinosinusitis: a systematic review. Otolaryngol Head Neck Surg. 2006;135(4):496-506. DOI: 10.1016/j.otohns.2006.06.1254.
11. Koch AK, Klose P, Lauche R, Cramer H, Baasch J, Dobos GJ, et al. A systematic review of phytotherapy for acute rhinosinusitis. Forsch Komplementmed. 2016;23(3):165-9. DOI: 10.1159/000447467.
12. Agache I, Song Y, Alonso-Coello P, Vogel Y, Rocha C, Sola I, et al. Efficacy and safety of treatment with biologicals for severe chronic rhinosinusitis with nasal polyps: A systematic review for the EAACI guidelines. Allergy. 2021;76(8):2337-53. DOI: https://doi.org/10.1111/all.14809.
13. Kim HJ, Lee K, Yoo JB, Song JW, Yoon JH. Bacteriological findings and antimicrobial susceptibility in chronic sinusitis with nasal polyp. Acta Otolaryngol. 2006;126(5):489-97. DOI: 10.1080/00016480500437385.
14. Wustrow TPU. Naturheilkundliche Therapie der akuten Otitis media. Eine Alternative zum primären Antibiotikaeinsatz. HNO. 2005;53:728-34.
15. Mathie RT, Fok YYY, Viksveen P, To AKL, Davidson JRT. Systematic review and meta-analysis of randomised, other-than-placebo controlled, trials of non-individualised homeopathic treatment. Homeopathy. 2019;108(2):88-101. DOI: 10.1055/s-0038-1677481.
16. Sistrom CL, Garvan CW. Proportions, odds, and risk. Radiology. 2004;230(1):12-9. DOI: 10.1148/radiol.2301031028.
17. Kim HY. Statistical notes for clinical researchers: Risk difference, risk ratio, and odds ratio. Restor Dent Endod. 2017;42(1):72-6. DOI: 10.5395/rde.2017.42.1.72.
18. Friese KH, Zabalotnyi DI. Homeopathy in acute rhinosinusitis: a double-blind, placebo controlled study shows the efficiency and tolerability of a homeopathic combination remedy. HNO. 2007;55(4):271-7. DOI:

10.1007/s00106-006-1480-x.

19. Centre for Evidence-Based Medicine. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). 2009-06-11. Retrieved 25.03.2015. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.
20. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464. DOI: 10.4193/Rhin20.600.
21. Bezshapochnyi SB, Loburets VV. Clinical practice of Cinnabsin administration for treatment of rhinosinusitis. Rynologiya. 2003;4:157-8. (In Russ.).
22. Bezshapochny SB, Podovzhnyy OG, Loburets VV. Administration of Cinnabsin for treatment of patients with rhinosinusitis. Rinologiya. 2006;2:24-9. (In Russ.).
23. Piskunov GZ. Experience with the use of cinnabsin in the treatment of acute and chronic sinusitis. Russian rhinology. 1998;(2):40. (In Russ.).
24. Kosakovsky AL. Treatment of acute rhinosinusitis in children using complex homeopathic remedies. Journal of the Ear, Nasal and Throat Diseases. 2018:(3-S):50. (In Russ.)
25. Deeva YV, Tarasenko MV. Complex treatment of acute viral and postviral rhinosinusitis. Journal of the Ear, Nasal and Throat Diseases. 2018;(3-S):153. (In Russ.).
26. Levytska SA. Use of Cinnabsin in treating and preventing upper respiratory tract infections in children. Journal of Ear, Nasal and Throat Diseases. 2018;(5-S):57-62. (In Russ.).
27. Bezshapochny SB, Podovzhniy OG, Dzirov OR. The modern concept of treatment of adenoiditis. Journal of the Ear, Nasal and Throat Diseases. 2018;(3-S):152. (In Russ.).
28. Deeva YV, Shevchuk YV. Use of Cinnabsin in complex treatment of children with purulent adenoiditis. Journal of the Ear, Nasal and Throat Diseases. 2018;(3-S):20. (In Russ.)
29. Melnikov OF, Bredun AY., Bil BN. Anti-inflammatory and antiviral effects of Cinnabsin (in vitro). Otolaryngology. 2019;(1- S2):69. (In Russ.).