


ORIGINAL CONTRIBUTION

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# A randomized, open-label, multicentre, comparative study of therapeutic efficacy, preventive potential and tolerability of BNO 1030 extract, containing Althea root, Chamomile flowers, horsetail herb, walnut leaves, yarrow herb, oak bark, dandelion herb in the treatment of acute non-bacterial tonsillitis in children aged 6 to 18 years

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**Abstract:** Acute tonsillitis tends to recur. In cases where patients do not meet the Paradise criteria, the possibilities of non-surgical treatment are more often considered. The objective of this study was to evaluate the therapeutic efficacy during the long-term follow-up and the effect on the recurrence of the phytonearing extract BNO 1030 (Imupret®) in patients with acute non-bacterial tonsillitis.

**Methods:** In this Randomized, Open-Label, Multicentre, Comparative Study, 238 outpatients aged 6–18 years were randomized to receive either BNO 1030 (Imupret®) for 4 weeks in addition to standard symptomatic treatment, or to receive standard treatment. Evaluation criteria: reduction in the symptom severity less than 1 point, the number of tonsillitis recurrences at each control point after 3, 6 and 12 months during the one-year follow-up.

**Results:** A significant reduction in the severity of local symptoms and the general condition at each control point within the year of follow-up and a significant decrease (by 66.56%) in the recurrence rate of tonsillitis were noted. The anti-recurrent action was manifested during within the year of follow-up. All patients tolerated phytotherapy well; no adverse reactions were noted.

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**Conclusions:** BNO 1030 (Imupret®) is a safe and effective medicinal product for acute non-bacterial tonsillitis in children aged 6–18 years. In addition to the main symptomatic treatment, it leads to a significant reduction in the clinical manifestations and the number of recurrences of tonsillitis within the year of follow-up.

**Trial registration:** This trial was registered in German Clinical Trials Register retrospectively on June 27, 2018.

Trial Acronym: ATI-1

DRKS-ID: DRKS00015020

**Keywords:** Acute tonsillitis, Recurrent tonsillitis, Recurrence, Phytotherapy, BNO 1030, Imupret®

## Introduction

The problem of inflammatory diseases of the lymphoid apparatus of the pharynx in children is one of the most relevant in modern clinical medicine. In Ukraine for the period from 2011 to 2015, there is an increase in the incidence rate of acute tonsillitis among children, from 58.9 cases to 62.6 cases per 1000 children; and the incidence rate among children exceeds the incidence rate among adults by 5.8 times [1]. A similar tendency is observed in Europe and the USA [2, 3].

Tonsillitis is characterized by a high incidence rate, the presence of tonsillogenic diseases, such as paratonsillar abscess, rheumatic fever, acute glomerulonephritis, etc. [4]. A consistently high incidence rate and low effectiveness of preventive measures served as the basis for revising the traditional understanding of the pathophysiology of tonsillitis. Present views are based on the fact that tonsils are constantly in a state of “minimal” inflammatory process without tissue alteration when fulfilling their main task — formation of immunity. This is their physiological norm and is histopathologically determined in anamnestic healthy patients [5, 6]. Given these views, the term “chronic tonsillitis” should not be used at present, since an erroneous opinion is being created about the absence of tonsillitis in clinically healthy patients, especially in children. In this regard, the term is excluded from ICD 11 (<https://icd.who.int/en/>).

Tonsillitis should be understood as inflammation of the tonsils beyond their physiological norm and, therefore, with additional clinical symptoms. Acute tonsillitis (AT) is a single or rare episode of acute occurrence of corresponding clinical symptoms and refers to viral (70–85%) or bacterial tonsillitis (15–30%). Recurrent tonsillitis (RT) (or recurrent throat infections) is the reoccurrence of AT after a time interval characterized by an asymptomatic course (without complaints) or with minor symptoms. The question of surgical treatment is very important for the patients with recurrent tonsillitis. The current clinical guidelines for tonsillectomy are based on the Paradise criteria: the analysis of the number of episodes of acute tonsillitis per year. If the patient has no less than 7 episodes of the acute tonsillitis in the last 12 months, or no less than 5 episodes a year in the

last 2 years, or no less than 3 episodes a year in the last 3 years, surgical treatment is definitely indicated, and conservative treatment is not effective enough [3, 7]. In such cases, tonsillectomy is considered, and surgical removal of the tonsils is a widely used procedure in recurrent tonsillitis [8]. In the United States, over 530,000 tonsillectomies are performed every year due to recurrent throat infections [3]. In cases where patients do not meet the Paradise criteria, tonsillectomy can be considered as an option, but the possibilities of non-surgical treatment are more often considered. Every year in Germany, more than 120,000 patients undergo treatment to eliminate recurring AT episodes [2]. Patients with RT have high expectations of such treatment which, in the absence of regimens with proven efficacy, is one of the main reasons for prescribing antibiotics [9]. However, studies have shown that there is insufficient evidence of the efficacy of antibiotic therapy to prevent AT recurrences [10]. Unjustified prescription of antibiotics is one of the main causes of the global problem of antibiotic resistance, since inadequate antibiotic therapy is prescribed in more than 50% of cases worldwide according to WHO data [11, 12]. However, it is indisputable that qualitative randomized controlled trials are required in order to clarify the possibilities of non-surgical treatment in patients with RT without indications for tonsillectomy (Paradise criteria) [2, 6].

In the light of the targeted effect on the recurrence rate of tonsillitis, the use of herbal medicinal products could be interesting, since according to studies, phytotherapy for inflammatory diseases of the pharynx is prescribed by 28% of doctors [13]. In clinical practice, a phytoneering aqueous extract of BNO 1030 consisting of seven medicinal herbs is used, namely: Marshmallow root (*Radix Althaeae*), Camomile flowers (*Flores Chamomillae*), Horstail herb (*Herba Equiseti*), Walnut leaves (*Folia Jugladis*), Yarrow herb (*Herba Millefolii*), Oak bark (*Cortex Quercus*), Dandelion herb (*Herba Taraxaci*), which is the active ingredient of Imupret® (known in some countries as Tonsilgon® N). The components of the drug provide antiviral, antibacterial, anti-inflammatory and immunomodulatory effects]. The active ingredients in Imupret increase the number of

phagocytic cells of the immune system with oxygen explosion. It helps to increase the efficiency of phagocytosis. This is very important for the treatment of tonsillitis because incomplete phagocytosis and incomplete elimination of the pathogen is one of the key factors in the development of recurrent tonsillitis [14–16].

Indications for use are “treatment of upper respiratory tract diseases (tonsillitis, pharyngitis, laryngitis) and the prevention of complications and recurrences in viral respiratory infections”. Clinical studies in children have shown that the additional use of the phytonering drug BNO 1030 (Imupret®) for the treatment of acute tonsillitis significantly reduces the clinical symptoms of tonsillitis, improves the assessment of the patients’ general condition and quality of life, reduces the use of NSAIDs and the overall duration of treatment with a good safety profile [17, 18]. Some studies of the preventive effect of Tonsilgon® N (Imupret®) in children with recurrent colds have also been conducted (Vavilova V, Abramov-Sommariva D, Steindl H, Wonnemann M, Ryzhova E, Rusova T, Lebedenko A, Kolchenko I: Effectiveness and tolerability of Tonsilgon® N in the treatment of recurrent upper respiratory tract infections in children: a non-interventional study in Russia, submitted) [19, 20]. However, in the scientific literature there are no reports of valid studies of the efficacy of Imupret®, which comply with GCP standards to reduce the number of recurrences of acute tonsillitis.

The objective of the present study was to evaluate the therapeutic efficacy of the phytonering extract BNO 1030 (Imupret®) in the long-term follow-up and the effect on the recurrence of acute non-bacterial tonsillitis compared to patients undergoing standard therapy according to recommendations.

## Materials and methods

### Trial design

Open-label, exploratory, comparative, multicentre, randomized, prospective, parallel-group study was performed in six outpatient institutions of Ukraine from June 2017 to March 2019. The study was performed in accordance with the GCP standards and the Declaration of Helsinki. All study sites received approval from the Ethics Committee. The parents of each child gave their written consent to participate in the study.

### Participants

Two hundred fifty subjects were enrolled; 238 outpatient subjects aged 6–18 years diagnosed with acute non-bacterial tonsillitis were randomized and allocated into two groups: the treatment group — patients taking BNO 1030, a standardized extract of seven medicinal herbs (Imupret®) in addition to a standard therapy; and the control group which undergo a standard symptomatic therapy. The treatment group (n = 118) included 52

(44.1%) boys and 66 (55.9%) girls (average age  $8.67 \pm 3.219$ ), the control group included 62 (51.7%) boys and 58 (48.3%) girls (average age  $9.66 \pm 3.296$ ).

Diagnostic and differential diagnostic criteria for acute tonsillitis were carried out in accordance with the DEGA M recommendations provided in clinical guidelines [2, 6]. A clinical diagnosis of AT was established in the presence of such symptoms as sore throat at rest and in swallowing, hyperaemia and swelling with possible plaque on the tonsils, cervical lymphadenitis and fever. Non-bacterial tonsillitis was diagnosed with – 1–3 points according to Mclsaac Scale for patients aged 3 to 14 years, and with 0–2 points according to Centor Scale for patients aged over 15 years. These scales are used to stratify patients with a sore throat symptom in terms of antibiotic therapy. Symptoms of acute tonsillitis are assessed according to the principle: indicated + 1 point, not indicated 0 points. According to the Mclsaac scale: body temperature  $> 38^\circ\text{C}$  + 1, no cough + 1, enlarged cervical lymph nodes + 1, enlargement or plaque on the tonsils + 1, age: 3–14 years + 1, 15–44 years- 0,  $\geq 45$  years minus 1. The Centor scale takes into account: body temperature  $> 38^\circ\text{C}$  + 1, no cough + 1, enlarged cervical lymph nodes + 1, tonsil plaque + 1. A score from – 1 to 3 points according to the Mclsaac scale or up to 2 points according to the Centor scale indicates a high probability of viral tonsillitis; antibiotics are not recommended for such patients.

### Inclusion criteria

Male and female outpatient subjects aged 6 to 18 years with a diagnosis of acute tonsillitis; the possibility to start treatment within 72 h after the disease symptoms occur; – 1–3 points according to the Mclsaac Scale for patients aged 3 to 14 years, 0–2 points according to Centor Scale: for patients aged over 15 years; no indications for scheduled tonsillectomy (Paradise criteria); willingness and ability of the patient and (or) parents to comply with the requirements of the Study Protocol; signed informed consent.

### Exclusion criteria

Patient from the study: the decision of the patient and/or parents to discontinue participation in the study and withdrawal of written informed consent; loss of contact with the patient, individual intolerance to the study drug and the reference treatment regimen, the occurrence of serious and/or unforeseen adverse events/reactions in a patient during the study; significantly reduced general condition, the development of complications of the underlying disease, which in the physician’s opinion require patient’s withdrawal from the study; patient’s violation of the procedures provided by the Protocol; prescription of systemic antibiotic therapy.

### Exclusion criteria

4–5 points according to the Mclsaac scale or 3–4 points according to the Centor scale; indications for the immediate start of systemic antibiotic therapy; suspected infectious mononucleosis (clinically); the use of systemic antibacterial or antifungal drugs, systemic glucocorticosteroids, cytostatics in the last 14 days; intolerance or increased individual sensitivity to any of the components of the investigational drug and the reference treatment regimen; indications for scheduled tonsillectomy (Paradise criteria).

The patients of two groups were of similar sex, age, clinical manifestations of the disease ( $p < 0.05$ ).

### Interventions

From the time of randomization, patients of two groups followed a sparing diet; irritating factors (physical and chemical) were eliminated; paracetamol (if case of pain, hyperthermia), benzydamine 3–4 times a day. Patients of the treatment group additionally received BNO 1030 (Imupret®) drops per os, from one batch, in the following dosage strength: in the acute phase of the disease (5 days) for children aged 6–11 years, 15 drops 6 times a day; at the age of 12 years, 25 drops 6 times a day. From Day 6 to 28 of follow-up, children aged 6–11 years should take 15 drops 3 times a day; children above 12 years, 25 drops 3 times a day.

BNO 1030 drops per os are a standardized alcoholic aqueous extract. *Active substances*: 100 g drops contain 29 g of an alcoholic aqueous extract (extracting agent: ethanol 59% (V/V) made from the following medicinal plants:

Marshmallow root (Radix Althaeae)	0.4 g;
Cammomile flowers (Flores Chamomillae)	0.3 g;
Horstail herb (Herba Equiseti)	0.5 g;
Walnut leaves (Folia Jugladis)	0.4 g;
Yarrow herb (Herba Millefolii)	0.4 g;
Oak bark (Cortex Quercus)	0.2 g;
Dandelion herb (Herba Taraxaci)	0.4 g;

*Excipients*: Ethanol 19% (V/V), purified water.

Name and address of the manufacturer: Bionorica SE, Kerschensteinerstrasse, 11–15, 92,318, Neumarkt, Germany.

The drug is registered in Ukraine and available over-the-counter (OTC). Therefore, formulation, manufacturing process, packaging and labelling of the drug comply with GMP and current national requirements of Ukraine. A detailed description of all aspects of the quality and safety of BNO 1030 drops is part of the corresponding product characteristics.

In Ukraine, approved indications for use are the treatment of upper respiratory tract diseases (tonsillitis, pharyngitis, laryngitis) and the prevention of complications and recurrences in viral respiratory infections.

ENT practitioners with experience of at least 5 years were involved in the study.

### Outcome measures

All data were evaluated by a physician at the beginning of the study and on six follow-up visits within 12 months (Table 1).

On Day 1, 10 and after 6 months, the physician evaluated the symptoms included in the scale of local manifestations of tonsillitis: hyperaemia of the posterior pharyngeal wall, hyperaemia, swelling and the presence of plaque on the tonsils. All symptoms were evaluated according to a 4-point scale (0 — no symptoms, 1 — mild, 2 — moderate, 3 — severe/pronounced). In addition, at each control point (Day 1, 5, 10, 3 months, 6 months, 12 months) the patients, either individually or with the help of parents, evaluated the general condition using a ten-point visual-analogue scale. The physician recorded the number of recurrences on the 3rd, 6th and 12th month of follow-up and compared with their predicted number according to the created additive model of recurrence of tonsillitis.

The primary criterion for the efficacy was a reduced symptom severity of tonsillitis to 1 point or less. Secondary outcome measures: a reduced symptom severity on Day 10 and after 6 months compared to Visit 1; the patient self-assessment of the quality of life at each control point; the duration and number of tonsillitis recurrences during the year preceding the inclusion of patients in the study and within the year of follow-up.

### Sample size

A clinical study has been developed to obtain a reliable description of the in vivo efficacy of active (additional) use of BNO 1030 compared to the standard treatment only. Depending on findings, several trial descriptive and statistical evaluations were performed so that a biometric estimate of the sample size is not required. However, in order to guarantee a sufficient sample size for data analysis, the sample size  $N = 250$  was chosen. Patients were sorted in a 1: 1.

### Randomization

The clinical part of the randomized study is open, without a blinding procedure. Subjects are randomized to one of two possible treatments according to the basic randomization list. Randomization was performed using the software [StatSoft is a random number generator].

**Table 1** Schedule of assessments

Day 1	Day 5	Day 10	Day 28	3 month	6 month	6 month 28 days	12 month
<i>Treatment group</i>							
Imupret (dosage acute phase)		Imupret (dosage subacute phase)				Imupret (dosage subacute phase)	
Reference treatment							
<i>Control group</i>							
Reference treatment							

day 1: Screening, randomization, prescription of treatment

day 5 ± 1: Evaluation of treatment efficacy, end of dosage acute phase (Imupret)

day 10 ± 1: Evaluation of treatment efficacy

day 28 ± 1: Evaluation of treatment efficacy, end of dosage subacute phase (Imupret)

3 month: Evaluation of treatment efficacy

6 month: Evaluation of treatment efficacy, prescription of treatment (Imupret, dosage subacute phase)

6 month ± 28 days: Evaluation of treatment efficacy, end of dosage subacute phase (Imupret)

12 month: Evaluation of treatment efficacy

Randomization was performed for each patient who signed an informed consent.

### Statistical methods

In order to analyse homogeneity of groups, descriptive statistics methods were used for the description of the baseline condition of the treatment and control group (for quantitative parameters – *n*, mean arithmetic, median, standard deviation, minimum and maximum values; for qualitative parameters – incidence and share as %). Verification of normality of data distribution in groups was performed for quantitative parameters using Shapiro-Wilk test. If the data in groups showed normal distribution according to certain parameters, the groups were compared by these parameters via Student's test for independent samples. Otherwise (if the data distribution was different from normal), comparison of groups was performed according to Mann-Whitney test. For categorial parameters, the groups were compared using Pearson's chi-squared test or Fisher's exact test.

For analysis of efficacy, descriptive statistics parameters were calculated in each group (*n*, mean arithmetic, median, standard deviation, minimum and maximum values) for all visits in accordance with patients' examination scheme.

Analysis of dynamics of the analysed parameters in each group was performed via two-way analysis of variance (ANOVA) according to the following scheme: "Visit" factor is fixed (levels: visit 1 ... visit *n*); "Subjects" factor is random.

Results of the subsequent visits were compared against the data of visit 1 via contrast analysis using simple contrasts.

Comparison between groups in dynamics of tested parameters was performed by differences  $dTi = (TVisit\ n - TVisit\ 1)$  of assessed parameters using Mann-Whitney test.

The level of confidence for Shapiro-Wilk test was accepted equal to 0.01, and for the rest of the criteria it was accepted equal to 0.05.

Prediction of the number of recurrences was carried out according to the additive model. The general view of the additive model is as follows:  $Y = T + S + E$ . This model assumes that each level of the time series can be represented as the sum of the trend (*T*), seasonal (*S*) and random (*E*) components. The predicted *Ft* value of the time series level in the additive model is the sum of the trend and seasonal components.

The analysis was performed in software environment IBM SPSS 22.0.

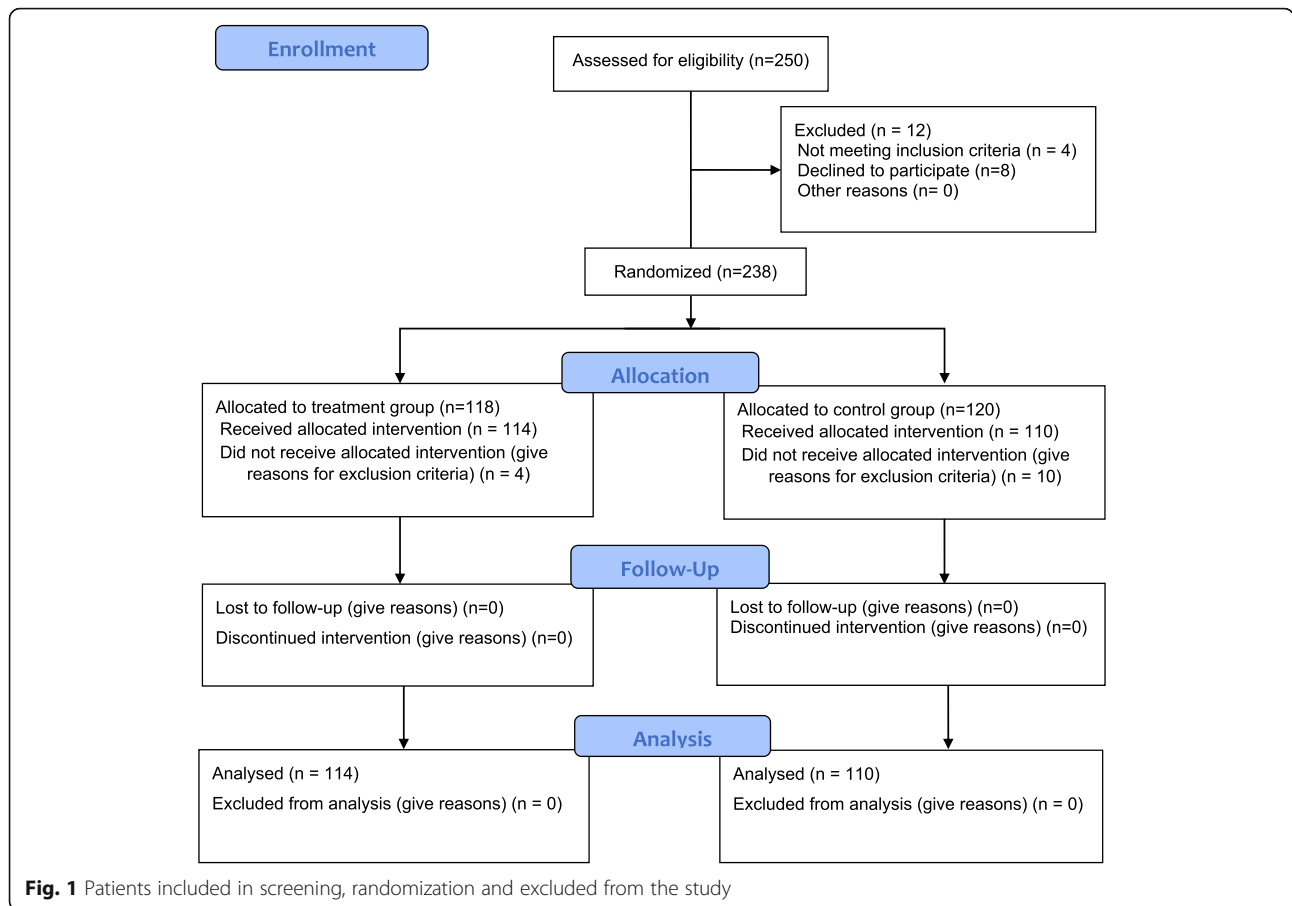
## Results

### Study sample

Two hundred fifty patients aged 6–18 years were enrolled in the study (Fig. 1).

Of the 250 patients enrolled, 12 (4.8%) were not included in the study. The reason was non-compliance with the study inclusion criteria: age non-compliance (*n* = 4) and the unwillingness of a patient and/or his/her parents to comply with the protocol requirements (*n* = 8). The remaining 238 patients were randomized to either the control group (*n* = 120) or the treatment group (*n* = 118). On Day 2, 14 patients (11.7%) were excluded from the study. The reason was the presence of exclusion criteria (the prescription of systemic antibiotic therapy) (*n* = 10) from the control group and (*n* = 4) from the treatment group. Thus, from June 2017 to March 2018, 224 (94.1%) out of the 238 randomized patients (*n* = 114 in the treatment group) and (*n* = 110 in the control group) completed the study and were analysed.

Table 2 presents sex distribution of patients in both groups: in the treatment group, 52 (45.6%) out of 114 patients were boys and 62 (54.4%) were girls; in the control group, 54 (49.1%) out of 110 patients were boys and 56 (50.9%) were girls.



In general, there were slightly more girls than boys (52.6% vs. 47.3%) among patients enrolled in the study. Table 3 presents age distribution of patients in both groups: the average age of the patients was 9.16 years:  $8.67 \pm 3.219$  in the treatment group and  $9.66 \pm 3.296$  in the control group.

In general, there were no significant differences in demographic characteristics among patients from the treatment and control groups at the baseline (Day 1) ( $p > 0.05$ ).

Table 4 presents a comparative description of the treatment and control groups according to a 4-point assessment of the symptom severity included in the scale of local manifestations of tonsillitis and 10-point patient

self-assessment of the general condition (VAS) before treatment.

Significant differences in the main local manifestations of tonsillitis: hyperaemia of the posterior pharyngeal wall, hyperaemia, swelling and the presence of plaque on palatine tonsils, as well as patient self-assessment of the severity of the general condition between patients of the treatment and control groups at the baseline (Day 1) were not observed ( $p > 0.05$ ).

**Outcomes and estimation**

Typical, objectively determined clinical symptoms of tonsillitis are hyperaemia of the posterior pharyngeal wall, hyperaemia, swelling and the presence of plaque on the tonsils. Figure 2 shows the dynamics of the severity of the principal symptoms in points, evaluated by a physician using a 4-point scale in patients with acute tonsillitis. When the physician assessed the symptom of hyperaemia of the posterior pharyngeal wall, both groups showed comparable severity parameters on Day 1: 2.88 points in the treatment group and 2.85 in the control group. In the course of treatment, regression of hyperaemia of the posterior wall was observed in patients of both groups on Day 10: 2.88 to 0.44 points in

**Table 2** Allocation of patients according to sex

Parameter	Group	Statistical indicators		
		n	boys	girls
Gender	Treatment	114	52 (45.6%)	62 (54.4%)
	Control	110	54 (49.1%)	56 (50.9%)
Total		224	106 (47.3%)	118 (52.6%)

**Table 3** Allocation of patients according to age

Parameter	Group	Statistical indicators			
		n	M ± SD	p-value	Homogeneity of the groups <sup>a</sup>
Age, years	Treatment	114	8.67 ± 3.219	0.071	Homogeneous
	Control	110	9.66 ± 3.296		

<sup>a</sup>The conclusion is drawn at the significance level of 0.05

the treatment group and 2.85 to 0.57 in the control group. Further follow-up of patients in the long-term period (after 6 months) showed a further regression of hyperaemia of the posterior pharyngeal wall to 0.29 points in patients from the treatment group. In the control group, this indicator remained almost unchanged compared to Day 10 and amounted to 0.85 (Fig. 2).

Table 5 presents on-treatment comparative assessment of the severity of the principal symptoms evaluated by the physician in patients with acute tonsillitis using the Mann-Whitney test. A comparison of the symptom severity of “hyperaemia of the posterior pharyngeal wall” between the groups shows insignificant differences between the groups on Day 1 and Day 10 ( $p > 0.05$ ), and significant differences on the 6th month ( $p < 0.05$ ).

When the physician assessed the symptom of hyperaemia of the tonsils, both groups showed comparable severity parameters on Day 1: 2.81 points in the treatment group and 2.74 in the control group (Fig. 2). In the course of treatment, regression of hyperaemia of the tonsils was observed in patients of both groups on Day 10: 2.74 to 0.45 points in the treatment group and 2.74 to 0.39 in the control group. In the long-term follow-up period in the 6th month, there is a tendency to further regression of hyperaemia of the tonsils in patients from the treatment group up to 0.17 points. In the control group, there is a tendency to increased severity of hyperaemia of the tonsils compared to Day 10: from 0.39 to 0.72 points. Table 5 shows a comparative assessment of the regression of the hyperaemia of the tonsils between the groups using the Mann-Whitney test.

Insignificant differences between the groups on Day 1 and Day 10 ( $p > 0.05$ ) and significant differences on the 6th month ( $p < 0.05$ ) were recorded.

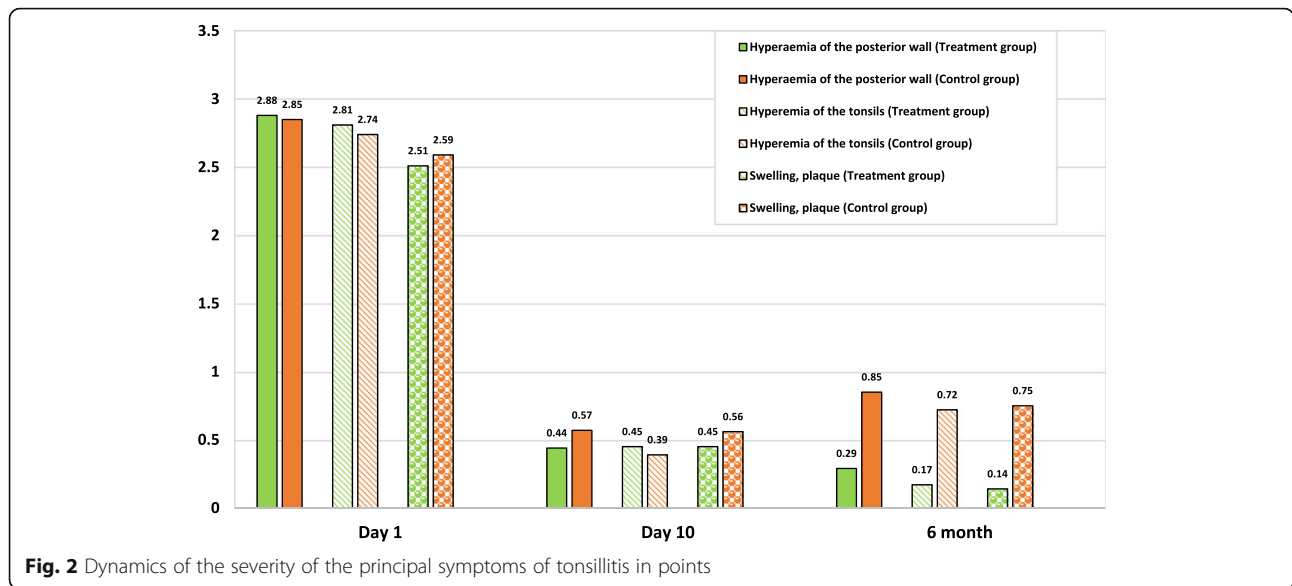
When the physician assessed the symptom of swelling and plaque on the tonsils, both groups with acute tonsillitis showed comparable severity parameters on Day 1: 2.51 points in the treatment group and 2.59 in the control group (Fig. 2). In the course of treatment, the regression of swelling and plaque on the tonsils was observed in patients of both groups on Day 10: 2.51 to 0.45 points in the treatment group and 2.59 to 0.56 in the control group. On Month 6, there is a further regression of swelling/plaque on the tonsils up to 0.14 points in patients from the treatment group. In the control group on the 6th month, there is no regression of this symptom: 0.75 compared to 0.56 on Day 10. There is a tendency to a more pronounced regression of swelling/plaque on the tonsils in the treatment group. In on-treatment comparative assessment of the severity of swelling and plaque on the tonsils using the Mann-Whitney test, insignificant differences between the groups on Day 1 and Day 10 ( $p < 0.05$ ) and significant differences on Month 6 ( $p > 0.05$ ) are shown (Table 5).

Thus, the severity assessment of the principal symptoms in points assessed by the physician according to a 4-point scale in patients with tonsillitis showed the absence of significant differences between the groups in the “acute follow-up period” (Day 1 and Day 10) and the presence of significant differences in the long-term follow-up period (Month 6).

**Table 4** The group analysis according to the local symptom severity and self- assessment value before treatment

Parameter	Group	Statistical indicators			
		n	M ± SD	p-value	Homogeneity of the groups <sup>a</sup>
Hyperaemia of the posterior wall	Treatment	114	2.88 ± 0.926	$P = 0.719$	Homogeneous
	Control	110	2.85 ± 0.877		
Hyperaemia of the tonsils	Treatment	114	2.81 ± 1.033	$P = 0.497$	Homogeneous
	Control	110	2.74 ± 0.957		
Swelling, plaque	Treatment	114	2.51 ± 1.044	$P = 0.537$	Homogeneous
	Control	110	2.59 ± 0.948		
Patient’s self- assessment, VAS	Treatment	114	6.30 ± 1.882	$P = 0.069$	Homogeneous
	Control	110	5.94 ± 1.616		

<sup>a</sup>The conclusion is drawn at the significance level of 0.05



Acute tonsillitis is a disease that is always accompanied by general health problems. According to the study design, the patients, either individually or with the help of parents, evaluated the general condition using a ten-point visual-analogue scale. Figure 3 shows the dynamics of self-assessment in groups.

As can be seen from the figure, self-assessment of the general well-being during the period of “acute clinical manifestations” in the treatment group showed an improvement in this indicator from 6.3 points on Day 1 to

3.02 on Day 5 and to 1.66 points on Day 10 of treatment. The control group showed an improvement in overall health from 5.94 points on Day 1 to 3.65 points on Day 5 and up to 2.72 points on Day 10. But, despite the pronounced dynamics of the improved general well-being, the symptom severity was more than 1 point. On Day 38, the patient self-assessment in the treatment group was 0.34, in the control group — 0.88 point.

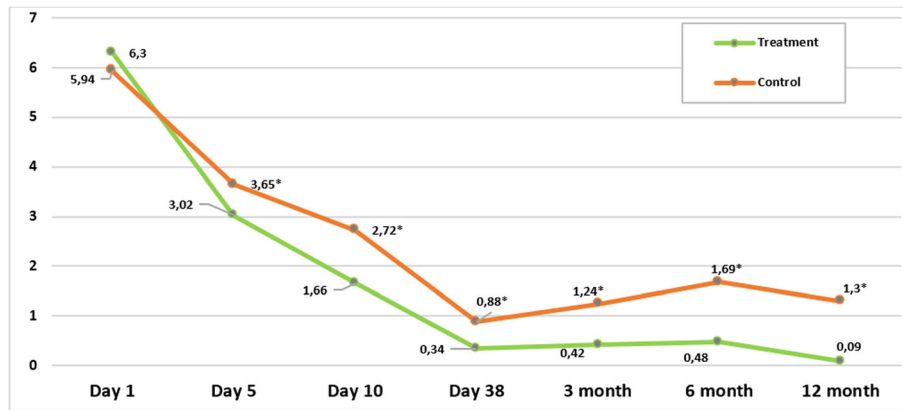
In the long-term follow-up period (3, 6, 12 month), self-assessment of general well-being in patients of the

**Table 5** The comparison of the groups according to the dynamics of the symptom severity using the Mann – Whitney U-test

Parameter	Visit	Mann–Whitney U-test	Wilcoxon W	Z-statistics	P-value (two-sided)	Significant differences <sup>a</sup>
Hyperaemia of the posterior wall	Day 1	7116.000	14,256.000	−0.047	0.962	Non-significant
	Day 10	6345.500	13,485.500	−1.276	0.202	Non-significant
	6 month	4619.000	11,759.000	−5.110	0.000	Significant
Hyperaemia of the tonsils	Day 1	6933.000	14,193.000	−0.404	0.686	Non-significant
	Day 10	6785.500	13,688.500	−0.374	0.708	Non-significant
	6 month	4509.000	11,530.000	−5.596	0.000	Significant
Swelling, plaque	Day 1	6845.000	13,985.000	−0.575	0.565	Non-significant
	Day 10	6116.000	13,256.000	−1.779	0.075	Non-significant
	6 month	4129.500	11,150.500	−6.485	0.000	Significant
Self-assessment of the patient	Day 1	6086.500	13,346.500	−2.011	0.044	Non-significant
	Day 5	5942.000	13,082.000	−2.277	0.023	Significant
	Day 10	5023.000	12,163.000	−3.908	0.000	Significant
	Day 38	5468.500	12,608.500	−3.632	0.000	Significant
	3 month	5124.500	12,264.500	−4.366	0.000	Significant
	6 month	4072.000	11,212.000	−6.229	0.000	Significant
	12 month	3945.000	11,085.000	−7.528	0.000	Significant

<sup>a</sup>The conclusion is drawn at the significance level of 0.05





\* $P \leq 0.05$

**Fig. 3** Dynamics of the indicator “Patient self-assessment”

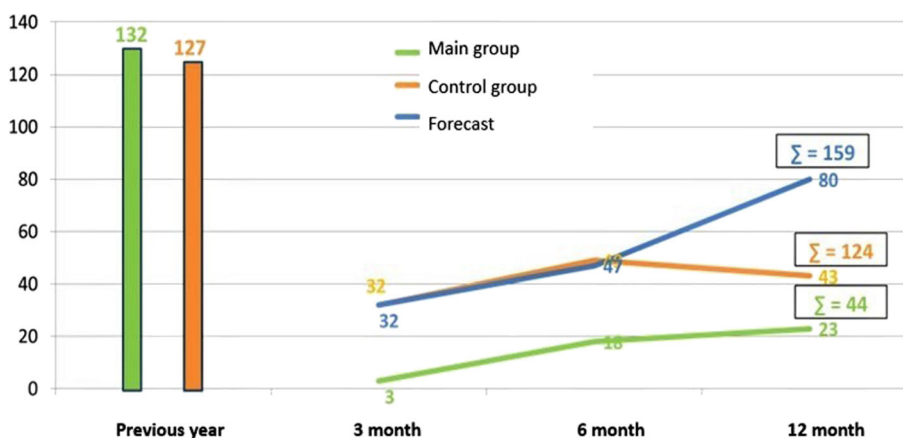
treatment group retained with an intensity of less than 1 point: 0.42, 0.48 and 0.09 points, respectively. In patients of the control group in the long-term follow-up period, a deterioration in indicators was observed: according to self-assessment, general well-being was assessed more than 1 point: 3 month — 1.24 points, 6 month — 1.69 and 12 month — 1.30 points. Comparison of the dynamics of improved general well-being according to patient self-assessment indicators using the Mann-Whitney test showed significant differences between the groups starting from Day 5 of treatment ( $p < 0.05$ ) (Table 5).

Tonsillitis is a disease known to have a tendency to recur. We have evaluated the recurrence rate of tonsillitis depending on the group. Within the year preceding the inclusion of patients in the study, 259 recurrences were recorded in 224 patients included in the study: 132 recurrences in 114 patients of the treatment group and 127 recurrences in 110 patients of the control group (Fig. 4).

When comparing the number of recurrences in the year preceding the study using the Pearson’s chi-square test, insignificant differences between the groups are shown ( $p > 0.05$ ) (Table 6).

Over the year of follow-up, a decrease in the number of recurrences was noted: 168 recurrence in 224 patients were recorded. However, in the control group, the number of recurrences remained almost unchanged: 127 (100%) cases in the previous year and 124 (97.63% of the previous year) cases in the current year of follow-up. In the treatment group, a significant decrease in the number of recurrences was recorded from 132 (100%) to 44 (33.44%), i. e. a decrease by 66.56% was noted (Fig. 4). The differences between the groups are significant ( $p < 0.05$ ) (Table 6).

At the start of the study, based on the received anamnestic data, an additive model for predicting the number of recurrences in patients included in the study was created. According to this model, 32 recurrences



**Fig. 4** The number of recurrences in groups

**Table 6** Comparison between groups according to the number of recurrences using Pearson's chi-square test

Parameter	3 mo	6 mo	12 mo	Current year	Previous year
Chi Square	25.970	30.164	7.778	25.436	0.068
P-value*	$p < 0.001$	$p < 0.001$	0.0053	$p < 0.001$	0.7950
Differences	Significant	Significant	Significant	Significant	Non-significant

\*The conclusion is drawn at the significance level of 0.05 and  $df = 1$

within the first 3 months, 47 recurrences after 6 months, and 80 cases of recurrences after 12 months were predicted in each group (Fig. 4). We analysed the number of recurrences within the year of follow-up in each group depending on the timing of their occurrence. In the first 3 months of follow-up, 3 (2.24%) recurrences were recorded in the treatment group and 32 (25.28%) cases in the control group. After 6 months, 18 (13.68%) cases in the treatment group and 49 (38.71%) cases in the control group, after 12 months 23 (17.48%) cases in the treatment group and 43 (33.97%) cases in the control group (Fig. 4). After 3 and 6 months, the actual and predicted number of recurrences in the control group almost coincided. In the treatment group, almost a 10-fold decrease in the number of recurrences after 3 months and a 2.7-fold decrease after 6 months of follow-up was noted. After 12 months of follow-up, the number of recurrences in the control group was 1.8-fold less and in the treatment group – 3.4-fold less than the predicted one. According to the prognostic model created, the main number of tonsillitis recurrences was predicted in the first 6 months of follow-up. When assessing, the recurrence rate in the control group coincides with the predicted one. In turn, most recurrences in the treatment group were noted in the second half of the year of the follow-up, i. e. a disease shifted to a later date. When comparing the recurrence rate using the Pearson's chi-squared test, significant differences between the groups ( $p < 0.05$ ) are shown at all checkpoints (Table 6).

We have studied the recurrence rate in groups depending on age.

It is important to note that the majority of recurrences were observed in children under the age of 12 years. In the year preceding the inclusion of patients in the study, 72% of recurrence cases in the treatment group and 75% in the control group (differences between the groups are insignificant ( $p > 0.05$ )) were in this age category. When observing patients within a year after inclusion in the study, almost the same number of recurrences was recorded in the control group compared to the previous year: 74.26% versus 75% (differences between groups are insignificant ( $p > 0.05$ )). Patients of the treatment group showed a significant decrease in the number of recurrences compared to the previous year and compared to the control group – 22.8% (differences between the groups are significant at all checkpoints ( $p < 0.05$ )).

### Safety and tolerability

An analysis of the tolerability assessment findings showed that the treatment was well tolerated or very well tolerated in all cases. No on-treatment side effects were observed in any patient.

### Discussion

According to present view, tonsillitis should be understood as inflammation of the tonsils beyond their physiological norm and, therefore, with additional clinical symptoms. In the present study, the main criterion for the efficacy of tonsillitis treatment was a reduced symptom severity of tonsillitis to 1 point or less. This indicates a “return” of the inflammatory process in the tonsils to the physiological norm, since there are no clinical manifestations of tonsillitis. Evaluation of the treatment results in the “acute phase” (Day 10) showed a reduced severity of local symptoms, such as hyperaemia of the posterior pharyngeal wall, hyperaemia, swelling and plaque on the tonsils in patients up to 1 point or less.

Recurrent tonsillitis is characterized as the reoccurrence of acute tonsillitis at a time interval characterized by an asymptomatic course (without complaints) or with minor symptoms. Many researchers have suggested that recurrent episodes of acute tonsillitis, i. e. the repeated development of the inflammatory process beyond the “physiological” norm in the tonsils is associated with the initial state of the tonsils [2, 5]. An important factor in the prevention of recurrent tonsillitis is to maintain control of inflammation within the “physiological” norm, which under clinical conditions is manifested by the absence or minimal manifestations of local objectively determined symptoms, especially in the long-term intercurrent period. The present study demonstrated that the use of a phytotherapeutic drug in addition to standard therapy has a proven long-term therapeutic effect. Compared to the control group, patients in the BNO 1030 group showed significantly lower indicators of the severity of hyperaemia of the posterior pharyngeal wall, hyperaemia, swelling and the presence of plaque on the tonsils at each control point within the year of follow-up. This can be explained by the presence of an anti-inflammatory effect in the studied drug and an increase in the intracellular elimination of pathogens.

Tonsillitis is a disease accompanied by general health problems. This is due to the fact that the tonsils are one of the main components of the peripheral immune system, and their inflammation beyond the “physiological” norm is always accompanied by a pronounced systemic symptoms. The study showed significantly better dynamics of the general condition of the patients from the study group according to the results of patient self-assessment starting from the fifth day of treatment. However, on Day 10, despite a significant difference in self-assessment, the symptom severity in both groups was more than 1 point. In addition to the standard therapy, the use of a phytotherapeutic drug provided a long-term therapeutic effect. Starting from Day 28 and throughout the follow-up period: 3 months, 6 months and 12 months, the severity of clinical manifestations in patients of the treatment group was less than one point. The severity of clinical manifestations in patients from the control group at all control points was more than 1 point; and during the long-term period, indicators worsened, especially pronounced after a 6-month follow-up.

An important conclusion of the study is the understanding that a pronounced improvement in clinical symptoms on Day 10 is not a sign of a final recovery. The symptom severity according to self-assessment in both groups was more than 1 point, which indicates the persistence of inflammation in the tonsils beyond the “physiological” norm. In this regard, patients with acute tonsillitis need a longer, up to 18 days, treatment with the use of BNO 1030. The presented conclusions confirm the need for effects not only on inflammation as the main clinical symptom, but also on the immunological pathogenetic mechanisms of its formation. The results are confirmed by previously published data on the immunological efficacy of BNO 1030 *in vitro* and *in vivo* [14–16].

According to the design, patients with Paradise criteria were not included in our study, i. e. the issue of tonsillectomy was not considered [6, 7]. Thus, it was possible to monitor patients for a long time and determine the clinical efficacy of the studied treatment regimens in relation to the recurrence rate of tonsillitis. In accordance with the created model for predicting recurrence, an increase in the number of tonsillitis recurrences was predicted in both groups within the year of follow-up. The actual recurrence rate in the control group almost coincides with both the predicted rate and the rate of the year preceding the inclusion of patients in the study. Within the year of follow-up, patients from the BNO 1030 group showed a significant decrease (by 66.56%) in the recurrence rate of tonsillitis.

An important study objective was to determine the duration of the clinical effect of BNO 1030 to prevent

recurrences of tonsillitis. Since recurrences of tonsillitis are associated with the initial state of the tonsils, their high rate in patients from the control group has a clear justification: significantly higher indicators for assessing the severity of both local and general clinical symptoms, as well as their deterioration after a 6-month follow-up. Thus, an important conclusion of the study relates to the necessity and feasibility of a repeated, after 6 months, course of treatment using BNO 1030 for the prevention of recurrences of tonsillitis in the long-term follow-up. An important result of the study is that a significant decrease in the recurrence rate of tonsillitis in patients from the BNO 1030 group was noted at all control points, both in the first and second half of the year of the follow-up.

The obtained results can be associated only with the effects of the herbal medicinal product, since the differences between the treatment and control groups are not significant when comparing the severity of clinical manifestations, the number of recurrences within the year preceding the study and the prognosis.

The obtained results are consistent with data previously obtained by other researchers (Vavilova V, Abramov-Sommariva D, Steindl H, Wonnemann M, Ryzhova E, Rusova T, Lebedenko A, Kolchenko I: Effectiveness and tolerability of Tonsilgon® N in the treatment of recurrent upper respiratory tract infections in children: a non-interventional study in Russia, submitted) [19]. Their conclusion suggests that BNO 1030 (Tonsilgon® N, Imupret®) is effective in treating acute viral respiratory infections and recurrent tonsillitis in paediatric patients. Our results are also consistent with data from Germany, which demonstrated the efficacy and safety of the drug in more than 1100 children with recurrent acute upper respiratory tract infections [20].

As is known, recurrence is associated with the danger of developing tonsillogenic comorbid diseases. The highest rate of such diseases is recorded in children aged 5–12 years, therefore, it is especially important to study the recurrence rate of tonsillitis in this age group [4].

In the year preceding the study, more than 70% of recurrences were observed between the ages of 6 and 12 years in both groups of patients, and the differences in the number of recurrences between the groups were not significant. Within the year of follow-up, recurrences in both groups were also observed mainly at the age of 6 to 12 years. However, the number of recurrences in the BNO 1030 group decreased 3.25-fold compared to the control group (from 74.26% to 22.8%).

An analysis of recurrences in patients under the age of 12 years showed a significantly greater number of tonsillitis recurrences in the first 6 months of follow-up in patients from the control group. The number of recurrences in the treatment group in the first and second half of the year of follow-up is not different.

Thus, an important conclusion of the study concerns the necessity and feasibility of treatment of acute tonsillitis with the use of BNO 1030 within 28 days, as well as a repeated course to prevent recurrence in the long-term follow-up, especially in patients under the age of 12 years.

As is known, patients with recurrent tonsillitis have very high expectations of the additional prescription of antibiotics, which is one of the main reasons for their unreasonable prescription [9, 10]. The significant reduction in tonsillitis recurrences in patients receiving Imupret shown in our study is an important conclusion of the study and an argument for reducing the desire of patients and physicians to use antibiotics.

The efficacy of BNO 1030, shown in this study, is an indisputable fact that there are real possibilities for effective non-surgical treatment of patients with recurrent tonsillitis and without unconditioned indication for tonsillectomy (Paradise criteria) [2, 7].

The obtained results confirm the results of earlier studies in patients with recurrent respiratory tract infections (Vavilova V, Abramov-Sommariva D, Steindl H, Wonnemann M, Ryzhova E, Rusova T, Lebedenko A, Kolchenko I: Effectiveness and tolerability of Tonsilgon® N in the treatment of recurrent upper respiratory tract infections in children: a non-interventional study in Russia, submitted) [19]. However, its strength is the diagnosis of tonsillitis established according to present criteria. The groups of randomized patients, homogeneous in terms of diagnosis and clinical manifestations, made it possible to draw reasonable conclusions regarding the evaluation of treatment results. The number of patients with significantly better results is higher in the treatment group compared to the control one.

The design involved a comparative study that did not allow for a placebo control. However, the comparison was carried out with treatment according to clinical recommendations, which provide for the mandatory prescription of only general and topical NSAIDs [2, 6]. Consequently, all the differences in treatment results can be attributed to the clinical effects of BNO 1030.

## Conclusions

It was shown that the additional use of the phytonering extract BNO 1030 (Imupret®) contributes to a significant reduction in clinical symptoms in the early and long-term follow-up and reduces the recurrence rate of recurrent tonsillitis. The inclusion of the drug in the treatment regimen is especially recommended for patients with tonsillitis under the age of 12 years.

The prospect of further research is to study the anti-recurrent drug efficacy in the long-term follow-up of patients with recurrent tonsillitis.

## Abbreviations

AT: Acute tonsillitis; RT: Recurrent tonsillitis; NSAIDs: Non-steroidal anti-inflammatory drugs; GCP: Good clinical practice; VAS: Visual analogue scale

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## Authors' contributions

VP, IK - participated in the protocol and documentation development of the study, solving of organizational issues, coordination with other investigators and manuscript writing. All the authors participated in recruiting, treating patients and registering study data. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. All data generated or analysed during this study are included in this published article.

## Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Ivano-Frankivsk Regional Clinical Hospital on the 24-th of May 2017.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests in this section.

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