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Effectiveness of an add-on treatment with the homeopathic medication SilAtro-5-90 in recurrent tonsillitis: An international, pragmatic, randomized, controlled clinical trial

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ABSTRACT

Objective: To investigate the effectiveness and safety of the homeopathic product SilAtro-5-90 in recurrent tonsillitis.
Methods: In this international, pragmatic, controlled clinical trial, 256 patients (6–60 years) with moderate recurrent tonsillitis were randomized to receive either SilAtro-5-90 in addition to standard symptomatic treatment, or to receive standard treatment only. The primary outcome was the mean time period between consecutive acute throat infections (ATI) within 1 year (analyzed via repeated events analysis).
Results: During the evaluation year, the risk of getting an ATI was significantly lower (hazard ratio: 0.45, proportional means model, $p = 0.0002$, *ITT*) with SilAtro-5-90 compared to control. Tonsillitis-specific symptoms were significantly reduced ($p < 0.0001$, *ITT*) and the need of antibiotics to treat acute throat infections ($p = 0.0008$; *ITT*) decreased. 3 non-serious adverse drug reactions were reported for SilAtro-5-90.
Conclusions: An integrative treatment approach where SilAtro-5-90 is given alongside mainstream symptomatic treatment may bring therapeutic benefit to patients suffering from recurrent tonsillitis.
Trial registration: ISRCTN registry: Registration number ISRCTN19016626, registered 23 January 2013.

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1. Introduction

Tonsillitis is a common condition, particularly in childhood, which is caused mainly by a viral or by a bacterial acute throat infection (ATI) and which is typically associated with sore throat [1]. Diagnosis of tonsillitis is mostly clinical and it is difficult to determine whether the cause is viral or bacterial [1–3]. Recurrent tonsillitis has been defined as the repeated occurrence of acute tonsillitis episodes followed by periods with only very few, or without any, symptoms [4]. Due to the frequent episodes of sore throat, fever, general illness, sleepless nights, impaired daily functioning and absence from school or work associated with it, recurrent tonsillitis is recognized to have a significant impact on families' daily life and healthcare costs [5–7].

Surgical removal of the tonsils (tonsillectomy) is a widely applied procedure in recurrent tonsillitis [5]. Whereas the "Paradise criteria" with 7 episodes of ATIs in 1 year, 5 episodes each year in 2 consecutive years, or 3 episodes each year in 3 consecutive years were considered as recommendation for tonsillectomy for a long time [3,8,9], the most recent guidelines merely advise to focus on the number of ATIs during the last 12 months: tonsillectomy is a therapeutic option when a patient has had 6 or more ATIs during this period and not at all, if a patient has had less than 3 ATIs. In case patient had between 3 and 5 ATIs, tonsillectomy may be an option if patient develops further ATIs during the next 6 months thereby reaching the number of 6 ATIs [4].

In recent years, however, the clinical efficacy of tonsillectomy has been under debate. Studies have shown that tonsillectomy can reduce the number of ATIs, but the effect is modest and mainly observed in children who are more severely affected. Simultaneously, the risks of the procedure have to be considered, as tonsillectomy is associated with a small but significant risk of primary and secondary hemorrhage, and in addition it is particularly painful for adults [2,5]. Moreover, it needs to be considered that even tonsillectomized patients can still suffer from sore throat, due to inflammation of other pharyngeal lymphoid tissues [5,10]. It is concluded that more randomized controlled trials (RCTs), with adequate long-term follow-up, are necessary to clarify the benefits of tonsillectomy versus non-surgical treatment in patients with recurrent tonsillitis [10].

Although antibiotics are still commonly prescribed for acute and for recurrent throat infection, reducing unnecessary use of antibiotics has become a priority to cope with the problem of antibiotic resistance. It has been shown that even if antibiotics reduce the incidence of tonsillitis-associated complications like rheumatic fever and acute glomerulonephritis, routine aggressive antibiotic use in resource-rich countries, where these diseases are rare, is not justified [2,11]. In this context, it has recently been reported that there is insufficient evidence for the effectiveness of antibiotics for preventing recurrent sore throat [12].

In the light of these discussions, the use of complementary and alternative medicine (CAM) in the treatment of recurrent tonsillitis may be an interesting option. A survey among pediatricians and other healthcare professionals has lately revealed that "natural remedies" are, among other things, also recommended in the management of recurrent tonsillo-pharyngitis [13]. In this survey, homeopathy was reported as a supportive therapy for recurrent tonsillo-pharyngitis by 59% of the respondents, phytotherapy by 28% and vitamins/nutritional supplementation by 37%. Studies have shown that some homeopathic medicinal products or (Chinese) herbal preparations may reduce symptoms of acute tonsillitis or pharyngitis [14–17]. In a randomized, controlled, double-blind trial in children with recurrent tonsillitis, homeopathic treatment was shown to significantly reduce the number of acute tonsillitis episodes [18]. However, more research in the treatment of recurrent tonsillitis with homeopathy is needed.

SilAtro-5-90 is a complex homeopathic medicinal product that is sold over-the-counter in many European and non-European countries for recurrent tonsillitis. It is applied according to the principles of homeopathy, a medical system that was developed 200 years ago by Samuel Hahnemann, a German physician and pharmacist. Homeopathy is one of the most frequently used CAM therapies in children as well as in adults [19–22]. First clinical experiences with SilAtro-5-90 in recurrent (chronic) tonsillitis were reported in the 1950s [23]. The first clinical studies with SilAtro-5-90 were conducted in the 1990s [24–27]. Among the latter was a multicenter observational study in which 1368 patients with tonsillitis were treated for 2 weeks with SilAtro-5-90, after which 605 patients with recurrent tonsillitis continued to take SilAtro-5-90 for a period of 6 weeks [24]. After the 6-weeks' treatment period 79% of the patients no longer reported throat complaints. In another multicenter, randomized, controlled, open-label study in 143 children with recurrent tonsillitis, the effectiveness of SilAtro-5-90 in addition to standard treatment (experimental group) was compared to standard treatment only (control group). In this study children were observed for 18 months, during which those from the experimental group were treated with SilAtro-5-90 for 3 cycles of 2 months. It was shown that the general symptoms of recurrent tonsillitis such as fatigue, decreased appetite and changes in body temperature, were reduced to a much greater extent in the experimental group than in the control group. In addition, the patients treated with SilAtro-5-90 had a more pronounced decrease of tonsillitis-specific symptoms compared to the children receiving standard treatment only [28].

The aim of the present study was to further explore the effectiveness and safety of SilAtro-5-90 in patients suffering from moderate recurrent tonsillitis (more than 3 ATIs per year, or 2 ATIs for 2 consecutive years). Since patients often use homeopathic medications, such as SilAtro-5-90, alongside mainstream medicine [13,29,30], a pragmatic comparative study design was chosen. After recruitment into the study, for a period of 1 year, patients received either SilAtro-5-90 for 3 treatment periods of 8 weeks, in addition to standard symptomatic treatment, or standard symptomatic treatment only.

2. Materials and methods

2.1. Trial design

A pragmatic, randomized, international, multicenter, open-label, controlled clinical trial with 2 parallel groups was conducted. The study complied fully with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), ethical principles founded in the Declaration of Helsinki and all appropriate regulatory requirements. The study took place at 19 study centers (private practices or medical institutions) in 3 countries (5 centers in Germany, 6 centers in Spain, and 8 centers in Ukraine). The study protocol was approved by independent ethics committees in the respective countries: in Germany, on August 27, 2012 by the central ethics committee "Ethics Committee of the Bavarian State Medical Association"; in Spain, on November 16, 2012 by the central ethics committee "Ethics Committee of the Joined Foundation of the Catalonian Hospitals"; in Ukraine, between July 16, 2012 and April 01, 2013 by the local ethics committees of the "Vinnytsia Regional Clinical Hospital Named after M.I. Pirogov", "Vinnytsia Regional Children Clinical Hospital", "Poltava Regional Clinical Hospital Named after M.V. Sklifosofskyi", "Odessa National Medical University", "National Specialized Children Hospital OHMATDYT, Kyiv", "Kyiv City State Administration Children Clinical

Hospital #7", "Lugansk Regional Children Clinical Hospital" and "Medical Center LLC Inter, Lugansk".

2.2. Participants

Female and male patients in the age range 6–60 years, presenting with clinical signs and symptoms of recurrent tonsillitis were screened for participation in the study at the respective study centers. Patients who were willing to participate were allowed to do so if they were diagnosed with a moderate recurrent tonsillitis characterized by the presence of at least 3 of the 5 following symptoms: hyperemia of the anterior palatine arches; edema of the angle of junction of the anterior and posterior palatine arches; caseous purulent plug and/or purulent exudates in the tonsillar crypts; friable tonsils or indurated tonsils or scarred adhesions between the tonsils and the palatine arches; enlarged submandibular lymph nodes. Furthermore, they were required to have had at least 3 ATIs (WHO International Classification of Diseases 10th Revision (ICD-10) codes J02 and J03) within the past 12 months, or 2 ATIs during each of the last 2 years, documented in the patient file.

Patients were excluded from the study in cases of: presence of ATI at inclusion; presence of peri-tonsillar abscess or acute and chronic respiratory tract disease; obstruction in the pharynx due to enlargement of tonsils; severe comorbidity including previous malignant disease during the past 5 years prior to enrolment; history of intolerance to non-steroidal anti-inflammatory drugs (NSAIDs); history or presence of all kinds of serious streptococcal complications; previous surgery in the past 6 months or need for surgery of the nose, paranasal sinuses, adenoids and/or tonsils; presence of neurological and/or psychiatric diseases interfering with patient's assessments; treatment with systemic acting antibiotics, gluco-corticosteroids or immune-modulating medications during 4 weeks and with NSAIDs as well as with locally acting antibiotics, gluco-corticosteroids or immune-modulators during the week prior to inclusion; known or suspected hypersensitivity to the study medication; heavy smoking ($\geq$20 cigarettes per day) or known/suspicion of drug or alcohol addiction; women who wanted to become pregnant, were pregnant, breast-feeding or without adequate contraception; prior enrolment into this trial; participation in another clinical trial 3 months prior to enrolment; incapability of understanding the nature, meaning or consequences of the trial; patients in custody by judicial or official order; a patient who was a staff member of either the study center, the sponsor or the involved clinical research organizations; the investigator him-/herself or a close relative of the investigator.

Principal investigators at the respective centers obtained signed informed consent for each patient and/or from the patients' parents or legal representative before any study-specific activity was performed. The first patient was included in the study on January 25, 2013 and the last patient completed the study on April 15, 2015.

2.3. Interventions

During the study, a total of 9 study visits were scheduled, including a visit on day 1 (V1), day 11 (V2), week 8 (V3), week 16 (V4), week 24 (V5), week 32 (V6), week 40 (V7), week 48 (V8) and week 60 (V9). Additionally, patients were followed up by phone calls: call 1 (week 4), call 2 (week 12), call 3 (week 20), call 4 (week 28) and call 5 (week 36). The total study duration for each patient was therefore a maximum of 61 weeks, taking into account that a time window of $\pm$1 week was allowed for all visits except for V2, where a time window of $\pm$3 days was accepted.

SilAtro-5-90 was the investigational medicinal product, which was taken by patients in 3 treatment periods of 8 weeks each during a period of 1 year. The first treatment period was from V1 to V3, the second treatment was from V4 to V5 and the third and last treatment period was from V6 to V7. Subsequently, there were 3 follow-up periods, the first from V3 to V4, the second from V5 to V6 and the last follow-up period from V7 to V9. The dosage regimen of SilAtro-5-90 in all 3 treatment periods was 1 tablet 3 times per day for children (age 6 to <12 years) and 2 tablets 3 times per day for adolescents and adults (patients $\geq$12 years). SilAtro-5-90 (Tonsilotren®, Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG) is a complex homeopathic medicinal product containing 5 active ingredients. While Atropinum sulfuricum (D5) and Mercurius bijodatus (D8) are well proven to treat the acute phase of the tonsillitis with typical symptoms such as dark red throat and difficulties in swallowing and Hepar sulfuris (D3) is helpful in the treatment of impending suppuration, Kalium bichromicum (D4) is more used for subacute course of inflammation with thick yellowish discharges [31,32]. Silicea (D2) is a commonly used homeopathic remedy in the treatment of chronic diseases which stimulates the regeneration of tissues and thus improves healing in chronic processes [31].

Standard symptomatic treatment for recurrent tonsillitis was defined in the study as the use of local antiseptics and local anesthetics for the throat (solution, lozenges). Patients were not allowed to use this symptomatic medication within 3 days before a regular study visit. In cases that antibiotic, antipyretic or analgesic therapy for treatment of ATIs was required, the following rescue medications were the sole options to be used: Amoxicillin tablets (liquid formulation for children) or, in case of documented Penicillin hypersensitivity, another antibiotic drug, and/or Ibuprofen tablets (liquid formulation for children) could be given. Rescue medication did not constitute the investigational medicinal product. A group A beta-hemolytic streptococci (GABHS) test was mandatory before start of antibiotic treatment as rescue medication. Depending on the regulations of the national health system in the involved countries, standard symptomatic and rescue treatment was either distributed by the sites or purchased by and reimbursed to the patients. Costs for standard symptomatic and rescue treatment were reimbursed by the sponsor. The costs of SilAtro-5-90 treatment were calculated based on the whole 3-period treatment dosage regimen as followed during one 1 year in the study and over-the-counter average prices in Germany, Spain and Ukraine.

Patients were asked to document in a diary the following variables related to recurrent tonsillitis: presence of symptoms (sore throat and/or difficulties in swallowing, bad breath/taste in mouth (halitosis) and complaints of infection-related exhaustion like fatigue, weakness, sleeping disorders, decreased appetite, lack of concentration or decreased productivity), impact on daily activity and the use of concomitant medication not routinely taken otherwise. For this purpose patients received 1 diary for each study period (except for the last study period where 2 diaries were given to the patient). Patients were requested to fill in the diary once a week and to give the information retrospectively for each day of the past week.

2.4. Outcome measures

The primary outcome variable was the mean period of time between consecutive ATIs within a 1 year period. Patients were instructed to visit their investigator for an additional visit in case they felt sick with acute complaints in the upper respiratory tract. An ATI had to be diagnosed by the investigator and was defined as the ICD-10 codes J02 and J03. Relapses of ATI within 7 days after end of its treatment belonged to the originating ATI and did not count separately. The time between 2 separate ATIs was calculated using first day of infection as reference point and the evaluation

year was defined as the period between V3 (Week 8) and V9 (Week 60).

The following secondary outcome variables were prospectively defined. For effectiveness, the standardized number of days (days of one period during which the patients suffered from a given recurrent tonsillitis symptom as documented in the patient's diary and as described in the interventions section 2.3, divided by the number of days in that period) was assessed in each single treatment period and each follow-up period. Additionally, at each regular study visit the investigator evaluated the severity of each of the 7 recurrent tonsillitis symptoms (difficulties in swallowing/sore throat, halitosis, hyperemia of the anterior palatine arches, edema of the angle where the anterior and posterior palatine arches join each other, caseous purulent plug and/or purulent exudates in the tonsillar crypts, friable tonsils or indurated tonsils or scarred adhesions between the tonsils and the palatine arches, enlarged submandibular lymph nodes) using a 3-item rating scale (0 = absent, 1 = mild, 2 = severe). Moreover, the number of upper respiratory tract infections (URTIs), diagnosed by the investigator as the ICD-10 codes J00, J06, J09, J10, J11, within 1 year (period between V3 and V9), was examined. Furthermore, frequency of antibiotic and analgesic/analgesic consumption due to ATIs (for description see interventions section 2.3), as documented in the patient's records, and the effect of treatment on performance of normal daily activity in each single treatment and each follow-up period as reported in the patient's diary, were assessed. Finally, patients reported their quality of life using a 5-item rating scale (very good, good, moderate, poor, very poor) at each regular visit (except V2), and both patients and investigators evaluated treatment outcome according to Integrative Medicine Outcome Scale (IMOS) [33], using a 5-point verbal rating scale (complete recovery, major improvement, slight to moderate improvement, no change, deterioration) at each post-baseline study visit, except at V2. Secondary outcome regarding safety of study treatment was assessed by the incidence of adverse events (AEs). Tolerability of treatment was evaluated only in the intervention group treated with SilAtro-5-90.

2.5. Sample size

The sample size was evaluated in simulations: assuming Poisson distributed events with a mean of 4 ATIs per year, 100 patients per group were calculated to be sufficient to detect an approximately 4 weeks difference in mean infection free time according to 4 versus 3.1 events per year, with 80% power (0.05% alpha level) in recurrent event analyses using intensity model and robust covariance matrix estimation. Since patients without complete information over the planned study period could be expected, a 20% larger sample size (120 patients per group) was considered to be appropriate. Patients dropping out before start of the evaluation year (until/at V3) were replaced.

2.6. Randomization

Randomization was performed centrally and in blocks of 2, 4 and 6 using the randomization tool RANSCH (version 1.0 within the SAS program, version 9.2). The 3 types of blocks were randomly distributed within each study center and the investigators did not know the block sizes. According to the randomization program, 50% of the patients were allocated to the SilAtro-5-90 group and 50% to the control group. After verification of the eligibility criteria at the study centers and entry of these criteria into electronic case report forms, randomization to 1 of the 2 treatment options was done via the internet-based electronic data capture system which ensured a proper allocation concealment.

2.7. Statistical methods

Data were analyzed in an exploratory setting and hypotheses regarding superiority or non-inferiority of either treatment concept were therefore not formulated. The primary analysis was performed on the intention-to-treat (ITT) sample, including those patients who were randomized and started the treatment concept (i.e. patients of the test group, who took at least one dose of SilAtro-5-90, and all patients of the control group) and had at least 1 post-baseline therapeutic effectiveness evaluation. Additionally, the per-protocol (PP) sample was evaluated.

Safety variables were assessed for the safety population, which included all patients that were randomized. Primary outcome variable “duration” was reported as mean infection-free time between ATIs. Time to event data were analyzed within an extension of the Cox proportional hazards approach. A model for recurrent events was calculated using a robust sandwich covariance estimate (primary approach: proportional means model) to fit the data. Modelling of the number of ATI event occurrences accounting for patient-specific number of days under observation has in addition been applied (secondary approach: Poisson regression).

Treatment-related differences in fractions were calculated by means of Chi-square (χ^2)-tests (nominal or 2 categories). Mann-Whitney-U- (MWU) was applied in an exploratory manner to test differences between treatment groups regarding continuously scaled outcome variables. Missing values of the primary variable were addressed by Cox proportional hazard model as censored data; missing data handling for variables related to secondary endpoints included application of several techniques depending on type and frequency of missing data (e.g. last observation carried forward, imputation of group-wise means, complete case analysis). Influence of covariates as baseline frequency of events and age on the primary outcome variable was analyzed.

A rejection level of $p \leq 0.05$ was set for all statistical tests. As the nature of the current study was exploratory, no type I error level adjustment for multiple comparisons has been done.

3. Results

3.1. Study sample

As shown in Fig. 1, a total of 494 patients were screened for participation in the study. Amongst them, 256 patients were randomized either to the SilAtro-5-90 group (N = 132) or control group (N = 124). 3 patients (SilAtro-5-90: N = 1, control: N = 2) were lost to follow-up and 34 patients (SilAtro-5-90: N = 20, control: N = 14) prematurely discontinued from study participation (Fig. 1) due to non-compliance to study or drug intake (N = 19), consent withdrawal (N = 11), tonsillectomy/throat surgery (N = 2) or other causes (N = 2). Additional 27 patients (SilAtro-5-90: N = 13, control: N = 14) were withdrawn because of military operations in the Eastern part of the Ukraine which affected 2 study sites.

Table 1 shows the demographic and clinical characteristics of patients in both groups. Overall there were more women than men (61% vs 39%, respectively) that participated in the study. No relevant differences between any of the characteristics were observed between the 2 groups at baseline (V1). Compliance to treatment with SilAtro-5-90, calculated on the basis of investigational medicinal product accountability, was evaluated as very good: overall, more than 90% of patients complied with the intake of SilAtro-5-90 according to the study dosage regimen.

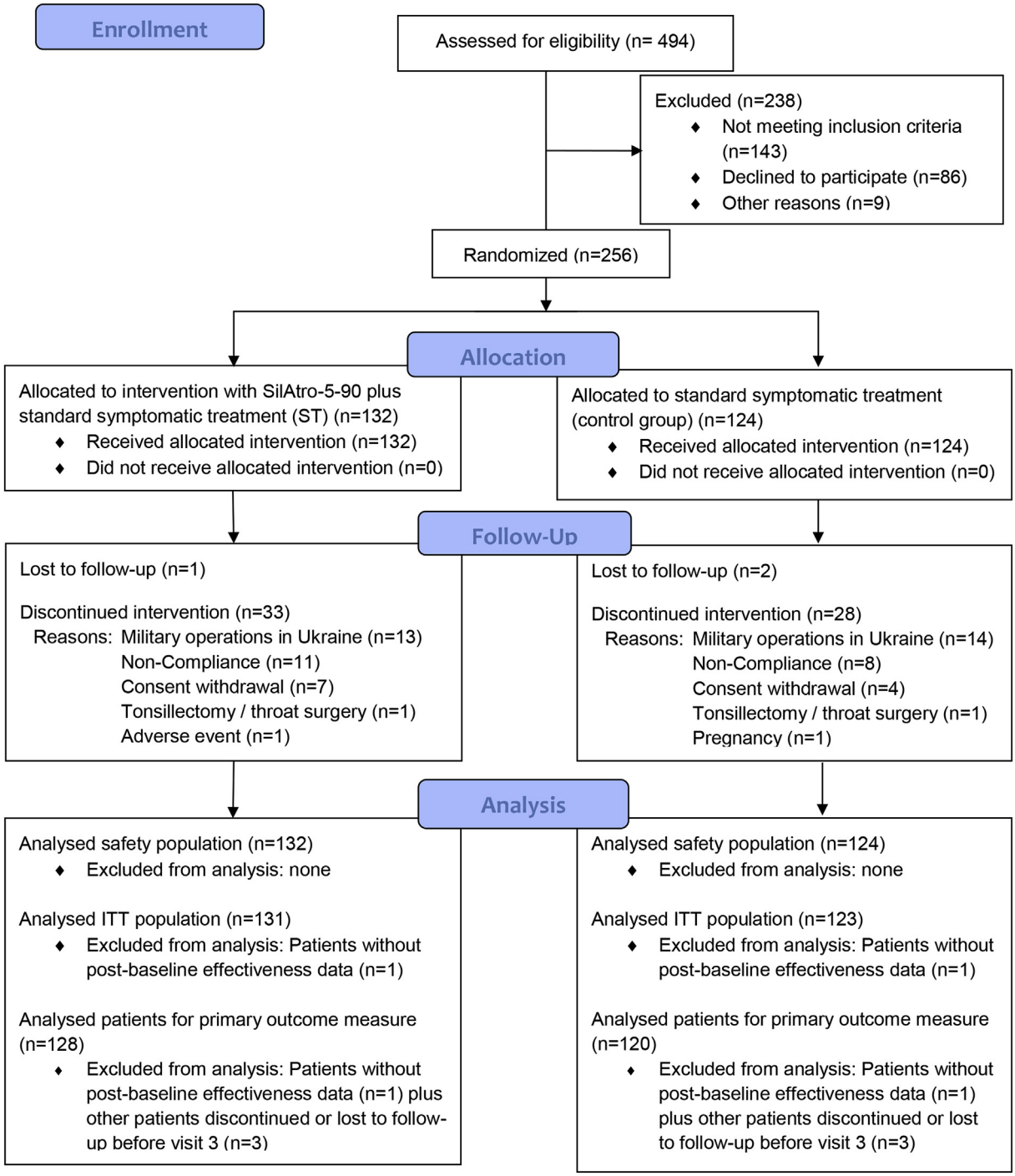

Fig. 1. Flow diagram of patients in the study.

3.2. Primary outcome variable

During the evaluation year (V3 until V9), a total of 68 ATIs were reported in the SilAtro-5-90 group and 148 ATIs in the control group. As shown in Table 2, the number of patients without an episode of ATI was higher upon treatment with SilAtro-5-90 compared to the control group (N = 86; 67.2% vs. N = 45; 37.5%). The difference between study groups was statistically significant in favor of SilAtro-5-90 (difference between SilAtro-5-90 and Control: 29.7% (95%-CI: 17.8–41.6), χ^2-Test: $p < 0.0001$; *ITT*). Table 2 also details the number of patients with their number of ATI episodes during the study.

The hazard ratio, calculated with the proportional means model, was 0.450 (95%-CI: 0.297–0.681), meaning that the risk of getting an ATI was significantly ($p = 0.0002$, *ITT*) lower in the SilAtro-5-90 group compared to the control group. The frequency of ATIs at baseline was included as covariate into the proportional means model and showed to have no influence on the primary endpoint (hazard ratio 1.025 (95%-CI: 0.862–1.218), $p = 0.7839$, *ITT*). Using the same model, it was also shown that the additionally included covariate "age group" had no effect on the primary endpoint ($p = 0.8437$, *ITT*).

Table 1
Demographic and baseline clinical characteristics, ITT.

Characteristics		Statistics	SilAtro-5-90 group	Control group
			N = 131 (100%)	N = 123 (100%)
Age (years)		Mean ± SD	21.6 ± 14.9	20.5 ± 13.2
		Median	15	16
		Q1 − Q3	9–32	9–31
		Range (Min − Max)	6–60	6–58
Age groups	<12 years	N (%)	45 (34.4%)	41 (33.3%)
	≥12 years	N (%)	86 (65.6%)	82 (66.7%)
Sex	Females	N (%)	85 (64.9%)	69 (56.1%)
	Males	N (%)	46 (35.1%)	54 (43.9%)
ATI frequency (last 12 months)	0–1	N (%)	3 (2.3%)	2 (1.6%)
	2–3	N (%)	102 (77.9%)	93 (75.6%)
	4–5	N (%)	26 (19.8%)	26 (21.1%)
	≥6	N (%)	0 (0%)	2 (1.6%)
Previous/Concomitant diseases		N (%)	91 (69.5%)	78 (63.4%)

ATI: Acute throat infection, ITT: Intention-to-treat analysis, Q1: Lower quartile, Q3: Upper quartile, SD: Standard deviation.

Table 2
Number of acute throat infections per patient, ITT*.

Number of documented ATIs per patient	Statistics	SilAtro-5-90 group N = 128 (100%)	Control group N = 120 (100%)
0	N (%)	86 (67.2%)	45 (37.5%)
1	N (%)	28 (21.9%)	39 (32.5%)
2	N (%)	10 (7.8%)	16 (13.3%)
3	N (%)	0 (0.0%)	12 (10.0%)
4	N (%)	2 (1.6%)	3 (2.5%)
5	N (%)	0 (0.0%)	2 (1.7%)
6	N (%)	2 (1.6%)	2 (1.7%)
7	N (%)	0 (0.0%)	1 (0.8%)

ATI: Acute throat infection, ITT*: Intention-to-treat analysis, patients who completed V3.

Sensitivity analysis related to the number of ATIs within the observational period has been done by Poisson regression modelling, accounting for baseline ATI frequency as well as the individual number of days under observation for each patient. An estimated rate of 0.59 ATI (95%-CI: 0.41–0.86) episodes per year was calculated for the SilAtro-5-90 group and 1.34 ATI episodes per year in the control group (95%-CI: 1.08–1.66). These values correspond to a significantly higher estimated mean time to an ATI in the SilAtro-5-90 group than in the control group (613.8 days (95%-CI: 426.4–883.6) versus 272.4 days (95%-CI: 219.4–338.1), Poisson regression model, relative risk 0.44 (95%-CI: 0.29–0.69, $p = 0.0003$, *ITT*)). The estimated time to ATI event (adjusted for treatment effect) is graphically depicted in Fig. 2. At the start of the study all patients (100%) were without ATI. During the course of the study the number of patients that were still without ATI decreased much more rapidly in the control group compared to the SilAtro-5-90 group (Fig. 2).

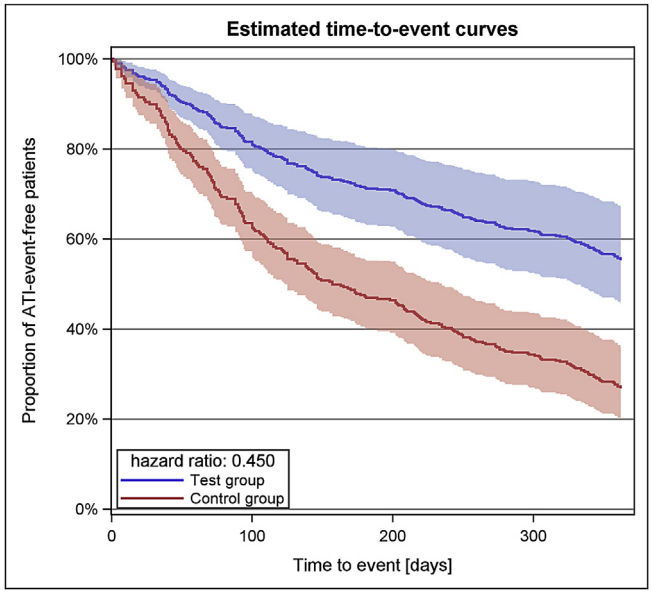

Fig. 2. Estimated time to ATI event by treatment arm as analyzed via recurrent event analysis, ITT*.
ATI: Acute throat infection, ITT*: Intention-to-treat analysis, patients who completed V3. Shaded areas represent the 95% confidence interval.

3.3. Secondary outcome variable: recurrent tonsillitis-specific symptoms

As shown in Fig. 3, the patient's reported number of days with occurrence of any recurrent tonsillitis-specific symptoms was significantly lower in the third follow-up period (week 40 ± 1 to week 60 ± 1) for patients in the SilAtro-5-90 compared to those in the control group (MWU-test: $p < 0.0001$, *ITT*). Similar significant results in favor of SilAtro-5-90 were observed at all treatment and all follow-up periods.

At each visit a total of 7 recurrent tonsillitis-specific symptoms were evaluated by the investigator during the course of the study. Fig. 4 shows the distribution pattern of the number of symptoms at the start of the first treatment period (day 1; upper graph) and at the end of the third follow-up period (week 60 ± 1; lower graph). Patients treated with SilAtro-5-90 had significantly fewer symptoms at study end compared to patients in the control group that only received standard treatment (MWU-test: $p < 0.0001$, *ITT*). More subjective symptoms such as sore throat and/or difficulty in swallowing and halitosis were already significantly decreased in the SilAtro-5-90 group compared to control from V2 (day 11) onwards

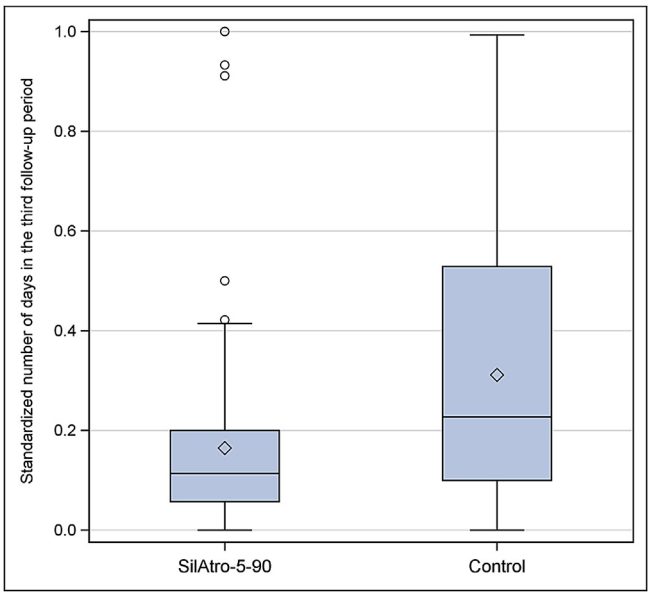

Fig. 3. Standardized number of days with any patient-reported recurrent tonsillitis-specific symptom in each treatment group during the third follow-up period. ITT.
Box & whisker plots showing mean (diamond), median (line within the box), minimum (lowest line outside the box), P25% (lower limit of the box), P75% (upper limit of the box) and maximum (top line outside the box) in the third follow-up period, MWU-test: $p < 0.0001$, ITT: Intention-to-treat analysis.
Measured symptoms were sore throat/difficulties in swallowing, halitosis or exhaustion. The number of days reported in the diary with symptoms' presence divided by the total number of diary days per period was calculated (ranging from 0 to 1, equivalent to a 0%–100% scale) and reported as "standardized number of days".

(χ^2-Test: $p < 0.005$; *ITT*). The occurrence of more objective symptoms, specific for alterations of tonsils (edema of angle where the anterior and posterior palatine arches join each other, caseous purulent plug and/or purulent exudates in the tonsillar crypts and hyperemia of the anterior palatine arches), were evaluated to be less significant in the SilAtro-5-90 group from V3 (week 8) and V4 (week 16) onward respectively (χ^2-Test: $p < 0.01$; *ITT*). Symptoms related to more profound objective alterations of tonsils (friable tonsils or indurated tonsils or scarred adhesions between the tonsils and the palatine arches, enlarged submandibular lymph nodes) revealed a statistically significant difference between both treatment groups from V7 (week 40) onwards (χ^2-Test: $p < 0.0001$; *ITT*).

3.4. Secondary outcome variable: antibiotics treatment

As shown in Table 3, in the SilAtro-5-90 group, 34 of 92 ATIs (37.0%), occurring between baseline and end of study, were treated with antibiotics. These 34 ATIs belonged to 26 patients. In the control group, 110 of 189 ATIs (58.2%), occurring between baseline and end of study, required treatment with antibiotics in 59 patients. The difference between both treatment groups regarding the percentage of ATIs without antibiotic treatment was statistically significant in favor of SilAtro-5-90 (difference between SilAtro-5-90 and Control: 21.2% (95%-CI: 9.13–33.36), χ^2-Test: $p = 0.0008$; *ITT*).

3.5. Secondary outcome variable: effects on daily activity

As shown in Table 4, the mean standardized number of days where patients' daily activities were affected by recurrent tonsillitis decreased from 0.048 in the first treatment period to 0.017 in the last follow-up period for patients in the SilAtro-5-90 group. In the control group, the standardized number of affected days decreased as well but remained significantly higher compared to the SilAtro-5-90 group in each study period (MWU-test; *p-values* < 0.001, *ITT*) (Table 4).

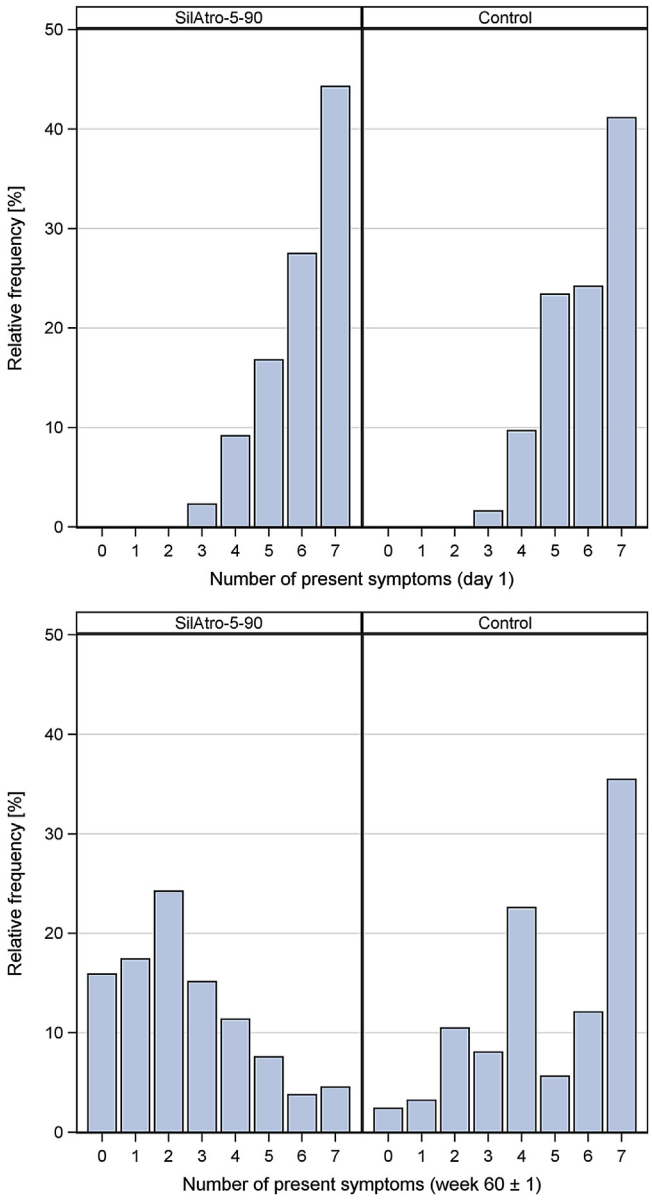

Fig. 4. Number of investigator-reported recurrent tonsillitis-specific symptoms in each treatment group at day 1 and at week 60, ITT.
Bar charts displaying distribution of recurrent tonsillitis-specific symptoms at day 1 (upper graph) and at the end of the third follow-up period (week 60 ± 1, lower graph), MWU-test: $p < 0.0001$, ITT: Intention-to-treat analysis.

3.6. Other secondary outcome variables

A total of 36 URTIs in 27 patients in the SilAtro-5-90 group and 68 URTI in 49 patients in the control group were reported during the evaluation year (V3 to V9). The number of patients with no URTI was significantly higher in the SilAtro-5-90 group compared to the control group (N = 101; 78.9% vs. N = 71; 59.2%, difference between SilAtro-5-90 and Control: 19.7% (95%-CI: 8.46–31.02), χ^2-Test: $p = 0.0008$; *ITT*).

With respect to analgesic treatment, no significant differences

Table 3
Antibiotics treatment of acute throat infections, ITT.

Characteristics		Statistics	SilAtro-5-90 group	Control group
			N = 50 patients with ATIs	N = 87 patients with ATIs
ATI treated with antibiotics	No	N (%)	58 (63.0%) in 24 patients (48%)	79 (41.8%) in 28 patients (32.2%)
	Yes	N (%)	34 (37.0%) in 26 patients (52%)	110 (58.2%) in 59 patients (67.8%)
	Total ATI events	N (%)	92 (100%) in 50 patients (100%)	189 (100%) in 87 patients (100%)

ATI: Acute Throat Infection, ITT: Intention-to-treat analysis.

Table 4
Standardized number of days with impact on performance of normal daily activity (patient-reported), ITT.

Study periods	Statistics	SilAtro-5-90 group	Control group
First treatment period	N (patients)	131	123
	Mean ± SD	0.048 ± 0.079	0.129 ± 0.152
	Median	0.018	0.082
	Q1 – Q3	0.000–0.054	0.018–0.179
	Range (Min – Max)	0.000–0.446	0.000–0.732
First follow-up period	N (patients)	128	120
	Mean ± SD	0.029 ± 0.050	0.088 ± 0.101
	Median	0.000	0.055
	Q1 – Q3	0.000–0.036	0.000–0.135
	Range (Min – Max)	0.000–0.250	0.000–0.446
Second treatment period	N (patients)	124	117
	Mean ± SD	0.024 ± 0.051	0.084 ± 0.114
	Median	0.000	0.018
	Q1 – Q3	0.000–0.018	0.000–0.143
	Range (Min – Max)	0.000–0.255	0.000–0.554
Second follow-up period	N (patients)	115	115
	Mean ± SD	0.023 ± 0.048	0.058 ± 0.094
	Median	0.000	0.000
	Q1 – Q3	0.000–0.018	0.000–0.096
	Range (Min – Max)	0.000–0.255	0.000–0.455
Third treatment period	N (patients)	114	112
	Mean ± SD	0.014 ± 0.038	0.054 ± 0.093
	Median	0.000	0.000
	Q1 – Q3	0.000–0.000	0.000–0.088
	Range (Min – Max)	0.000–0.241	0.000–0.464
Third follow-up period	N (patients)	107	104
	Mean ± SD	0.017 ± 0.032	0.065 ± 0.088
	Median	0.000	0.022
	Q1 – Q3	0.000–0.021	0.000–0.100
	Range (Min – Max)	0.000–0.184	0.000–0.355

ITT: Intention-to-treat analysis, Q1: lower quartile, Q3: upper quartile, SD: Standard deviation.
The number of days reported in the diary with impact on normal daily activity divided by the total number of diary days per period was calculated (ranging from 0 to 1, equivalent to a 0%–100% scale) and reported as "standardized number of days".

were observed between the treatment groups, both with respect to the percentage of ATIs treated (SilAtro-5-90: 62.0% vs control: 66.1%, χ^2-Test: $p = 0.4911$; *ITT*) as well as to the mean number of days with documented analgesic consumption due to ATI (SilAtro-5-90: 5.25 days vs control: 5.15 days, MWU-Test: $p = 0.4802$; *ITT*). Patients in the SilAtro-5-90 group assessed their classifications of quality of life during the course of the study significantly more favorably than patients in the control group (χ^2-Test: $p < 0.0001$; *ITT*). Similarly, treatment outcome using the IMOS scale was better scored, both by investigators and patients, upon treatment with SilAtro-5-90 compared to standard symptomatic treatment (control) only (χ^2-Test: $p < 0.0001$; ITT).

3.7. Safety and tolerability

During the course of the study, a total of 389 AEs were reported by 115 patients: 225 AEs (55 patients) in the SilAtro-5-90 group and 164 AEs (60 patients) in the control group (see Table 5). There were 7 serious adverse events (SAEs) that occurred in 7 patients, 4 patients in the SilAtro-5-90 group and 3 patients in the control group. 6 reported SAEs involved hospitalization because of disease other than recurrent tonsillitis (lower limb fracture, appendicitis (2 patients), ureteric calculus, sinusitis, endometriosis); 1 was rated as a medically important event (uveitis) and none of the SAEs was evaluated to be causally related to intake of SilAtro-5-90. The majority of the 389 reported AEs were mild in nature and only 3 AEs (1.33%) experienced by 2 patients were evaluated to be causally related to the investigational medicinal product SilAtro-5-90 (Table 5). These 3 adverse drug reactions were gastroenteritis, nausea and foul taste, and were rated as severe, moderate and mild, respectively. 1 patient in the SilAtro-5-90 group was withdrawn from the study due to an AE (gastroenteritis) and most AEs were resolved at the end of the study (Table 5). The number of patients and investigators having rated the tolerability of SilAtro-5-90 either as "very good" or "good" at the end of the 3 treatment periods (V3, V5 and V7) ranged between 98.4% and 100.0%, indicating that the treatment was overall very well tolerated.

4. Discussion

Patients often use homeopathic medications alongside mainstream medical therapies and in the present study it was demonstrated that, in the case of recurrent tonsillitis, this is of therapeutic benefit to them. 3 periods of 8-weeks' treatment with the

Table 5
Adverse events and adverse drug reactions, SAF.

Occurrence		SilAtro-5-90 group	Control group
		N (%)	N (%)
All Events		225 (100%)	164 (100%)
Serious		4 (1.8%)	3 (1.8%)
Intensity of AE	Mild	132 (58.7%)	76 (46.3%)
	Moderate	83 (36.9%)	81 (49.4%)
	Severe	10 (4.44%)	7 (4.3%)
Most likely Cause of AE	SilAtro-5-90	3 (1.3%)	NA
	Symptomatic treatment of chronic tonsillitis	0 (0%)	0 (0%)
	Rescue medication	4 (1.8%)	2 (1.2%)
	Other	218 (96.9%)	162 (98.8%)
AE necessitating withdrawal		1 (0.4%)	0 (0.0%)
Outcome of AE	Resolved	218 (96.9%)	159 (97.0%)
	Resolved with sequelae	0 (0%)	1 (0.6%)
	Ongoing at study end	6 (2.7%)	3 (1.8%)
	Unknown at study end	1 (0.4%)	1 (0.6%)

AE: Adverse event; SAF: Safety analysis set.

homeopathic medicinal product SilAtro-5-90, in addition to standard symptomatic treatment, significantly reduced the number of ATIs during the course of 1 year compared to standard treatment only. The risk that patients in the SilAtro-5-90 group would get an ATI was found to be 0.45 times that of the control group. As the patients were followed-up for a period of 1 year, a seasonal influence on the occurrence of ATIs was not to be expected. Furthermore, patients in the SilAtro-5-90 group experienced significantly fewer days with recurrent tonsillitis-specific symptoms in the SilAtro-5-90 group compared to the control group over all study periods.

Patients in the SilAtro-5-90 group exhibited an overall significant decrease in subjective symptoms from V2 onward and in the objective symptoms associated with recurrent tonsillitis from V3 and V4 onward. Previously, it was reported that recurrent tonsillitis has a major impact on normal daily functioning, relating for example to sleep deprivation and absence from school or work [5,7]. It was therefore not surprising that in the present study patients in the SilAtro-5-90 group rated their quality of life to be higher, as well as their performance of normal daily activities to have improved, most likely due to the lower number of ATIs and related symptom burden upon treatment with SilAtro-5-90. The latter was reflected by a significant lower number of days with impact on the daily activity in the SilAtro-5-90 group compared to the control group in each study period. The observation that long-term treatment with the homeopathic medicinal product SilAtro-5-90 was safe and highly tolerated, without the occurrence of any complications, might have contributed to this as well.

Another important and interesting finding was that patients in the SilAtro-5-90 group used overall less antibiotics for treatment of recurrent tonsillitis: indirectly, because they experienced fewer ATIs, but also directly because in the SilAtro-5-90 group fewer actual ATIs (37%) required antibiotic treatment compared to the control group (58%). Since a GABHS test was mandatory before the start of antibiotic treatment, it may appear that patients in the SilAtro-5-90 group were less susceptible to bacterial throat infections than patients in the control group. The mechanisms by which SilAtro-5-90 may reduce ATI and recurrent tonsillitis-specific symptoms were not investigated in the current study and therefore remain unknown. SilAtro-5-90 was developed on the basis of homeopathic clinical experience and according to the general homeopathic principle that a homeopathic medication can stimulate the body's own adaptive healing processes. Through such stimulation, it has been proposed that the organism is enabled to initiate a systemic self-reorganization toward more robust functioning as a whole [34]. Further studies are warranted to investigate how SilAtro-5-90 can decrease the susceptibility of patients to ATIs in recurrent tonsillitis.

The present finding that patients treated with homeopathy use less antibiotics is now being observed in a growing number of studies [30,35–38]. This reduction in antibiotic consumption with homeopathic treatment is not associated with the occurrence of more infection-related complications or other safety issues, since homeopathy overall has been shown to be a very safe therapeutic treatment option [39]. Integration of homeopathic medicinal products, such as SilAtro-5-90, into mainstream medicine may therefore be an effective strategy to reduce excessive antibiotic use. This is particularly relevant since excessive and unnecessary antibiotic use is one of the main reasons for antibiotic resistance, which poses nowadays a serious worldwide threat to public health [11,40–42].

The effectiveness of SilAtro-5-90 in the treatment of recurrent tonsillitis, as observed in the present study, confirms the findings of earlier studies in which SilAtro-5-90 was found to lower the symptom burden of recurrent tonsillitis [24,28]. Strengths of the current study, compared to the previous ones with SilAtro-5-90, are that ATIs were medically confirmed by an ICD-10 diagnosis made by the investigators and not merely based on subjective symptom scores. Furthermore, results of the primary endpoint analysis with the statistically significant finding from time-to-event analyses (based on Cox model) were confirmed by a sensitivity analysis on ATI event count data (Poisson regression), demonstrating the robustness of the findings. Another strength of the present study was the pragmatic comparative design, providing the study a high external validity. It indeed closely resembled the real-world setting in which SilAtro-5-90 is bought by patients over-the-counter as supportive treatment for their ailment. As previously mentioned, patients often combine mainstream and homeopathic medications [29,30] because they want 'the best of both worlds' [43]. The roadmap for further guidance on research in CAM recommends the pragmatic study design due to the information it yields on comparative effectiveness and safety of CAM services [44,45]. A further strength of the study is that it included a large number of patients in 3 different countries and followed them during the course of 1 full year.

Besides its strengths, the present study also has some inevitable limitations. Because of the pragmatic comparative design, SilAtro-5-90 was compared to standard symptomatic treatment and so a placebo-arm was not included. However, the efficacy of SilAtro-5-90 in acute tonsillitis has previously been demonstrated

in 2 randomized placebo-controlled double-blinded trials [26,27]. By day 4 of the treatment in both studies, children treated with SilAtro-5-90 experienced a significant reduction of tonsillitis-associated symptoms (difficulties in swallowing, pain in throat, salivation, reddening and fever [26,27], plus coatings on both tonsils [27]) compared to children in the placebo group. It is therefore unlikely that the observed effectiveness of SilAtro-5-90 in the present study is merely due to placebo effects. Another limitation of the study is the open-label design, since patients as well as investigators knew who received the investigational medical product and who did not. Therefore results should be regarded with caution due to the risk of bias associated with the expectation that patients in the SilAtro-5-90 group would perform better in the study. Another limitation is that several secondary outcome variables such as tonsillitis-specific symptoms, quality of life and overall treatment outcome (IMOS) were measured using non-validated scales. A further significant limitation of the study might refer to the situation, that the drop-out rate of 14.5% (37 out of 256 patients) during the 1-year course was elevated by additional 10.5% (27 patients). Those 27 patients prematurely dropped out from the trial due to reasons that were not related to the study design or to the treatment: indeed, they came from 2 study sites located in Eastern Ukraine and were prematurely withdrawn from the study due to the war situation in that region during summer 2014. Regardless of the drop-out reasons, missing data of the prematurely withdrawn patients were adequately addressed in the statistical models used in the primary outcome analysis (time-to-event analyses based on Cox model) and in the sensitivity analysis on ATI event count data (Poisson regression).

It has been suggested that homeopathic treatment that is integrated into mainstream medicine may be cost-effective. In Switzerland, practice costs of primary care physicians, who also practice homeopathy, were found to be 15% lower than those of colleagues practicing mainstream medicine only [46]. These findings were confirmed in a study in the Netherlands, where patients whose primary care physician additionally practiced homeopathy had 15% lower healthcare costs than patients visiting mainstream practices [47]. Although the present study did not collect data with the aim to perform a cost-effectiveness analysis of SilAtro-5-90 versus standard symptomatic treatment in recurrent tonsillitis, several secondary outcomes were measured in the study that are of relevance to this topic. SilAtro-5-90 was shown to be more effective in reducing ATIs than standard symptomatic treatment only, and at the same time to significantly reduce the use of antibiotic medication, to decrease the number of days with absence from work or school, and to improve quality of life. These therapeutic benefits were gained at an average cost of €6.50 per month for SilAtro-5-90 treatment in children and €13.00 per month for SilAtro-5-90 treatment in adults. These costs fall well within the reported expenditures for homeopathic remedies (ranging from €3.70 to €124.54 per month) that patients in Germany have shown to pay out of their own pocket [20]. On the basis of these findings, further research to investigate the possible cost-effectiveness of SilAtro-5-90 in the treatment of recurrent tonsillitis is warranted.

Patients in the present study suffered from moderate recurrent tonsillitis and therefore, according to current guidelines [3,4,8,9], did not meet criteria for tonsillectomy. Only 2 out of 256 patients (0.8%) - 1 in the SilAtro-5-90 and 1 in the control group - dropped out because they needed to undergo tonsillectomy/throat surgery. Since the efficacy of tonsillectomy in recurrent tonsillitis is subject to debate, a watchful waiting period is advised in patients with less severe recurrent tonsillitis [8]. SilAtro-5-90 can be recommended as an effective therapeutic option in this watchful waiting period: there are very few side effects with SilAtro-5-90, and its use does not contribute to anti-microbial resistance.

5. Conclusions

Conjunctive use of the homeopathic medicinal product SilAtro-5-90 in the treatment of recurrent tonsillitis was found to significantly prolong the interval between consecutive ATIs and to reduce tonsillitis-specific symptoms and use of antibiotics, with no complications and very few side effects. An integrative approach, in which SilAtro-5-90 is given alongside mainstream symptomatic treatment, may be recommended as a treatment option for moderately affected patients or for patients in the watchful waiting period before undergoing tonsillectomy. Further studies on the mechanisms by which SilAtro-5-90 can decrease the susceptibility of patients to ATIs are warranted.

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Conflict of interest

DHU-Arzneimittel GmbH & Co. KG provided the fees described below:

JP and VVK received a fee for coordinating the study and conducting the research; JPF received a fee for coordinating the study; AU, AK, KK, IMK, SMP, ZT and KW received a fee for conducting the research; MCJ received a fee for writing manuscript; TK and SW received a fee for analyzing the data. SDJ and PK are employees of Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG, Karlsruhe, Germany. They were responsible for the project management in terms of conceptualization, planning and coordination of the study as well as data management, analysis and documentation of the study.

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