Tavipec® in acute rhinosinusitis: a multi-centre, double-blind, randomized, placebo-controlled, clinical trial*

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Abstract

Background: This randomized clinical trial was designed to evaluate the efficacy and safety of Tavipec® (Spicae aetheroleum), a phytomedicine obtained by steam distillation of the flowering tops of Lavandula latifolia, as compared to placebo in adult patients suffering from acute viral rhinosinusitis.

Methodology: Patients with acute viral rhinosinusitis were randomly assigned to treatment with 2 capsules Tavipec® 150 mg or placebo thrice daily over a period of 7 days in a double-blind, parallel-group design. No additional treatment was admitted. The efficacy endpoints comprised the improvement of the main rhinosinusitis symptoms as per Major Symptom Score (MSS) and Sino-Nasal Outcome Test (SNOT-22) as well as of quality of life (QoL) by global assessment scale, evaluated at baseline, day 5 and day 8, respectively.

Results: 288 patients were enrolled and randomized to treatment. At day 8 the patients in the Tavipec® group had a significantly lower MSS compared to placebo and the impact of rhinosinusitis symptoms on QoL was significantly reduced. A significantly higher proportion of Tavipec® treated patients experienced a change in SNOT-22 score ≥ 10 points at day 5 or day 8. No new safety signals were identified.

Conclusions: The treatment with Tavipec® effectively reduced the symptoms of acute rhinosinusitis in adult patients.

Key words: sinusitis, respiratory tract infections, Lavandula, Sino-Nasal Outcome Test (SNOT)-22, quality of life

Introduction

Acute rhinosinusitis (ARS) is a respiratory disease with very high prevalence, thus constituting one of the most common reasons for which patients consult their general practitioner (GP). ARS in adults is characterized by inflammation of the paranasal sinuses and the nasal cavity with two or more symptoms, one of which should be either nasal blockage or nasal discharge; with or without facial pain/pressure and/or reduction or loss of smell, lasting for <12 weeks [1, 2]. With respect to healthcare systems ARS imposes a major socioeconomic burden both, in terms of direct expenses for outpatient visits, laboratory tests, antibiotic treatment failures, etc., and in terms of decreased productivity, reduced job effectiveness and impaired quality of life (QoL) [2-5].

Although approximately 98% of ARS are viral and self-limiting, antibiotics are often prescribed in primary care [1, 5-11]. In fact, only 0.5-2.0% of patients eventually develop acute bacterial rhinosinusitis (ABRS) secondary to a viral infection [1]. Consequently, viral ARS resolves without antibiotic treatment, which is also reflected in the current European guidelines, which recommend that the management of viral ARS should primarily rely on symptomatic treatment, i.e. the alleviation and reduction in duration of the clinical symptoms [1, 6, 7, 10].

Herbal remedies are commonly and extensively used for symptomatic treatment of viral respiratory tract infections (RTIs) including viral ARS. Despite a growing body of evidence, the benefit of many herbal remedies still needs to be confirmed by more

well-designed, double-blind, placebo-controlled, randomized clinical trials (RCTs) [1, 12]. Also, some herbal medicines have not been completely analysed in respect of the pharmacodynamic and pharmacokinetic properties of their active compound(s). The anti-inflammatory properties and mode of action (MoA) of plant derived monoterpenes as well as their efficacy to control signs and symptoms of RTIs including viral ARS have been thoroughly investigated [13-29]. Monoterpenes are resorbed in the gastrointestinal tract and enter the circulation and reach the mucosal secretory glands, where they have secretolytic effects by enhancing mucus production and ciliary beat frequency (CBF) as well as stimulating ciliary cell differentiation, thus supporting the cleaning function and the recovery process of the mucosa [14, 15, 22, 30, 31]. Ciliary impairment and the disruption of the normal mucociliary flow have been demonstrated to be a feature of both viral ARS and ABRS [1, 8].

Numerous pre-clinical trials have addressed the anti-inflammatory MoA of monoterpenes, i.e. linalool and/or cineol [13, 18, 29, 32-35] whereas several RCTs have demonstrated their therapeutic benefits in inflammatory airway diseases [24-28, 36, 37]. Being rich in linalool and 1,8-cineole, Spicae aetheroleum is extensively used for its mucolytic, anti-inflammatory and spasmolytic activity [38, 39]. Recently, Kähler et al. demonstrated the efficacy and tolerability of Spicae aetheroleum (Tavipec®) for symptom relief in patients with acute bronchitis in a double-blind, placebo-controlled RCT [28]. However, equivalent data evaluating Tavipec® in the treatment of viral ARS are still lacking. The present double-blind, placebo-controlled RCT was designed to fill this gap by assessing the efficacy and safety of Tavipec® in adult patients with viral ARS.

Materials and methods

Study subjects

Male and female outpatients aged ≥18 and ≤75 years with signs of viral ARS and a Major Symptom Score (MSS, composed of the five major symptoms nasal obstruction, rhinorrhoea, postnasal drip, sinus headache and facial pain) >5 but <12, a sublingual temperature <38,3°C, without dental involvement or need of antibiotic treatment at screening (baseline, visit 1, day 0) were included. Need for antibiotic treatment was defined as signs and symptoms suggestive of ABRS. According to EPOS criteria [1], ABRS was assumed, if patients had at least 3 of the 5 symptoms purulent secretions, severe pain, fever >38°C, increased CRP (C-reactive protein) or ESR (Erythrocytes sedimentation rate) and/or double sickening.

Enrolment was within 3 to (after study amendment) 5 days after the onset of the first symptoms [40]. Patients with signs or symptoms suggestive of ABRS, chronic (recurrent) rhinosinusitis as well as patients with nasal tumours or need/application of any concomitant local or systemic medications (e.g. antibiotics during the preceding 4 weeks, corticosteroids, antihistamines, immunosuppressive therapy at any time) were excluded or withdrawn from the study. To overcome a possible influence on the outcome of the study, apart from saline nasal douche / spray no other concomitant medications were allowed for symptom relief. If any other treatment than permitted by the study protocol was taken by the study participants, these treatments were recorded, and the study participants consequently excluded from the study due to protocol violations. Study participants were recruited by GPs or ear nose throat specialists at ten study centres located in Austria and Poland. The study was approved by the respective ethics committees and registered at the European Medicines Agency, EudraCT number: 2013-002977-23. All patients provided written informed consent. The trial was conducted in full correspondence with the principles of the ICH guideline (E6), the Declaration of Helsinki and with local national laws and regulations.

Study design

This was a prospective, randomized, placebo-controlled, double-blind, parallel-group, multi-centre, interventional clinical phase IV study to assess the efficacy and safety of Spicae aetheroleum (Tavipec®, verum) compared to placebo in patients suffering from viral ARS. Diagnosis and treatment success were based on effects on relevant symptoms assessed by MSS as well as in terms of impact of the disease on QoL from patient's view by QoL global assessment (verbal rating) and the Sino-Nasal Outcome Test (SNOT-22) questionnaire [40, 41]. A sum score was formed for evaluation purposes. The sum scores of MSS, QoL and SNOT-22, i.e. the change scores from baseline or the comparison between the achieved scores in the verum and placebo group after 4 and 7 days of full medication composed the efficacy endpoints.

Interventions

Pharmazeutische Fabrik Montavit Ges.m.b.H., Austria, conducted the study and provided the study medication. Verum capsules with gastroresistant coating contained 150 mg Spicae aetheroleum (Tavipec®, manufacturer: Pharmazeutische Fabrik Montavit Ges.m.b.H., Absam, Austria) as the active ingredient; placebo capsules with gastroresistant coating were filled with medium-chain triglycerides (manufacturer: Catalent, Eberbach, Germany). Tavipec® is a herbal medication containing Spicae aetheroleum, an essential oil extracted by steam distillation from the flowering tops and stalks of Lavandula latifolia. The main components are the monoterpenes linalool, 1,8-cineol and camphor in concentrations of 34-50%, 16-39% and 8-16% as sourced from the European Pharmacopoeia (http://online6.edqm.eu/ep800/). According to the summary of product characteristics recommendations, two capsules were taken three times daily (2-2-2) with some liquid, 30 minutes before a meal. The dose schedule was the same for all patients and did not change during the 7 days

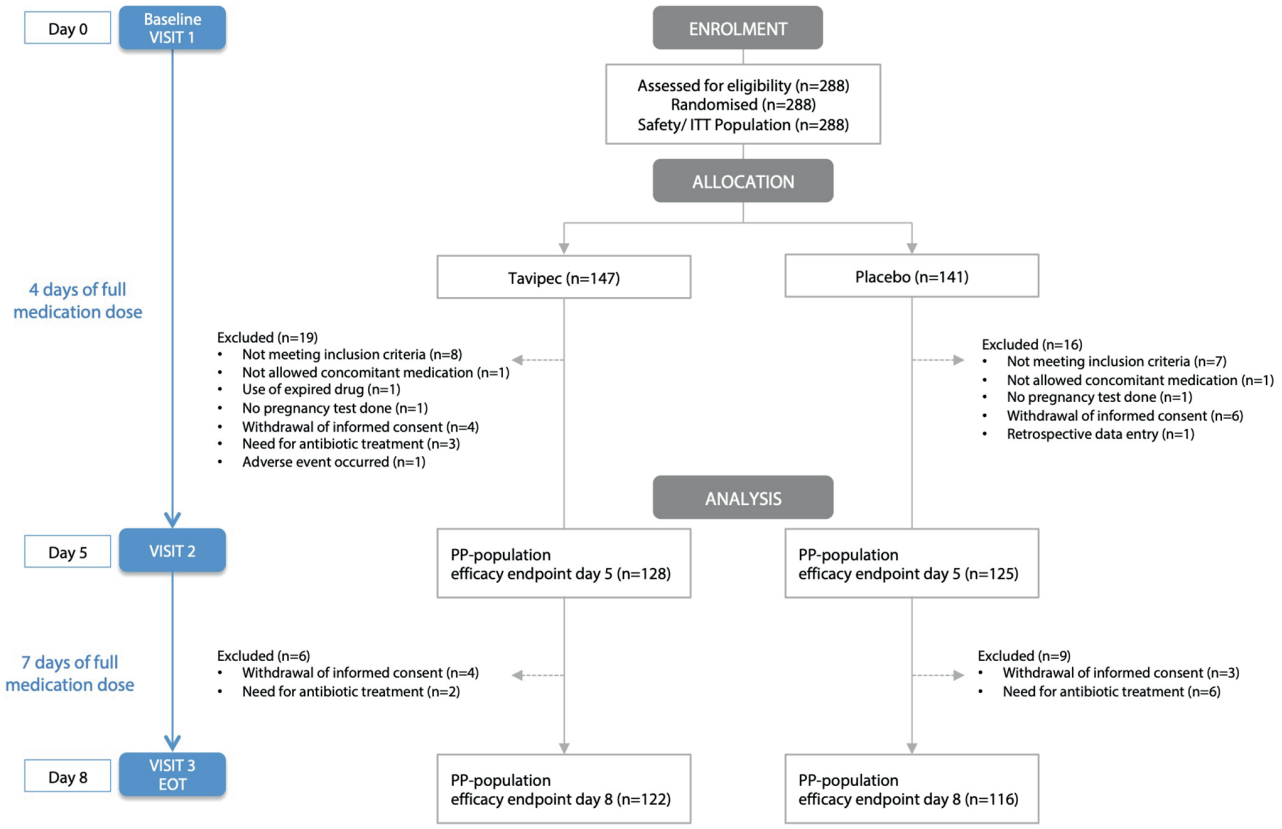

Figure 1. Timeline and disposition of study patients. Patient flow through each stage of the study including the reasons for losses and exclusions after randomization. EOT: end of treatment, ITT: intention to treat, PP: per protocol.

of treatment. Adherence was tracked by counting the number of remaining capsules from each individual patient by the study nurse and the study monitor (four eyes principle).

Assessments

Data were recorded using case report forms (CRF) at the beginning of therapy (visit 1, day 0, baseline), and after 4 (visit 2, day 5) and 7 days (visit 3, day 8, end of treatment, EOT) of taking the full dose of the medication. For each patient the investigators filled in one CRF which was reviewed by the monitor. At each visit the patients were evaluated for signs and symptoms of rhinosinusitis (including sublingual temperature), their subjective general condition, the SNOT-22, the QoL global assessment, adverse events, compliance and intake of any other medication than permitted by the study protocol. The MSS was calculated from the sum of five major symptoms (i.e. rhinorrhoea, postnasal drip, nasal congestion/stuffiness, sinus headache and facial pain), each rated from 0 to 3 (0=none, 1=slight, 2=moderate, 3=severe). The SNOT-22 represents a patient-reported outcome measure for rhinosinusitis based on 22 items. Patients rate the severity of the symptoms on a 6-point (0–5) Likert scale, giving a total score between 0 and 110 by adding up the scores. Patients were asked to complete the questionnaire on day 0, 5 and 8.

The global impact of disease on QoL was verbally assessed by patients via rating scale 0–10 ("not troublesome" to "worst thinkable troublesome"). Scores from 0–3, 4–7, and 8–10 indicated mild, moderate and severe impact, respectively. Adverse events were either reported by the patient and/or observed by the investigator. Safety assessments were performed at visit 2 and 3. No interim analysis was planned or performed.

Statistical analyses

The sample size calculation was based on information from previous trials and considering the objectives of this trial [5, 26, 42]. Since the efficacy variables were quantitative, but not necessarily normally distributed, a two-sided (α= 5%) Mann-Whitney test (rank-sum test) was applied to test the null hypothesis. For categorical variables, Chi-Square tests were performed. Further parameters were summarized using descriptive statistics, i.e. number (%) of patients for categorical variables and mean, SD (standard deviation), SEM (standard error of the mean), median, minimum/maximum for continuous variables. Descriptive statistics were produced by treatment group. The baseline characteristics were analysed for the Intention to treat (ITT) / safety population which comprised all patients with at least one documented administration of study drug and any post-base-

Table 1. Baseline characteristics (ITT subset).

Parameter	Tavipec® (n=147)	Placebo (n=141)	Total (n=288)
Age (years)			
Mean (SD)	38.1 (13.5)	41.2 (14.9)	39.6 (14.2)
Range	18 to 72	18 to 81	18 to 81
Gender (n, (%))			
Female	87 (59.2%)	76 (53.9%)	163 (56.6%)
Male	60 (40.8%)	65 (46.1%)	125 (43.4%)
Body weight (kg)			
Mean (SD)	74.1 (15.5)	74.7 (15.8)	74.4 (15.6)
Range	44.2 to 136.0	48.0 to 122.0	44.2 to 136.0
Body height (cm)			
Mean (SD)	172.5 (8.9)	171.9 (8.6)	172.2 (8.8)
Range	156 to 196	154 to 190	154 to 196
Body temperature (°C)			
Mean (SD)	37.2 (0.56)	37.1 (0.62)	37.1 (0.59)
Range	34.8 to 38.2	34.2 to 38.3	34.2 to 38.3
MSS			
Mean (SD)	8.82 (1.40)	8.69 (1.39)	8.75 (1.39)
Range	5 to 12	6 to 12	5 to 12

Data about body weight was missing for one patient in the Tavipec® group and data about body temperature was missing for one patient in the placebo group (n=146/n=140; total: n=287). MSS: Major Symptom Score; SD: standard deviation.

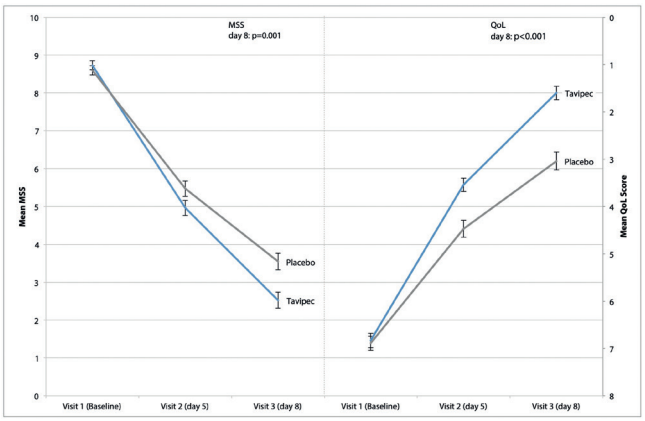

Figure 2. Mean MSS at different treatment days and stepwise amelioration of patient's QoL with continuation of therapy. Mean MSS at visit 1 (baseline), visit 2 (day 5) and visit 3 (day 8, EOT) in the PP day 8 patient subset (Tavipec® n=122; placebo n=116). All analyses: ANCOVA with baseline MSS as covariate. Impact on QoL by global assessment scale at visit 1 (baseline), visit 2 (day 5) and visit 3 (day 8, EOT) in the PP day 8 patient subset (Tavipec® n=122; placebo n=116). ANCOVA: analysis of covariance, EOT: end of treatment, MSS: major symptom score, PP: per protocol, QoL: quality of life, SEM: standard error of the mean.

line safety data. The per-protocol (PP) subset equal to the subset for the efficacy analysis included all patients who completed the defined course of treatment (4 or 7 days). For exploratory purposes the efficacy endpoints were tested using a superiority hypothesis versus placebo employing ANCOVA with "MSS at baseline" as covariate and t-tests. Statistical programming and analysis were done using SPSS® 24.0 (IBM, New York, USA). Missing data and unclear or illegible entries in the case report forms were collected and documented in a data clarification form and clarified by the investigators. No data imputation was performed. All data changes after database closure were documented in a note to file.

Results

Patient disposition

From Jan 2014 to Oct 2016 a total of 288 patients were enrolled and randomized to treatment (n=147 Tavipec®, n=141 placebo), thus forming the ITT population equal to the safety analysis subset. Thirty-five patients were initially excluded due to protocol violations or lost to follow-up, and a further 15 patients were excluded due to withdrawal or need for antibiotic treatment, resulting in a PP patient subset for efficacy analyses (day 8, visit 3) of 238 patients (Figure 1).

Table 1 summarizes the baseline demographics and clinical characteristics in the ITT subset. Both treatment groups as well as the gender groups were comparable and exhibited no obvious bias. At baseline all patients suffered from nasal obstruction and rhinorrhoea, almost all suffered from postnasal drip (99.2%), sinus headache (98.4%), hyposmia (97.6%) and impairment of general condition (99.2%). The first onset of rhinosinusitis symptoms was 2.3 and 2.2 days before the first visit in the Tavipec® and the placebo group, respectively.

Efficacy evaluation

After 7 days of full medication, the patients in the Tavipec® group had a significantly lower MSS compared to placebo (2.52 vs. 3.55; p=0.001; CI_{95}: 0.425; 1.618). A trend towards superiority of Tavipec® was apparent after 4 days of treatment with a mean MSS of 4.96 vs. 5.47 (p=0.074; CI_{95}: 0.050; 1.063), respectively (Figure 2L (MSS)). Similarly, the QoL was significantly better in Tavipec® vs. placebo-treated patients with 3.54 vs. 4.47 (CI_{95}: 0.48; 1.37) score points after 4 days and 1.60 vs. 3.04 (CI_{95}: 0.98; 1.91) after 7 days of full medication (both: p<0.001; Figure 2R (QoL)) thus revealing a significantly lower impact of rhinosinusitis symptoms on the individual QoL in the Tavipec® arm, and confirming the results obtained by the MSS assessment. At EOT 5.7% of patients in the Tavipec® vs. 39.6% in the placebo arm reported a moderate or severe impact of rhinosinusitis on QoL.

With the exception of postnasal drip the improvement of the MSS in favour of Tavipec® was also evident in the individual MSS symptoms: After a 7-day treatment course, the mean symptom scores for nasal obstruction, rhinorrhoea and sinus heada-

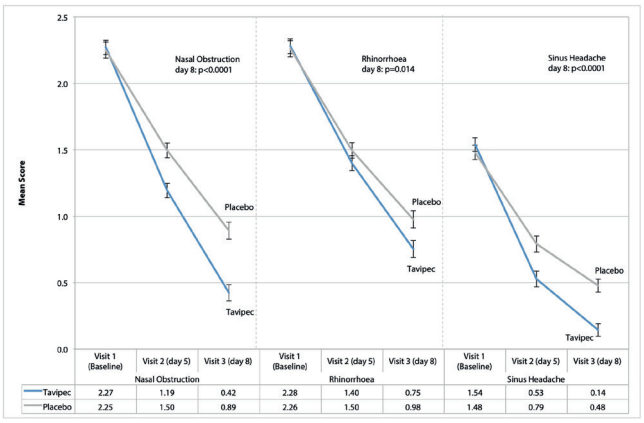

Figure 3. Mean symptom scores for nasal obstruction, rhinorrhoea, and sinus headache at different treatment days, each rated from 0 to 3 (0=none, 1=slight, 2=moderate, 3=severe), at visit 1 (baseline), visit 2 (day 5) and visit 3 (day 8, EOT) in the PP day 8 patient subset (Tavipec® n=122; placebo n=116). All analyses: ANCOVA with baseline value as covariate. ANCOVA: analysis of covariance, EOT: end of treatment, MSS: major symptom score, PP: per protocol

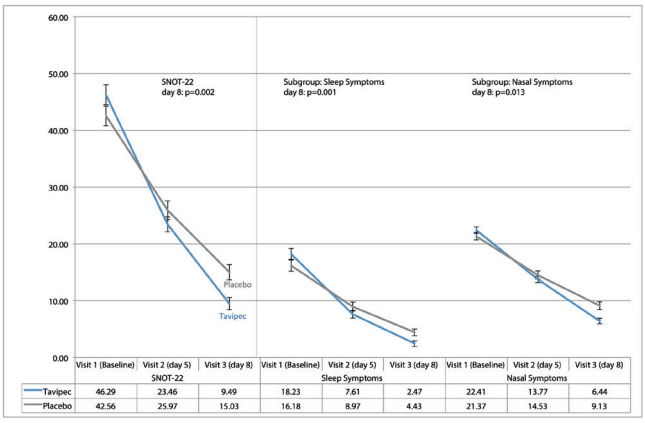

Figure 4. Results of the mean SNOT-22 total score at different treatment days, i.e. visit 1 (baseline), visit 2 (day 5) and visit 3 (day 8, EOT) in the PP day 8 patient subset (visit 1 and 2: Tavipec® n=122; placebo n=115; visit 3: Tavipec® n=120, placebo n=115). Detailed results of the SNOT-22 subgroups "sleep" (8 questions) and "nasal" symptoms (5 questions) at different treatment days, i.e. visit 1 (baseline), visit 2 (day 5) and visit 3 (day 8, EOT) in the PP day 8 patient subset (visit 1 and 2: Tavipec® n=122; placebo n=115; visit 3: Tavipec® n=120, placebo n=115). EOT: end of treatment, PP: per protocol, SEM: standard error of the mean, SNOT: Sino-nasal outcome test.

che were 0.42 vs. 0.89 ($p<0.001$; CI_{95}: 0.29; 0.64), 0.75 vs. 0.98 ($p=0.014$; CI_{95}: 0.05; 0.40) and 0.14 vs. 0.48 ($p<0.001$; CI_{95}: 0.20; 0.47), respectively, in the Tavipec® vs. the placebo group (Figure 3). At EOT the score for postnasal drip was 0.86 vs. 1.16 ($p=0.002$; CI_{95}: 0.11; 0.49) in the placebo vs. Tavipec® group. At the same time 4.9% vs. 25% of patients reported their nasal obstruction and 6.6% vs. 26.7% reported rhinorrhoea as moderate or severe in the Tavipec® vs. the placebo group.

The impact of treatment on rhinosinusitis symptoms and QoL was also evaluated by means of the holistic SNOT-22 change score, i.e. the difference between pre-treatment and post-treatment score. By EOT, the mean reduction of the SNOT-22 score was 37.09 vs. 27.53 ($p<0.001$; CI_{95}: 4.75; 14.37) resulting in final scores of 9.49 vs. 15.03 ($p=0.002$) in the Tavipec® vs. the placebo group, thus revealing a significant therapeutic effect with Tavipec® as compared to placebo. A significantly higher proportion of Tavipec® treated patients experienced a change in SNOT-22 score ≥10 points after 4 (82.0% vs. 60.0%; $p=0.0002$) or 7 days (95.8% vs. 84.3%; $p=0.003$) of treatment. Figure 4 shows the results for the entire 22-item SNOT assessment and a detailed illustration of the individual scores for "sleep" (8 questions) and "nasal" symptoms (8 questions) at different treatment days according to the 4-subdomain structure as validated by Feng et al. [43].

Safety evaluation

Nearly 90% of the patients in the Tavipec® (88.4%) and the placebo group (89.4%) were exposed to the allocated intervention for at least 6 days. A total of 39 adverse events (AEs) were reported by 34 patients during the study (Table 2). In the Tavipec® arm 26/147 patients and in the control arm 8/141 had an AE ($p<0.005$). Two out of the 30 AEs from the Tavipec® group have been rated as probably and 20 as possibly related; Of the 30 AEs from the Tavipec® group, 19 were reported as mild compared to 7/9 in the placebo. Twenty-one patients in the Tavipec® group reported 23 gastrointestinal disorders including nausea (4), abdominal pain (14), appendicitis (1), upper abdominal pain (1), diarrhoea (1), breath odour (1) and dysgeusia (1). One case of abdominal pain and the one with appendicitis were both assessed as unrelated, all others with exception of upper abdominal pain and dysgeusia (probably related) were rated as possibly related to study medication. No new safety signals were identified, no adverse event was classified as serious. Additionally, neither in the Tavipec® group nor in the placebo group patients discontinued treatment due to AEs.

Discussion

Viral ARS is one of the most common reasons why patients seek medical advice in ambulatory care. Although clinical studies have demonstrated that antibiotics are not indicated for treatment of viral ARS, antibiotics are still prescribed at high rates while guideline-oriented management suggests symptomatic treatment and reassurance for patients with mild symptoms [1, 5-10]. Herbal medicinal products containing plant-derived monoterpenes represent a well-tolerated therapeutic option for uncomplicated upper RTIs based on long-standing use, however,

Table 2. Adverse Events (Safety population/ITT subset).

		Tavipec® (n=147)	Placebo (n=141)
Patients with at least one adverse event		26 (17.7%)	8 (5.7%)
Total number of adverse events		30	9
Organ Class	Gastrointestinal disorders	23 (76.7%)	5 (55.6%)
	Nervous system	2 (6.7%)	-
	Psychiatric disorders	1 (3.3%)	1 (11.1%)
	Reproductive System & breast disorders	1 (3.3%)	-
	Infection and infestation	1 (3.3%)	1 (11.1%)
	Ear and labyrinth disorders	1 (3.3%)	1 (11.1%)
	Investigations (cardiac & vascular)	1 (3.3%)	-
	Respiratory, thoracic & mediastinal disorder	-	1 (11.1%)

Data are presented as n with % reporting in parentheses.

the evidence for beneficial effects of herbal compounds for the treatment of viral ARS is limited and there is a real need for more RCTs in this field [1].

To the best of our knowledge this is the first placebo-controlled, multinational RCT evaluating the efficacy and safety of Tavipec® in adult patients with ARS. A 7-day treatment course with an oral dose of 300 mg Tavipec® three times daily led to a significant improvement of ARS symptoms by means of the MSS, the SNOT-22 and QoL assessment as compared to placebo. The dosage regimen was well tolerated; neither specific areas of concern nor new safety signals were identified during the study.

Our findings are in accordance with previously published RCTs that found good efficacy and safety of comparable monoterpenes in the treatment of ARS or uncomplicated upper RTIs, underlining their anti-inflammatory and secretolytic properties as mentioned above [24-28, 36, 37]. A recent review from Paparoupa and Gillissen highlighted the antioxidative, anti-inflammatory and antibacterial potential of a standardized combination of d-limonene, 1,8-cineole and alpha-pinene (Myrtol® standardized) in several acute and chronic RTIs [27]. The authors concluded that this kind of medication should be initiated in several acute and chronic RTIs, especially in cases when bacterial infection is uncertain. Federspil et al. found out that Myrtol® standardized was significantly superior to placebo in the treatment of 330 patients with ARS [25]. In a double-blind, placebo-controlled RCT cineole was significantly more effective for timely treatment of non-purulent rhinosinusitis in 150 patients [24]. To date, one placebo-controlled RCT examined the efficacy and safety of Tavipec® in acute RTIs: Kähler et al. administrated 300 mg Tavipec® three times daily to 256 patients with uncomplicated acute bronchitis [28]. The treatment with Tavipec® exhibited a significant mean difference of 25% of a defined total bronchitis severity score (BSS) between verum and placebo after 7 ($p<0.005$) and 10 days ($p<0.009$) of full medication as well as a significant amelioration of the patients' QoL ($p<0.001$) as compared to placebo.

In our study we focused on symptom relief and health-related QoL patterns by using the MSS, SNOT-22 and patients' verbally rated QoL as outcome measures. The MSS was explicitly designed to measure the severity of the most relevant rhinosinusitis symptoms and has been previously applied in numerous rhinosinusitis clinical trials in this field [5, 40, 44-46]. Our results revealed a significant improvement of the mean MSS in verum treated patients after 7 days of full medication ($p<0.001$), however, the initially aimed-for difference of 20% in the mean MSS between Tavipec® and placebo after both 4 and 7 days of full medication was not achieved. This may be due to the self-limiting nature of ARS attenuating the magnitude of treatment effects when compared against placebo within the given time frame. This could also reflect the fact that our study design included patients with mild symptoms (MSS >5 and <12). When we conducted a post-hoc sensitivity analysis that included only patients with a baseline MSS >6 (n=228) – excluding ten patients with milder symptoms at baseline – we found significant results with a 20% difference in the mean MSS between Tavipec® and placebo treated patients after 4 and 7 days of full medication (both $p<0.001$). Other than that, the strikingly high scores for postnasal drip in the Tavipec® group might have adversely affected the total MSS. This may be due to the established MoA of monoterpenes, whose secretolytic properties based on the increase of mucus production and CBF of the nasal mucosa are mainly responsible for the desired treatment effect [14, 15, 22, 30, 31].

Apart from the MSS, the significant drop of the mean SNOT-22 score by 37 score points in verum treated patients after a 7-day treatment course is particularly noteworthy. With 22 disease-specific, health-related questions, the validated SNOT-22 questionnaire is widely used to evaluate the disease-related burden on patients suffering from chronic rhinosinusitis. The main advantage of the SNOT-score is the holistic assessment of the various symptom-dimensions of rhinosinusitis [41]. It has been used in previous trials in ARS, however not yet formally validated for ARS [45]. In a population with chronic rhinosinusitis, Hopkins et al established the minimal clinically important difference in SNOT-22 perceptible by the patient being 8.9 score points. In the Tavipec® group a significantly higher proportion of patients achieved a change in SNOT ≥10 score points after 4 and 7 days of treatment compared to placebo, underlining the high clinical relevance of the obtained results. Lange et al. found that a median value of 7 can be taken as normal SNOT-22 reference

score in persons without chronic rhinosinusitis [47]. In our study the mean SNOT-22 score of Tavipec® vs. placebo-treated patients at EOT was 9.5 vs. 15.0 thus revealing a substantial difference and noticeable amelioration of rhinosinusitis symptoms, confirmed by the significant improvement of QoL assessed by patient verbal rating.

Approximately 18% of the patients in the Tavipec® group reported AEs compared to 6% of the patients in the placebo group ($p<0.005$). This difference is due to the known gastrointestinal side effects of monoterpenes. As in this trial, these gastrointestinal complaints are mild and transient. No patient in the Tavipec® group discontinued treatment due to AEs. However, the patients must be informed about this and this is stated in the package leaflet of the medicine. In a recent trial of Tavipec® in uncomplicated acute bronchitis, AEs including gastrointestinal complaints were reported in 15/131 (12%) patients in the Tavipec® arm and in 12/127 (10%) in the placebo arm ($p=0.69$).

Conclusion

The results of our study demonstrate that Tavipec® effectively reduces the symptoms associated with ARS in adult patients. The treatment with Tavipec® provided a perceptible symptom relief and amelioration of health-related QoL thus constituting a feasible alternative to the prescription of antibiotics in a guideline-oriented management of ARS.

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Author contribution

HR was the coordinating investigator in Austria and provided scientific advice for the trial protocol and for drafting the manuscript, participated in the design and conception of the study, contributed to acquisition, analysis and interpretation of data. DD collected and analysed data, contributed to literature search, data interpretation and provided intellectual advice for drafting the manuscript. JBS and WS participated in data acquisition, data analysis and critical revision of the manuscript. GZ concepted, designed and monitored the study, edited and composed the trial protocol and participated in data management, data interpretation and manuscript writing. VH edited and composed the final study report, designed and adapted all illustrations, participated in data management, data interpretation and statistical analysis. All authors critically reviewed the manuscript for important intellectual content and approved the final manuscript.

Conflict of interest

DD, HR, JBS and WS received financial support from Pharmazeutische Fabrik Montavit Ges.m.b.H. during the conduct of the study. GZ and VH are employees of Pharmazeutische Fabrik Montavit Ges.m.b.H.

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