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Effects of EPs 7630 on the duration of inability to work in acute bronchitis – a meta-analysis

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ABSTRACT

Background: Acute bronchitis (AB) has an enormous economic impact through lost working time. We investigated whether treatment with *Pelargonium* extract EPs 7630 may reduce the time of inability to work.

Methods: A meta-analysis of double-blind, randomized, placebo-controlled trials with adult patients suffering from AB was performed. The average number of days of inability to work and the proportion of patients who were still unable to work after one week's treatment were assessed.

Results: Four clinical trials with a total of 1,011 evaluable patients who received the marketed dosage of EPs 7630 (n=505) or placebo (n=506) for seven days were included in the meta-analysis. At baseline, 845/1,011 patients (83.6%) were unable to work. In the four trials, the proportion decreased to between 19 and 14% for EPs 7630 and to between 41 and 55% for placebo (meta-analysis risk ratio and 95% confidence interval: 0.35; 0.26-0.45; p<0.001). For the number of sick days, a weighted mean difference of 1.73 days (1.17-2.29 days; p<0.001) favoring EPs 7630 was observed.

Conclusions: For adults suffering from AB, this meta-analysis demonstrates that seven days' treatment with *Pelargonium sidoides* extract EPs 7630 significantly reduces the average number of sick days and significantly increases the proportion of patients who are able to return to work.

Key words: *Pelargonium*; EPs 7630; acute bronchitis; adults; inability to work; meta-analysis.

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Conflict of interest: HM has received honoraria from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. PF and AZ are employees of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. WL has received honoraria from Dr. Willmar Schwabe GmbH & Co. KG for statistical consulting. This research and its publication were supported by Dr. Willmar Schwabe GmbH & Co. KG. The funder was involved in the design, conduction, analyses, and manuscript preparation of the work. Final decision to submit the manuscript for publication remained with the authors.

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Availability of data and materials: The datasets presented in this article are not readily available because raw data cannot be shared both due to ethical reasons and to data protection laws. To the extent permitted by law, the trial data required for validation purposes have already been disclosed in results reports on corresponding databases. All relevant data are within the paper. Reasonable requests to access the datasets should be directed to the corresponding author.

Ethics approval and consent to participate: The studies included in our meta-analysis were reviewed and approved by the responsible competent, independent Ethics Committees. Further details can be found in the original publications.

Consent for publication: Not applicable.

Introduction

Acute bronchitis (AB) is an inflammation of the larger lower airways and is commonly caused by viral infection [1,2]. Characteristic symptoms include cough with or without phlegm production, fever, malaise, difficulty in breathing, and wheezing [1]. In the USA, cough is the most common illness-related reason for ambulatory care visits, accounting for 2.7 million outpatient visits and more than 4 million emergency department visits annually [1,3]. An episode of AB is reported in an estimated 5% of the general population each year, causing more than 10 million physician visits annually in the USA [4]. Even though the majority of episodes of AB are uncomplicated, they may nevertheless have a detrimental effect on essential activities of daily living [5]. In Europe, acute cough and lower respiratory tract infections (LRTIs) are among the main causes of lost working hours in adults and the most common reason people take sick leave. The GRACE study performed in primary care networks in 12 European countries revealed that advice to take time off work was given to 55.6% of employed patients who consulted a physician for an episode of acute cough, and that patients were absent from work/school for an average of 4 (SD 5) days, with noticeable differences between countries [6,7]. Based on a rate of 5% of the population affected per year and an average of 4 days of sick leave per episode, it may be estimated that AB induces economic damage of about 200 missed working days per 1,000 people of the working population annually. Therefore, AB and other acute respiratory tract infections cause a significant economic burden not only on the healthcare system, but also on the economy in general through decreased productivity and lost work time due to disease-related disability and inability to go to work [7-9].

In accordance with the updated Cochrane review on antibiotics for AB, which concluded that the still widely prescribed antibiotic treatment has a limited effect, if any [10], best practice and disease management guidelines generally discourage the use of antibiotics in AB. Instead, they advocate symptomatic treatment that is focused on the improvement of the patients' well-being and on the restoration of their daily living skills [4,11,12].

EPs 7630 (EPs® 7630 is a proprietary extract and active ingredient in pharmaceuticals manufactured by Dr. Willmar Schwabe GmbH and Co. (KG, Karlsruhe, Germany), is an herbal drug preparation from the roots of *Pelargonium sidoides*, which has been approved as a medicinal product for the treatment of respiratory tract infections, including AB, in countries as Asia, Europe, Australia, and in Central and South America. *In vitro* experiments with EPs 7630 and isolated constituents have shown pharmacological activities including moderate direct antiviral and antibacterial action and notable immune-modulatory capabilities. The latter involve the activation of the mitogen-activated protein kinase pathway [13] and a subsequent regulation of different cytokines such as tumor necrosis factor α, interferon-β, or interleukin-22, depending on the experimental context [14,15]. Furthermore, antitussive, secretolytic, and anti-inflammatory effects of EPs 7630 were observed in animal models after oral administration at human equivalent doses [16]. EPs 7630 was also shown to interfere with the replication of seasonal influenza A virus strains (H1N1, H3N2), respiratory syncytial virus, human coronavirus 229E, parainfluenza 3 virus, and coxsackie virus A9 [17]. Moreover, EPs 7630 was reported to reduce rhinovirus infection to human bronchial cells. This effect was associated with the downregulation of cell-membrane docking proteins and the up-regulation of host defense proteins [18] as well as the increased expression and nuclear translocation of vitamin D receptor [19]. In various *in vitro* experiments, EPs 7630 was further demonstrated to inhibit SARS-CoV-2 replication and modulate innate immune responses in the human lung cell line Calu-3 [20,21]. *In vitro* inhibitory activity against SARS-CoV-2 was also shown for a commercial form of EPs 7630 and the biomolecules scopoletin and umckalin contained in the extract [22]. Comprehensive presentations of the pharmacological properties of EPs 7630 have been published elsewhere [23,24].

As shown in several reviews [24-30], the clinical effects of EPs 7630 in AB and other acute respiratory tract disorders have been studied extensively and meta-analyses have demonstrated that EPs 7630 is superior to placebo in reducing the severity of bronchitis-related symptoms assessed by means of a validated scale [31,32]. Moreover, a meta-analysis showed that the proportion of patients who were completely symptom-free after a seven-day treatment with EPs 7630 exceeded that in the placebo group by about factor six [29]. Results from another meta-analysis further demonstrated that children suffering from acute respiratory tract infections who were treated with EPs 7630 required less paracetamol co-medication [33]. In addition, EPs 7630 treatment outcomes in common cold patients with confirmed human coronavirus infection (HKU1, OC43, NL63, 229E) were shown to be as favorable as in patients with other viral infections [34].

While these findings indicate that EPs 7630 accelerates the course of recovery and thus shortens the duration of AB-associated symptoms, two clinical trials reported by Matthys and colleagues explicitly assessed the association between EPs 7630 administration and inability to work [35,36]. The results suggest that EPs 7630 may not only reduce the symptom burden of adults suffering from AB and accelerate recovery, but may also enable patients to return to work earlier. Given the enormous economic impact of the inability to work due to AB, this would be a significant economic advantage. Despite this fact, current evidence from meta-analyses focuses on symptom-based results of the primary outcome (*i.e.*, the validated Bronchitis Severity Score BSS) of the analyzed trials only. The inability to work, which not only reflects the perceived symptom severity and duration of those affected but also the subjective assessment of the attending physician, has not been comprehensively addressed in meta-analyses so far. To investigate the association between treatment with EPs 7630 and the duration of inability to work due to AB, we, therefore, performed a meta-analysis of randomized, placebo-controlled trials from which information on medical leave could be derived, also if assessed as a secondary outcome measure.

Methods

Eligibility criteria, search strategy

Clinical trials were eligible for inclusion into our meta-analysis if they were double-blind, randomized, and placebo-controlled and investigated the treatment of AB with EPs 7630 in patients ≥18 years of age. Moreover, data referring to the patients' ability to work during the course of recovery from AB had to be reported as primary or secondary outcome.

Clinical trials were identified by means of searches of the PubMed database and the ISRCTN clinical trials registry using the search terms 'EPs 7630' or 'Pelargonium, 'clinical trial', 'placebo', and 'acute bronchitis'. Language restrictions were not applied. Relevant data of the trials identified during our searches was provided by the manufacturer of EPs 7630. This study was not preregistered.

All trials included into this meta-analysis were planned, conducted, and analyzed according to the principles of Good Clinical Practice and the Declaration of Helsinki. The trial protocols and

other required trial documents were approved by the respective independent Ethics Committee and competent authorities. All participants in the studies gave their informed consent.

Dosage and presentation

EPs 7630 is an herbal drug preparation from the roots of *Pelargonium sidoides*, drug extract ratio 1:8–10, extraction solvent: ethanol 11% (w/w), that is marketed as a solution, as tablets, and as a syrup for children. The recommended daily doses for adult patients are 3x30 drops of solution or 3x1 tablet containing 20 mg of the herbal extract, corresponding to the quantity contained in 30 drops of the solution.

Outcomes of interest

In the trials that met our eligibility criteria, assessments of whether a patient was able to work were obtained either during each scheduled visit or by means of a patient diary. From this we calculated the average number of sick days during the trial period as well as the number and proportion of subjects who were unable to go to work at baseline (immediately prior to the start of the investigational treatment) and on treatment day 7 (treatment end).

Statistical methods

Analyses were performed based on the raw data of the included trials, which were obtained from the study sponsor.

For comparability with the procedure applied in Matthys *et al*. [35], the calculation of sick days was based on the number of days between baseline and the actual dates of the documented post-baseline visits or diary entries; for patients who were still unable to work at the last visit / last diary entry, it was assumed that the participant had remained unable for another three days after the day of the last visit. To assess the impact of this assumption, sensitivity analyses were performed in which two, one, and zero days were added to the last visit instead of three.

Procedures for the handling of missing data were adapted from the corresponding procedures applied in the eligible trials. Missing data on day 7 were replaced by the last observed value (last observation carried forward method). In case of missing baseline data, patients were assumed to be unable to work if there was at least a post-baseline assessment with inability to work, and able to work otherwise.

All analyses were performed based on the full analysis set of study participants which was the primary data set for the original analysis of efficacy in all trials analyzed. Sample characteristics were analyzed using applicable descriptive summary measures. For the number of sick days, meta-analysis was performed by computing the difference between the mean values of the treatment groups and the associated 95% confidence intervals (CIs) in their original scale. Meta-analysis of the proportion of patients who were unable to go to work at the treatment end was based on the risk ratio and its 95% CI. Heterogeneity between the primary trials was assessed using the I^2 statistic. Random effect models were computed in case of I^2>5%, and fixed effect models were used otherwise. Review Manager (RevMan) Version 5.3 or higher was used for all meta-analyses [37]. All specified p are two-sided. Treatment differences were considered descriptively significant if the 95% CI of the point estimate did not include the value of 0 for differences between means or the value of 1 for risk ratios, corresponding to a descriptive $p \leq 0.05$.

Results

Search results and study populations

The literature searches conducted covered the earliest database record to the end of December 2020 (Figure 1). They identified a total of 20 relevant publications and one registry entry that were assessed in detail for eligibility for our meta-analysis. Two papers [38,39] were duplicates or reported additional analyses performed on clinical trials for which an original publication was available. Six were review articles from which no additional original publications meeting our selection criteria could be inferred [25,26,33,40-42]. Five published trials [43-47] and the trial identified from the ISRCTN registry investigated the effects of EPs 7630 in a different patient population (children, adolescents) and/or in an indication other than AB. Three papers did not present results from a randomized, placebo-controlled clinical trial but discussed methodological issues, reported on a post-marketing surveillance study, or were based on a press release [48-50]. The remaining four publications [35,36,51,52] met our eligibility criteria as outlined in the *Methods* section.

All eligible studies were randomized, placebo-controlled clinical trials that assessed the efficacy of EPs 7630 in adults suffering from AB; they were included in our meta-analysis without further restrictions (Table 1). Three trials investigated EPs 7630 solution while one trial used the tablet formulation. The study reported by Matthys *et al*. 2010 [51] was a four-arm dose-finding study that compared EPs 7630 3x10 mg/day, 3x20 mg/day, and 3x30 mg/day to placebo. For comparability, only the marketed dosage of 3x20 mg/day was included in the meta-analysis. According to the study protocols of the eligible trials, the pre-defined primary outcome measure for efficacy was the absolute change of the total score of the BSS [32] between baseline and treatment end scheduled at day

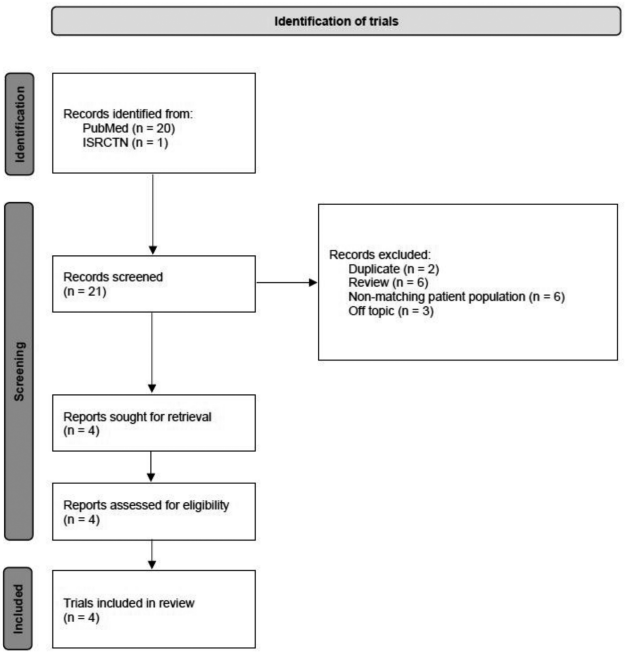

Figure 1. Search results.

7, while the ability to work was assessed as a secondary outcome measure. Clinical trials addressing patients' ability to work as the primary outcome measure could not be found.

All eligible trials were planned, performed, and analyzed under consideration of the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocols and other required study documents were submitted to and approved by the competent independent ethics committee and regulatory authorities. All participants provided informed consent.

A total of 1,011 patients (EPs 7630 505; placebo 506) were included in the meta-analysis since one patient in the EPs 7630 group of Matthys *et al*. [35] did not provide any data for inability to work at any visit and was excluded in the original analysis as well. Demographic characteristics are shown in Table 1. The majority of the participants were male. In the study of Matthys *et al*. [35], about $^{2}/_{3}$ of participants were unable to work at baseline, whereas the proportion of absentees in the remaining trials exceeded 90% (Table 2).

Number of days off work

On an individual study level, the average number of sick days ranged between 4.7 and 7.5 for EPs 7630 and between 6.3 and 9.1 for placebo, assuming that patients who were still unable to work at treatment end remained so for another three days beyond end of study in accordance with our pre-defined assumptions. Since I^2=61%, a random effects meta-analysis was performed which determined a weighted mean difference of 1.73 days (95% CI 1.17-2.29 days) between the treatment groups favoring EPs 7630 (p<0.001). Figure 2 also shows that the number of sick days is significantly lower in the EPs 7630 group as compared to the placebo group when each study is considered separately, with treatment group mean differences ranging between 1.15 and 2.36 days.

Sensitivity analyses assuming between two and zero additional days off work in patients who were still on inability to work at treatment end led to the same conclusion as the pre-defined primary analysis and all resulted in p<0.001 favoring EPs 7630. Since the number of patients who were still unable to work at the end of treatment was larger in the placebo group than in the EPs 7630 group (see below), the absolute mean difference between the treatment groups was reduced when fewer additional sick days were assumed, but this had only a minor influence on the calculated meta-analysis effect sizes.

Patients still unable to work at the end of the study

Table 2 shows that the proportions of patients who were unable to work before the start of treatment were comparable for EPs 7630 and placebo. While more than 90% of the patients in three out of the four trials included in the meta-analysis had been unable to work at baseline, the proportion decreased to between 19% and 14% in patients treated with EPs 7630 and to between 41% and 55% in the placebo group. Due to I^2=27%, a random-effects meta-analysis was performed for the proportion of study participants still unable to work at the treatment end as well, resulting in a weighed risk ratio of 0.35 (95% CI 0.26-0.45; p<0.001) favoring EPs 7630 (Figure 3). Significant superiority of the herbal medicinal product over the placebo was also observed for each of the four clinical trials assessed individually, with risk ratios ranging between 0.26 and 0.47.

Discussion

The secondary costs of viral RTIs such as AB due to decreased productivity and disease-related inability to work have been recognized as a major economic burden [7-9]. Even if such conditions are mainly uncomplicated, the symptoms may be disabling and may significantly impair the patients' physical comfort. Efficient treatment that reduces the symptom burden and accelerates the

Table 1. Characteristics of trials and patients included in the meta-analysis (age: means ± SD [range]; sex: absolute frequencies and %; full analysis set).

Trial	Treatment duration, dosage	Treatment	Patients	Age (years)	Sex: females
Matthys *et al.*, 2003 [35]	7 days, 30 drops t.i.d	EPs 7630	233*	41.1±14.1 [18-92]	94 (40.3%)
		Placebo	235	39.9±14.2 [18-81]	75 (31.9%)
Chuchalin *et al.*, 2005 [52]	7 days, 30 drops t.i.d.	EPs 7630	64	36.2±13.0 [18-71]	15 (23.4%)
		Placebo	60	35.9±13.2 [18-68]	22 (36.7%)
Matthys and Heger, 2007 [36]	7 days, 30 drops t.i.d	EPs 7630	108	38.3±13.4 [18-64]	30 (27.8%)
		Placebo	109	36.5±11.4 [18-66]	23 (21.1%)
Matthys *et al.*, 2010 [51]	7 days, 20 mg tablet t.i.d.	EPs 7630	101	41.8±13.2 [19-64]	24 (23.8%)
		Placebo	102	38.5±12.6 [18-65]	39 (38.2%)

*Due to missing data, one patient from the full analysis set could not be evaluated for disease-related inability to work.

Table 2. Patient unable to work (absolute frequencies and %; full analysis set).

Trial	Treatment	Baseline	End of study
Matthys *et al., 2*003 [35]	EPs 7630	157 (67.4%)	37 (15.9%)
	Placebo	159 (67.7%)	101 (43.0%)
Chuchalin *et al.*, 2005 [52]	EPs 7630	64 (100.0%)	9 (14.1%)
	Placebo	60 (100.0%)	33 (55.0%)
Matthys and Heger, 2007 [36]	EPs 7630	107 (99.1%)	21 (19.4%)
	Placebo	109 (100.0%)	45 (41.3%)
Matthys *et al.*, 2010 [51]	EPs 7630	94 (93.1%)	14 (13.9%)
	Placebo	95 (93.1%)	55 (53.9%)

restoration of the patients' well-being and fitness to work while not presenting an appreciable, treatment-emergent risk, therefore appears to be justified both ethically and economically.

In patients with AB and other acute RTIs, *Pelargonium sidoides* extract EPs 7630 has been demonstrated to significantly reduce symptoms such as coughing and related chest pain and dyspnea, and to facilitate expectoration [24-27,29]. For AB, a recent meta-analysis demonstrates that the proportion of patients who were completely symptom-free after one weeks' treatment with EPs 7630 was significantly higher than in placebo-treated patients [29].

However, results obtained from meta-analyses so far mainly focus on symptoms assessed by the Bronchitis Severity Score, which was the primary outcome in most clinical trials investigating EPs 7630. Our study adds to currently available evidence by analyzing the number of sick days, which was only assessed as a secondary outcome measure so far. The results of our analysis demonstrate that the acceleration of recovery from AB symptoms observed in placebo-controlled trials has practical implications and enables patients to return to work significantly earlier, with an average meta-analysis difference to placebo of 1.73 days in the underlying patient population of adults with AB.

Preparations of *Pelargonium* are available in various forms and extracts may be prepared using different extraction agents. While many preparations are poorly characterized, the pharmacological properties of EPs 7630 have been thoroughly investigated in nonclinical studies and clinical trials. Therefore, in this context, it should be noted that the clinical evidence presented for EPs 7630 in our and previous studies only refers to this proprietary extract.

Given the number of episodes of AB encountered annually in the working population [4], a saving of disease-related inability to work in the range of nearly two days per episode may translate into an appreciable economic advantage. These results were supported by our meta-analysis of fitness to work at the study end: whereas about half of the patients treated with placebo were still on inability to work after one week's treatment, more than 80% of those in the EPs 7630 group had returned to (or remained at) work. The observed risk ratio of 0.35, with the upper bound of the 95% CI at 0.45, indicates that patients treated with EPs 7630 were about 2.9 times as likely (and at least 2.2 times as likely) to go to work after one week than those who received a placebo. A recent analysis of medical record data confirmed that this effect observed in controlled clinical trials translates into a benefit in routine clinical care [53].

Measured against the standards proposed by the Cochrane Collaboration [54], heterogeneity in our meta-analyses was in the moderate to lower substantial range. Figure 2 and Figure 3 clearly indicate, however, that heterogeneity between the trials was attributable to differences in magnitude, not to differences in the direction of the observed treatment effect, and thus it is unlikely to interfere with the basic interpretation of the aggregated meta-analysis results.

Among the trials included in this meta-analysis, some results referring to the observed number of sick days and/or inability to work by the end of the study were also included in the original papers by Matthys and colleagues published in 2003, 2007 and 2010 [35,36,51], as well as in a secondary publication by Matthys and Funk [38] referring to the trial published in 2007 [36]. We observed some minor discrepancies between the results in Matthys *et al*. 2010 [51] and those of our meta-analysis, which were, however, fully explained by differences in the handling of missing data and in the assumptions about the duration of disease-related inability to work in patients who had still not resumed work by the end of the study.

The clinical trials included in the meta-analysis were designed to demonstrate the superiority of EPs 7630 over placebo with a focus on the pre-defined primary outcome measure, i.e., BSS total score change between baseline and day 7. A potential weakness of this investigation was therefore that patients were observed only

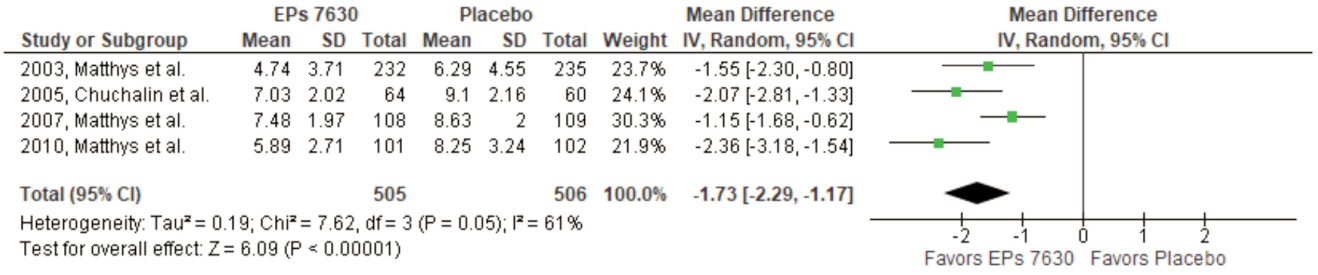

Figure 2. **Meta-analysis of number of days off work**

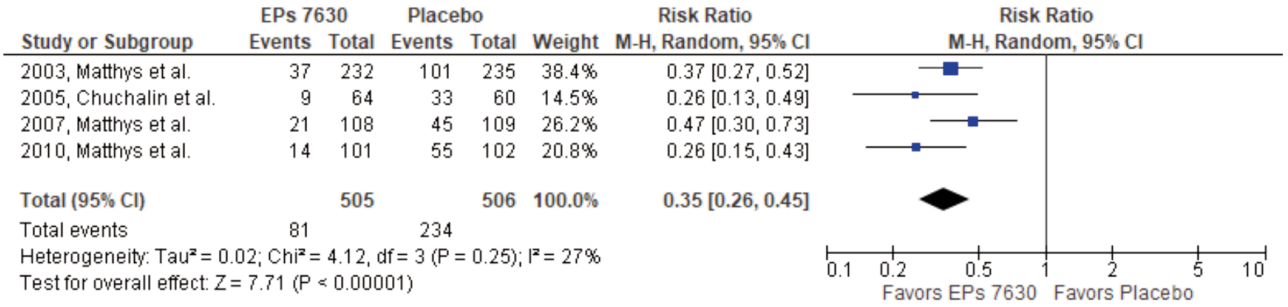

Figure 3. **Meta-analysis of number of patients still incapable to work at the last visit.**

for a week after the start of treatment so that for those who were still unable to return to work at the study end the number of sick days had to be estimated by assuming another three days off work after the end of study. This procedure was chosen for comparability with the computational procedure applied by Matthys *et al*. [35]. While it is certainly not realistic to assume that all patients who still stayed at home at the end of the study returned to work promptly the next day, it is worth mentioning that even under this 'worst case scenario' a significant advantage of EPs 7630 over placebo in the number of sick days could be demonstrated.

Conclusions

For adults suffering from AB, this meta-analysis demonstrates that seven days' treatment with *Pelargonium sidoides* extract EPs 7630 using the marketed dosage significantly reduces the average number of sick days and significantly increases the proportion of patients who are able to return to work after one week. Since the risk of side effects of EPs 7630 is low [28], EPs 7630 presents an interesting therapeutic option that accelerates the restoration of the patients' well-being while reducing the secondary economic burden of AB.

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