

# TREATMENT OF SORE THROAT AND HOARSENESS WITH PELARGONIUM SIDOIDES EXTRACT EPS 7630: A META-ANALYSIS

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## SUMMARY

The extract EPs 7630 from the roots of *Pelargonium sidoides* has been proven safe and effective in the treatment of acute respiratory tract infections (aRTI). The aim of this study was to perform a meta-analysis on the efficacy of EPs 7630 in patients suffering from acute non-streptococcal tonsillopharyngitis (ATP) or common cold (CC) regarding the symptoms sore throat and hoarseness.

This meta-analysis encompasses double-blind, placebo-controlled, randomized clinical trials investigating the efficacy of EPs 7630 in ATP or CC. Relevant publications were identified by searching PubMed and clinical trial registries (ISRCTN, ClinicalTrials.gov; search terms: acute tonsillopharyngitis, common cold, EPs 7630, Umckaloabo, hoarseness, and sore throat) and the assessment report on *Pelargonium sidoides* of the European Medicines Agency. Clinical study reports of unpublished trials were provided by the manufacturer of EPs 7630. Meta-analysis was performed separately for both indications, for formulations found, and for patient groups. Efficacy analyses were based on the change of symptom severity of 'sore throat' and 'hoarseness' as assessed by the respective indication-specific symptom scores, and on complete remission. Disease-related quality of life was also analyzed.

Seven trials with a total of 1,099 participants could be included into the meta-analysis. Clinical trials investigating EPs 7630 in CC comprised adults only, whereas those in ATP only included children. Results showed EPs 7630 to be superior to placebo in reducing both symptom severity and time until complete recovery for the symptoms 'sore throat' and 'hoarseness' in the indications investigated.

These findings suggest that EPs 7630 is effective in reducing severity and time to remission of the symptoms sore throat and hoarseness in ATP and CC, respectively.

## Key words

Acute Tonsillopharyngitis;  
Common Cold; EPs 7630;  
Hoarseness; Sore Throat;  
Umckaloabo.

## Impact statement

The provided evidence for superiority of EPs 7630 over placebo in reducing the symptom severity of sore throat and hoarseness in acute tonsillopharyngitis and common cold, respectively, and the fast symptom reduction seen suggest the herbal drug to

be a considerable alternative to therapy by analgesics or even antibiotics, which is a particularly important finding for the management of acute respiratory tract infections in children and adults.

### Abbreviations

AB: Acute Bronchitis; aRTI: Acute respiratory tract infections; ATP: Acute Tonsillopharyngitis; CC: Common Cold; CI: confidence interval(s); CIS: Cold Intensity Score; FGK: Fragebogen zum Gesundheitszustand für Kinder; ICOS: inducible co-stimulator; ICOSL: inducible co stimulator ligand; IFN: interferon; IL: interleukin; QoL: quality of life; RCT: randomized controlled trial(s); RPS: Rhinopharyngitis-relevant Symptoms; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TSS: Tonsillitis Severity Score.

## INTRODUCTION

Acute respiratory tract infections (aRTI) are diseases that frequently affect otherwise healthy subjects of all ages (1-3). Whereas adults experience aRTI 2-3 times per year, children experience about twice as many (3, 4).

Of all aRTI, acute tonsillopharyngitis (ATP) is one of the most common conditions in children (5). Inflammations of pharynx, larynx, and neighboring areas appearing with symptoms of sore throat or hoarseness are also highly prevalent in common cold (CC), accompanied by acute cough and overall malaise (6, 7). These conditions are associated with a considerable degree of discomfort and pain and related interference with daily life activities (8-10). Therefore, in order to quickly reduce symptom severity, pharmacological therapy is often expected by patients consulting with primary care (11), which has currently led to excessive over-prescription and misuse of antibiotics (12), even though most cases have a viral origin (3, 5, 13, 14), in which no antibiotic treatment is needed (15, 16). This scenario has recently been subject to increasing criticism by the scientific community for reasons of medical consideration (low effectiveness in aRTI management (15)) and for economic aspects (unnecessary cost explosion (17)), as well as for reasons of sensible health care (increase in the risk of undesired side effects of antibiotics and development of antimicrobial resistance (18)), with the last aspect of sensible health-care being of particular interest for

aRTI therapy in children, who are frequently affected.

Alternative and efficacious options for the treatment of aRTI exist and have gained increasing scientific interest. This group includes herbal medicines, some of which have a long-standing tradition of successful aRTI treatment (19), such as *Pelargonium sidoides*. EPs 7630<sup>1</sup>, an extract from the roots of *Pelargonium sidoides* (1 : 8–10), extraction solvent: ethanol 11% (w/w), is used in children from the age of one year, adolescents and adults for the treatment of aRTI in several countries in Europe, Asia, Australia, as well as Central and South America. Tablet as well as liquid (syrup and drops) formulations are available.

EPs 7630 is classified by the European Pharmacopoeia as "other extract". It is therefore not adjusted to a specific content of constituents. To confirm the quality and identity of the herbal material, the dried material was tested in an array of biochemical and phytochemical methods. Approximately 80% m/m of the extract are assigned to six major groups of constituents, namely unsubstituted and substituted oligomeric prodelphinidins, monomeric and oligomeric carbohydrates, minerals, peptides, purine derivatives, and highly substituted benzopyranones (20). With a share of about 40%

1 EPs<sup>®</sup> 7630 is the active ingredient of the product Umckaloabo<sup>®</sup> (ISO Arzneimittel, Ettlingen, Germany).

of the dried extract, oligomeric prodelphinidins (in this context commonly designated as polyphenols) are the most significant of this groups.

Medicinal products with EPs 7630 as active substance are authorized by numerous authorities worldwide based on nonclinical studies as well as on their proven clinical safety (21-23). EPs 7630 contains a small amount of highly substituted coumarin derivatives that are exclusively 7-hydroxycoumarin derivatives (24) which do not possess the structural characteristics of the known anticoagulant coumarins (25-27). No influence of EPs 7630 on plasma coagulation, as well as possible pharmacokinetic or pharmacodynamic interactions with warfarin, was observed in animal experiments (24). On this ground, it appears unlikely that an increased tendency towards bleeding complications arises in patients due to intake of EPs 7630 (24). Furthermore, unlike other coumarins, 7-hydroxycoumarin derivatives contained in EPs 7630 do not possess hepatotoxic properties (28).

The proanthocyanidin-rich extract EPs 7630 displays immune-modulating as well as antiviral properties (29, 30). Several non-clinical studies demonstrated activity against a variety of respiratory viruses such as influenza A virus (H1N1, H3N2), respiratory syncytial virus, human coronavirus (HCoV) HCoV-229E, and parainfluenza virus (31, 32). Although the distinct contributions of the individual constituents of EPs 7630 are not fully defined yet, the polyphenolic compounds, in particular prodelphinidins, are thought to be responsible for the antiviral effects described (31, 32). EPs 7630 also inhibited the attachment of human immunodeficiency virus 1 to human immune cells and viral entry in cell culture experiments (33). Furthermore, the herbal extract inhibited replication of influenza A virus by inhibition of hemagglutinin and neuraminidase activity (31), which was at least partly mediated by the proanthocyanidin constituents. In human bronchial epi-

thelial cells, EPs 7630 reduced replication of rhinovirus-16 by downregulating the expression of inducible co-stimulator (ICOS) and its ligand (ICOSL) as well as the surface calreticulin receptor, whereas levels of proteins supporting host defense were increased (34). Mechanistically, EPs 7630 significantly reduced host cell attachment of various viruses and prevented the release of viruses from infected cells. The extract was also shown to stimulate the release of nitric oxide, type I interferon (IFN), and different cytokines involved in host defense mechanisms (35-37). In athletes, EPs 7630 modulated the immune response during strenuous exercise by increasing the production of immunoglobulin  $\alpha$  in saliva, decreasing serum interleukin (IL)-15 and IL-6 levels, and reducing IL-15 in the nasal mucosa (38). In children, the *Pelargonium sidoides* extract was also found to prevent asthma attacks provoked by rhinovirus, probably by interfering with IL-6-, IL-8-, and IL-16-mediated inflammation (39). Moreover, most recent results from in vitro experiments showed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry inhibition and differential immunomodulatory functions of EPs 7630 against SARS-CoV-2 (30).

Over the past 25 years, more than 30 clinical trials were conducted investigating EPs 7630 for the treatment of acute respiratory tract infections (aRTI) (40). Several systematic reviews and meta-analyses of controlled, randomized clinical trials (RCT) investigating the efficacy and safety of EPs 7630 in aRTI (22, 23, 41-48) have been published, providing evidence for the efficacy and safety of the herbal medicinal drug in the treatment of acute bronchitis (AB), common cold, ATP, and acute rhinosinusitis (ARS). We now performed a meta-analysis of double-blind, placebo-controlled RCT in order to evaluate the efficacy of EPs 7630 compared to placebo regarding the symptoms sore throat and hoarseness, the most impairing symptoms that come with ATP and CC.

## METHODS

### Included trials

Double-blind, placebo-controlled RCT investigating the efficacy of EPs 7630 in the indications ATP or CC available until the end of the year 2021 were eligible. Relevant publications were identified by free-text searches of all fields of PubMed as well as of clinical trial registries (ISRCTN registry; ClinicalTrials.gov) using the search terms 'acute tonsillopharyngitis', 'common cold', 'hoarseness', and 'sore throat', each in combination with either 'EPs 7630' or 'Umckaloabo', and from the List of references supporting the assessment of *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix of the European Medicines Agency (EMA) (49). Moreover, clinical study reports of unpublished trials were provided by the manufacturer of EPs 7630 (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany). The literature from the earliest record until 31 December 2021 was covered.

### Outcome measures

Primary outcome measure of treatment effects was the change of the respective indication-specific symptom scores of 'sore throat' and 'hoarseness' between baseline and pre-defined day under EPs 7630 as compared to placebo, as well as the number of patients with partly or complete recovery from these symptoms. Response to therapy was also calculated (defined as the number of patients with a symptom reduction concerning 'sore throat' or 'hoarseness', respectively, by at least 50% between baseline and pre-defined day). A further objective was to gain insight into data reflecting the change of disease-related quality of life (QoL) under EPs 7630 therapy as compared to placebo.

Only data of patients in whom the respective symptom ('sore throat', 'hoarseness') was present at baseline was included into the meta-analyses. Study selection and methods of the analysis were specified in advance and documented accordingly.

### Ethics

All trials included into this meta-analysis were reported to be 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 or informed consent was provided by their legal representative, respectively.

### Statistics

All meta-analyses performed were based on the full analysis sets of the RCT included. Review Manager (RevMan) Version 5.4 software (50) developed by the Cochrane Collaboration was employed. Heterogeneity between the primary trials was assessed using the I<sup>2</sup> statistic. Random effects models were computed in case of I<sup>2</sup> > 5%, otherwise fixed effect models were used. Meta-analyses of treatment efficacy for continuous outcome parameters were based on the mean change in the corresponding symptoms between baseline and the pre-defined day for each treatment group in the single trials. The difference between mean values of the treatment groups and the associated 95% confidence intervals (CI) on the respective scales subsequently resulted from RevMan. Risk ratios and their 95% confidence intervals were the chosen estimates from the meta-analyses related to binary parameters such as the number of patients with partial or complete recovery. As we conducted descriptive analyses, the resulting 95% confidence intervals and p-values must be interpreted accordingly.

### Results

A total of 9 eligible records (6 published (51-56), 3 unpublished (57-59)) were identified. For these records, the full text was assessed for further eligibility. One record reported a different dosing scheme compared to the other trials found and was therefore excluded to

ensure a better comparability of the studies (51). Thus, 8 records reporting on a total of 7 clinical trials (for one clinical trial, each of two trial parts was published separately (54, 55)) were included. Data in our meta-analysis were thus taken from publications and unpublished data of seven RCT investigating the efficacy and safety of EPs 7630 in the indications ATP and CC (**table I**).

Overall, the 7 RCT comprised 1,099 trial participants (549 randomized to EPs 7630, 550 randomized to placebo); of these, 267 were

children (aged 6-10 years) and 832 adults (18 years or older). Mean demographic data are summarized in **table II**.

In those RCT investigating EP 7630 in ATP (Trials 1 (52) and 2 (53)), patients were children aged 6-10 years (EPs 7630: 133, placebo: 134). In those RCT investigating EPs 7630 in CC (Trials 3-7 (54-59)), patients were 416 adults randomized to EPs 7630 and 416 adults randomized to placebo. Two of the trials investigated the efficacy of EPs 7630 film-coated tablets (Trials 4 (56) and 7 (59)), whereas the solution

**Table I.** Trials included.

Indication	Trial	Age range	Treatment duration/ dosage	Primary efficacy variable	Number of patients (FAS)	
					EPs 7630	Placebo
Acute tonsillo-pharyngitis	1 (52)	6-10 years	6 days: 20 drops t.i.d.	Change of TSS total score from baseline to day 4	60	64
	2 (53)	6-10 years	6 days: 20 drops t.i.d.	Change of TSS total score from baseline to day 4	73	70
Common Cold	3 (54, 55)	≥ 18 years	10 days 3a: 3*30 drops/d	Change of CIS total score from baseline to day 5	3*30 drops: 52	51
			or 3b: 3*60 drops/d		3*60 drops: 52	52
	4 (56)	≥ 18 years	10 days 3*40 mg/d	Change of CIS total score from baseline to day 5	53	52
	5 (57)	≥ 18 years	10 days 3*30 drops/d	Change of RPS total score from baseline to day 5	99	101
	6 (58)	≥ 18 years	10 days 3*30 drops/d	Change of RPS total score from baseline to day 5	101	100
	7 (59)	≥ 18 years	10 days 3*20 mg/d	Change of RPS total score from baseline to day 5	59	60

Reference's number in parentheses.

**Table II.** Demographics.

Indication	Trial	Treatment group				
			Mean age (SD)	Male	Female	Total
ATP	1 (52)	EPs 7630	7.60 ( 1.09)	29	31	60
		Placebo	7.44 ( 1.19)	28	36	64
	2 (53)	EPs 7630	7.58 ( 1.26)	40	33	73
		Placebo	7.46 ( 1.13)	30	40	70
	<b>EPs 7630</b>		<b>7.59 ( 1.18)</b>	<b>69</b>	<b>64</b>	<b>133</b>
	<b>Placebo</b>		<b>7.45 ( 1.15)</b>	<b>58</b>	<b>76</b>	<b>134</b>
CC	3a* (standard dose) (54)	EPs 7630	34.52 (10.60)	16	36	52
		Placebo	37.35 (10.52)	16	35	51
	3b* (high dose) (55)	EPs 7630	36.81 ( 9.91)	14	38	52
		Placebo	33.75 (10.84)	12	40	52
	4 (56)	EPs 7630	34.98 (10.86)	13	40	53
		Placebo	37.69 (10.48)	11	41	52
	5 (57)	EPs 7630	37.11 (13.58)	33	66	99
		Placebo	37.13 (12.46)	35	66	101
	6 (58)	EPs 7630	44.76 (14.10)	37	64	101
		Placebo	46.18 (14.09)	30	70	100
	7 (59)	EPs 7630	32.63 (11.02)	33	26	59
		Placebo	33.33 (10.64)	31	29	60
	<b>EPs 7630</b>		<b>37.70 (12.93)</b>	<b>146</b>	<b>270</b>	<b>416</b>
	<b>Placebo</b>		<b>38.43 (12.80)</b>	<b>135</b>	<b>281</b>	<b>416</b>

\*Trials 3a and 3b are two parts of the same clinical trial, each part was published separately (54, 55).

ATP = acute tonsillopharyngitis; CC = common cold.

Reference's number in parentheses.

formulation was investigated in the remaining three trials (54, 55, 57, 58).

As defined by the respective protocols, the trials investigating ATP (52, 53) employed a tonsillitis severity score (TSS) (60) for symptom severity rating, which comprises five subscores, namely 'dysphagia', 'sore throat', 'salivation', 'redness', and 'fever'. Each of these symptoms was rated by the responsible investigator on a four-point rating scale ranging from severe (= 3), moderate (= 2), mild (= 1) to not present (= 0).

Secondary efficacy variables of the ATP trials considered for the analysis were: Single items of the FGK Questionnaire (Fragebogen zum Gesundheitszustand für Kinder) (60) as supportive indicators of the children's health state and its change in relation to symptom severity.

The single items of FGK for children ≤ 18 years include 'Everything is too much for me', 'I am feeling ill', 'I am scared', 'I have trouble playing or learning', 'I sleep badly',

'I have problems getting into conversation with others'. Results for each item were documented on a 5-point scale (not at all (= 1), a little bit (= 2), moderate (= 3), distinctive (= 4), very distinctive (= 5)) in the patient diaries.

For those RCT investigating the efficacy of EPs 7630 in adult patients diagnosed with CC, two identical symptom severity rating tools named differently were employed, *i.e.* Rhinopharyngitis-relevant Symptoms (RPS) (57-59) and Cold Intensity Score (CIS) (54-56). Both rating tools include the CC symptoms 'nasal drainage', 'sore throat', 'nasal congestion', 'sneezing', 'scratchy throat', 'hoarseness', 'cough', 'headache', 'muscle aches', and 'fever', which had to be evaluated by the investigator on a five-point scale ranging from inexistent (= 0) to very severe (= 4).

Secondary efficacy variables of the CC trials considered for the analysis were the single items 'Mobility', 'Self-care', 'Usual activity', 'Pain/discomfort', and 'Anxiety/depression' of the EQ-5D Questionnaire (61) as further indicators for the disease-related QoL of patients. Each item was measured on a scale from 1 to 3 (1 = no problems, 2 = some problems, 3 = severe problems).

## Participants

Patients included in the respective RCT had to be between 6 and 10 years old and to present with a diagnosis of non-streptococcal ATP and an overall symptom severity of at least 8 points as measured on the TSS.

Patients who participated in the CC trials employing the RPS (57-59) had to be 18 years or older and to present with both major rhinopharyngitis-relevant symptoms ('nasal discharge' and 'sore throat') rated with  $\geq 2$  points each and at least two minor rhinopharyngitis-relevant symptoms ('nasal congestion', 'sneezing', 'scratchy throat', 'hoarseness', 'cough', 'headache', 'muscle aches', or 'fever') rated with  $\geq 2$  points each or one major RPS rated with  $\geq 2$  points and

at least three minor rhinopharyngitis-relevant symptoms rated with  $\geq 2$  points each on the RPS. Eligible patients who participated in the CC trials employing the CIS (54-56) were required to present with at least two major and one minor or with one major and three minor CC symptoms (maximum symptom score 40 points) present for no longer than 48 hours.

## Interventions

In the clinical trials included in this meta-analysis, the solution (drops) and film-coated tablet formulations were investigated. In the ATP trials (Trials 1, 2 (52, 53)), children were administered 20 drops EPs 7630 t.i.d. over 6 days.

In the CC trials (Trials 3-7 (54-59)), patients were treated with EPs 7630 over 10 days. Medication formulation and dosage were usually 3 x 30 drops per day. In trial 3, a high-dose cohort received 3 x 60 drops per day (55). In Trial 4 (56), EPs 7630 was administered as 1 tablet t.i.d. each containing 40 mg of EPs 7630. In Trial 7 (59), participants received 3 x 20 mg tablets per day.

## Outcome measures

The time point chosen for the assessment of change in symptom severity and in disease-related QoL was day 4 in the ATP trials, and day 5 in the CC trials.

The symptom 'sore throat' as rated by the investigator on the four-point TSS (ATP trials, trials including children) and on the five-point CIS/RPS (CC trials, trials including adults), respectively, was assessed in all eligible RCT. The symptom 'hoarseness' was rated by the investigator on the five-point CIS/RPS and was assessed in CC studies only.

In addition, the following responder criteria (number of patients) for the respective pre-defined days were calculated: Complete remission/recovery with respect to the symptom 'sore throat'/'hoarseness' ('sore throat'/'hoarseness' = 0 at pre-defined day); Reduction of 'sore throat'/'hoarseness' by at

least 50% between baseline and pre-defined day (response to therapy); FGK questionnaire items (RCT including children): number of participants with remission as measured for single items at day 4; EQ-5D Questionnaire (RCT including adults): number of participants with remission as measured for single items at day 5.

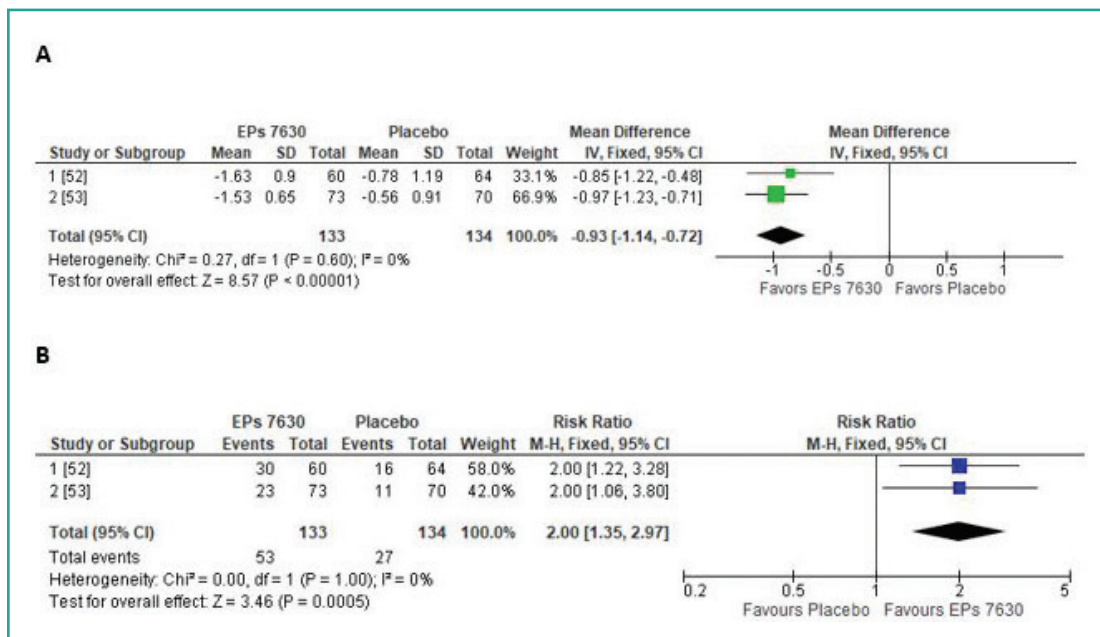
### Meta-analysis results

#### Sore throat

Meta-analysis results of the two RCT investigating the efficacy of EPs 7630 in ATP revealed that children treated with EPs 7630 showed a significantly pronounced improvement of the symptom 'sore throat' after four days compared to placebo treatment (- 0.93 ([- 1.14; - 0.72] 95% CI); (figure 1 A). Accordingly, a significant advantage of the herbal extract was shown for the number of patients with complete remission of the symptom 'sore throat' by Day 4, which resulted in a relative risk of 2.00 ([1.35; 2.97] 95% CI) favoring EPs 7630 (figure 1 B). Calculated responder rates

(indicated by a  $\geq 50\%$  improvement of the symptom 'sore throat' by day 4 as rated on the TSS) were 88.0% for EPs 7630 and 41.8% for placebo, respectively. Therapy response rates under EPs 7630 by day 4 were therefore significantly higher than those achieved under placebo. Corresponding risk ratios calculated for therapy response in the indications and age groups under evaluation are shown in table III.

Meta-analysis results of the five RCT investigating the efficacy of EPs 7630 in adults with CC demonstrated a significant superiority of the herbal extract in reducing the severity of the symptom 'sore throat' by day 5 as assessed by CIS/RPS, resulting in a mean difference of -0.24 ([- 0.38; - 0.11] 95% CI) (figure 2 A). Similar results were obtained regarding the number of patients who showed an at least 50% reduction in symptom severity for 'sore throat' by day 5 - a goal that was achieved by 78.5% of the patients randomized to EPs 7630 and 65.2% of the patients randomized to placebo (table III). Calculations for patients who had completely



**Figures 1.** Children with acute tonsillopharyngitis: **(A)** change of symptom 'sore throat' until day 4 (patients with impairment at baseline); **(B)** complete remission of symptom 'sore throat' until day 4 (patients with impairment at baseline).



**Table III.** Meta-analysis results for responder rates ( $\geq 50\%$  reduction in symptom severity at pre-defined day) in acute tonsillopharyngitis and common cold, based on Trials 1 and 2, and 3-7, respectively.

Outcome measure	Trial	EPs 7630			Placebo			Total relative risk [95% CI]† p-value
		n (participants impaired)	Responders		n (participants impaired)	Responders		
$\geq 50\%$ Reduction of symptom 'sore throat' in children with ATP at day 4	1, 2 (52, 53)	133	117	88.0%	134	56	41.8%	2.11 [1.71;2.61] p < 0.01
$\geq 50\%$ Reduction of symptom 'sore throat' in adults with CC at day 5	3-7 (54-59)	386	303	78.5%	374	244	65.2%	1.24 [1.05;1.46] p = 0.01
$\geq 50\%$ Reduction of symptom 'hoarseness' in adults with CC at day 5	3-7 (54-59)	345	258	74.8%	339	212	62.5%	1.23 [1.02;1.47] p = 0.03

† values > 1 favor EPs 7630. ATP = acute tonsillopharyngitis; CC = common cold. Reference's number in parentheses.

recovered from the symptom 'sore throat' by day 5 resulted in a relative risk of 1.13 ([0.87; 1.48] 95% CI) indicating no statistically significant differences between the treatment groups (**figure 2 B**).

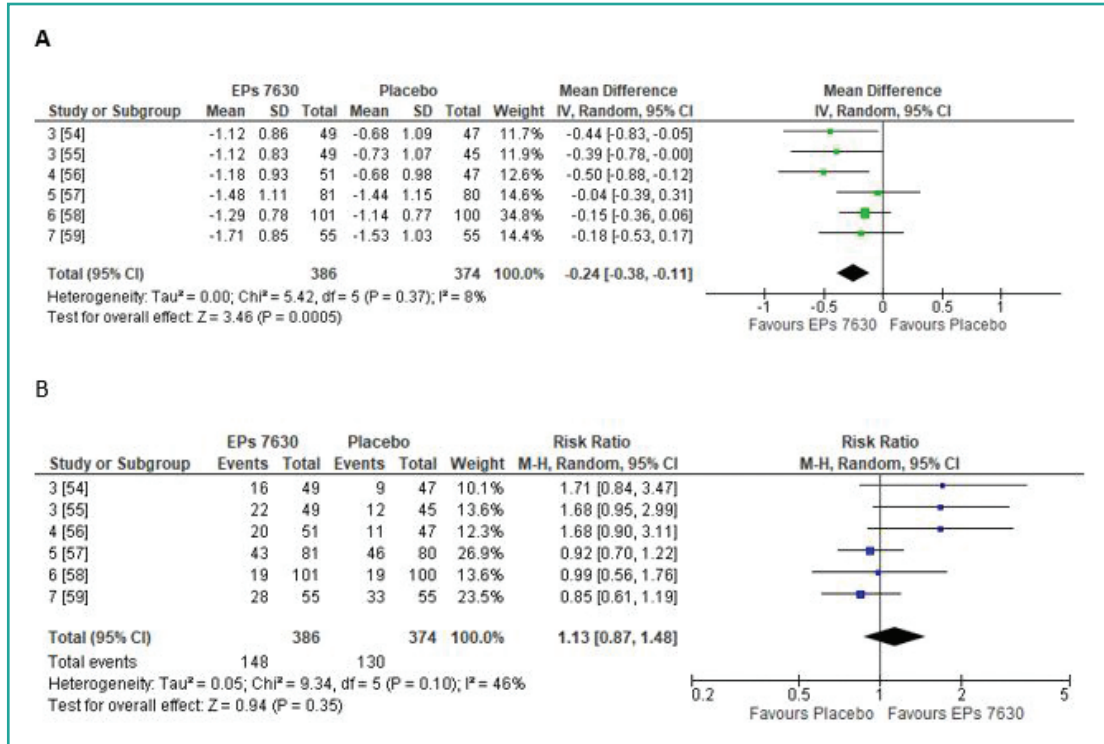
### Hoarseness

Meta-analysis results of the five RCT in adults with CC regarding symptom severity reduction by day 5 were also statistically significant, resulting in a mean difference of - 0.30 ([- 0.55; -0.04] 95% CI) favoring EPs 7630 (**figure 3 A**). Calculations regarding complete recovery from this symptom by day 5 resulted in a relative risk of 1.34 ([0.99; 1.81] 95% CI) favoring EPs 7630 (**figure 3 B**). The meta-analysis of response rate (indicated by a symptom severity improvement of  $\geq 50\%$  by day 5) showed statistically significant results in favor

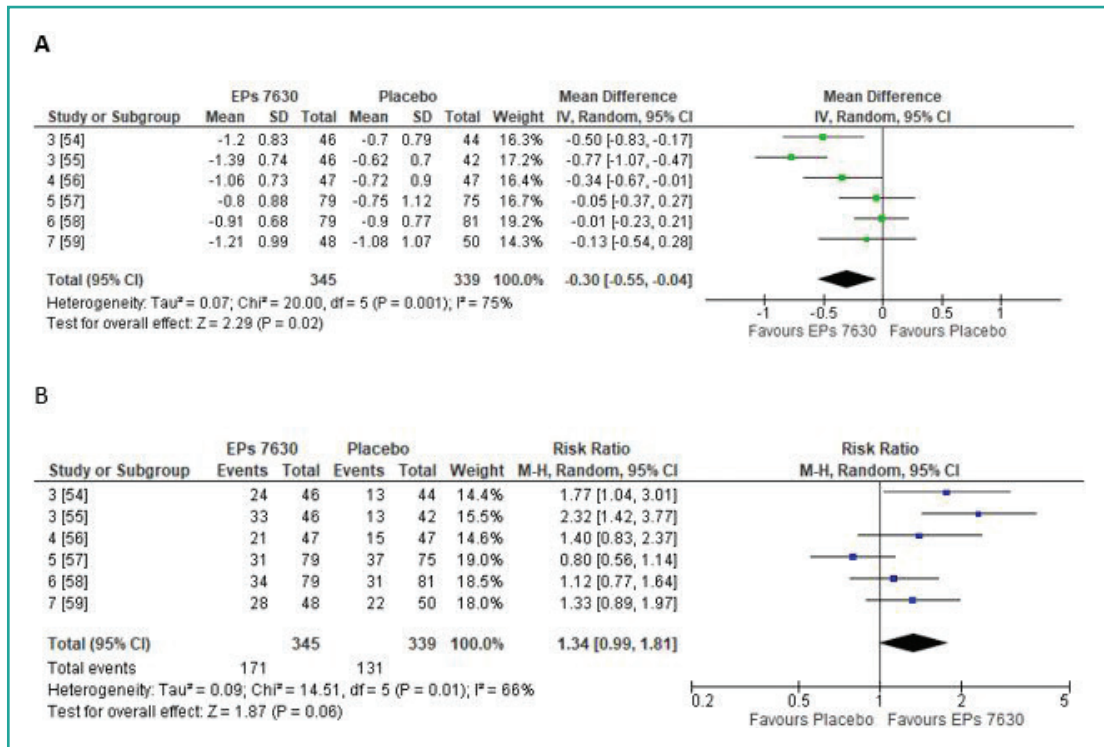
of EPs 7630, with response rates of 74.8% for EPs 7630 and 62.5% for placebo, respectively (**table III**).

### Disease-related quality of life

Disease-related QoL in children with ATP was assessed by the FGK questionnaire. Regarding the change calculated for the single FGK items, children treated with EPs 7630 showed greater remission by day 4 than those treated with placebo. The meta-analysis of those FGK items that particularly reflect the immediate impact of ATP, namely item 1 ('Everything is too much'), item 3 ('Trouble playing/learning'), and item 5 ('Sleeping badly') resulted in considerable remission rates under EPs 7630 as compared to placebo (54.2% vs 17.8%, 44.0% vs 14.6%, and 74.4% vs 29.9%, respectively). All meta-analysis results regarding the change



**Figure 2.** Adults with common cold: **(A)** change of symptom ‘sore throat’ until day 5 (patients with impairment at baseline); **(B)** complete remission of symptom ‘sore throat’ until day 5 (patients with impairment at baseline).



**Figure 3.** Adults with common cold: **(A)** change of symptom ‘hoarseness’ until day 5 (patients with impairment at baseline); **(B)** complete remission of symptom ‘hoarseness’ until day 5 (patients with impairment at baseline).

**Table IV.** Meta-analysis results regarding change of disease-related quality of life in children with ATP (Trials 1-2): full remission rates by day 4.

Indication	Outcome measure	Remission rates		Risk ratio [95% CI]
		EPs 7630	Placebo	
ATP in children	FGK item 1 ('everything is too much')	54.2%	17.8%	3.06 [2.05;4.57]
	FGK item 2 ('feeling ill')	28.6%	10.5%	2.79 [1.60;4.88]
	FGK item 3 ('scared')	88.2%	51.6%	1.71 [1.39;2.11]
	FGK item 4 ('trouble playing/learning')	44.0%	14.6%	3.02 [1.91;4.78]
	FGK item 5 ('sleeping badly')	74.4%	29.9%	2.49 [1.87;3.31]
	FGK item 6 ('troubles getting into conversations')	71.8%	39.3%	1.82 [1.42;2.35]

ATP = acute tonsillopharyngitis.

in disease-related QoL are summarized in **table IV**.

Disease-related QoL in adults with CC was assessed by the EQ-5D questionnaire. Data analysis related to QoL assessed at baseline and day 5 showed an advantage of EPs 7630 over placebo in numbers of patients who achieved full remission regarding the single EQ-5D categories assessed. Improvement in disease-related QoL in CC therefore corresponds to the likewise improvement in the symptoms 'hoarseness' and 'sore throat' at day 5.

## DISCUSSION

Sore throat and hoarseness belong to the most bothering symptoms occurring in aRTI as they are associated with pain and difficulties in conducting daily life requirements such as work or school attendance (9, 10). The presented meta-analysis results demonstrate the superiority of EPs 7630 over placebo in reducing the severity of disease-related symptoms and in expediting the onset of symptom alleviation. Thus, the actual duration of perceived impairment as assessed by patient-reported data was reduced. In the ATP trials, the symptom 'sore throat' was present in all patients at trial start and meta-anal-

ysis results showed a clear benefit with respect to the symptom relief until day 4 for EPs 7630 compared to placebo. This finding is supported by a significant advantage of the herbal extract when comparing the number of patients with complete symptom remission at day 4 between treatment groups (**figure 1 B**). Response to therapy regarding the symptom 'sore throat' by day 4 was significantly higher for children in the EPs 7630 group compared to the placebo group (**table III**), which also suggests an earlier onset of recovery under the herbal extract than under placebo. These findings are further supported by the results of FGK assessments at day 4: For any of the single FGK items, a significantly greater number of children with complete remission was reported in the EPs 7630 group compared with the placebo group. These findings are thus indicative of a beneficial impact of EPs 7630 on well-being and a fast return to daily-life activities. For adults with CC, the meta-analysis results also demonstrated a statistically significant superiority of EPs 7630 over placebo in reducing the severity of the symptom 'sore throat' by day 5. These findings are also in line with results of a meta-analysis performed earlier (45), in which data from the whole study population of the same trials was analyzed with fo-

cus on CIS results. In this former investigation, findings for severity change of 'sore throat' were comparable to those found in the present analysis in which only patients presenting with the symptom 'sore throat' at baseline were evaluated. In a recently published secondary subgroup-analysis of an open-label, uncontrolled clinical trial in adults suffering from CC, it was also shown that the presence or absence of the CC-associated human corona viruses HCoV-HKU1, HCoV-OC43, HCoV-NL63, or HCoV-229E did not have an impact on treatment outcomes, with patients of both subsets showing comparable improvements in symptom severity of 'sore throat' (62). The analysis revealed a somewhat faster response during treatment with EPs 7630 in the HCoV subset. However, the group differences were not statistically significant.

Results of our analysis for the severity change of the symptom 'hoarseness' correspond with the findings on the symptom 'sore throat' favoring EPs 7630 over placebo. Again, results for the symptom severity reduction by Day 5 are in line with earlier results obtained for the complete study population (45).

Efficacy of EPs 7630 with respect to the analyzed symptoms could most evidently be shown in the studies with children suffering from ATP. Nevertheless, the efficacy of the herbal drug could be demonstrated for both indications and target populations. As both published and unpublished RCT could be assessed for inclusion in this meta-analysis, a publication bias, which is often associated with systematic reviews, can be excluded.

When performing a meta-analysis that aims at the achievement of credible results, the impact of spontaneous remission on efficacy assessment must be considered. The appropriateness of the time points for assessment of symptom severity change chosen in the RCT included in this meta-analysis (day 4 in ATP, day 5 in CC) is proven by the obtained results which in most cases show significant differences in effectiveness between EPs 7630 and placebo with regard to the reduction of the symptoms 'sore

throat' and 'hoarseness', thus suggesting a minimal impact of spontaneous remission.

## CONCLUSIONS

The meta-analysis presented provides evidence for superiority of EPs 7630 over placebo in reducing the severity of the symptoms 'sore throat' in children with ATP and adults with CC, respectively, as well as 'hoarseness' in adults suffering from CC. Furthermore, the results suggest an earlier onset of symptom remission as well as a shortened duration of the disease achieved by administration of the herbal drug. The fast reduction of these most impairing aRTI symptoms by EPs 7630 suggests the herbal drug to be a considerable alternative to therapy by analgesics or even antibiotics, which is a particularly important finding for aRTI management in children and adults.

## ETHICS

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### Conflict of interests

WK, WL, GJS and PK have received honoraria from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany for scientific services. WK and GJS also received research funds from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. PK also received lecture and advisory board honoraria from AstraZeneca, Chiesi, GSK, Menarini, Novartis, and Teva. WL also received personal fees from Bayer, Biotronik, Merz, Scope, Cassella, optima, Oxular, Fresenius, Hennig, Occlutech, CRM Biometrics, Clin-

Competence for Statistical Consulting and Analyses, and IDMCs, outside the submitted work. AZ, JBS and PF are employees of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

### Authors' contribution

All authors listed have significantly contributed to the development and the writing of this article.

### Availability of data and material

Due to ethical reasons and in terms of data protection law, raw data cannot be shared. To the extent permitted by law, trial data required for validation purposes is already disclosed in result reports on corresponding databases. All relevant data are within the paper.

### Ethical approval

All trials included into this meta-analysis were reported to be 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 or informed consent was provided by their legal representative, respectively.

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