Efficacy and Tolerability of a Fluid Extract Combination of Thyme Herb and Ivy Leaves and Matched Placebo in Adults Suffering from Acute Bronchitis with Productive Cough

A prospective, double-blind, placebo-controlled clinical trial

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Summary

Study objective: **To assess the efficacy and tolerability of a fixed fluid extract combination of thyme and ivy leaves (thyme-ivy combination) and matched placebo in patients suffering from acute bronchitis with productive cough.**

Methods: **In a double-blind, placebo-controlled, multicentre Phase IV study 361 outpatients with acute bronchitis and ≥ 10 coughing fits during the day, onset of bronchial mucus production with impaired ability to cough up at a maximum of 2 days prior to recruitment, and a Bronchitis Severity Score (BSS) ≥ 5 score points were randomly assigned to an 11-day treatment (5.4 ml three times daily) with either thyme-ivy combination syrup (Bronchipret® Saft; N = 182) or placebo syrup (N = 179). After the baseline examination (Visit 1 = Day 0), 2 control examinations were scheduled (Visit 2 = Day 4; Visit 3 = Day 10/end of treatment).**

The efficacy of study treatment on acute bronchitis was evaluated by the patient's daily counting of coughing fits during the daytime (manual counter), assessment of acute bronchitis related symptoms and by the investigator's assessment of the most important symptoms of acute bronchitis using the BSS.

Evaluation of tolerability was based upon adverse event (AE) monitoring, measurement of vital signs as well as the patient's and investigator's global judgement of tolerability at study end.

Primary outcome was the change in frequency of coughing fits during daytime on days 7–9 according to patient's accurate daily recording with a manual counter and documentation in the diary.

Treatment effects were analysed by analysis of variance (ANOVA) adjusted for centre effects. Due to significant deviation from the "preconditions" of the ANOVA, the Wilcoxon test (stratified by centre) was carried out additionally.

Results: **The mean reduction in coughing fits on days 7 to 9 relative to baseline was 68.7 % under thyme-ivy combination compared to 47.6 % under placebo ($p < 0.0001$). In the thyme-ivy combination group, a 50 % reduction in coughing fits from baseline was reached 2 days earlier compared to the placebo group. The symptoms of acute bronchitis (BSS) improved rapidly in both groups, but regression of symptoms was faster and the responder rates ($p < 0.0001$) compared to placebo were higher at Visit 2 (83.0 % vs 53.9 %) and Visit 3 (96.2 % vs 74.7 %) under the treatment of thyme-ivy combination.**

Treatment was well tolerated with no difference in the frequency or severity of AEs between thyme-ivy combination and placebo groups. Severe or serious AEs were not reported.

Conclusion: **Oral treatment of acute bronchitis with thyme-ivy combination for about 11 days was superior to placebo in terms of efficacy. The treatment was safe and well tolerated.**

Key words

- **Acute bronchitis**
- **Bronchipret® Saft**
- **Bronchitis Severity Score**
- **Coughing fits**
- **Double-blind, randomised, placebo-controlled phase IV clinical trial**
- **Ivy leaves *(hederae helicis folium)*, combination with thyme herb *(thymi herba)***
- **Thyme herb *(thymi herba)*, combination with ivy leaves *(hederae helicis folium)***

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Zusammenfassung

Wirksamkeit und Verträglichkeit einer Flüssigextrakt-Kombination aus Thymian und Efeublättern sowie Plazebo bei Erwachsenen mit akuter Bronchitis mit produktivem Husten / Eine prospektive, doppelblinde, Plazebo-kontrollierte klinische Studie

Studienziel: **Untersuchung der Wirksamkeit und Verträglichkeit einer fixen Kombination aus Thymian und Efeublättern (Thymian-Efeu-Kombination) im Vergleich zu Plazebo bei Patienten mit akuter Bronchitis mit produktivem Husten.**

Methodik: **In einer doppelblinden, Plazebo-kontrollierten, multizentrischen Phase IV-Studie, wurden 361 ambulante Patienten mit akuter Bronchitis und ≥ 10 Hustenanfällen am Tag, Beginn der bronchialen Schleimproduktion mit eingeschränkter Fähigkeit abzuhusten seit maximal 2 Tagen vor Rekrutierung, und einem Bronchitis-Schweregrad-Score (BSS) ≥ 5 Punkten randomisiert einer 11-tägigen Behandlung (5,4 ml dreimal täglich) mit Thymian-Efeu-Saft (Bronchipret® Saft; N = 182) oder Plazebo-Saft (N = 179) zugeordnet. Nach der Erstuntersuchung (Visite 1 = Tag 0) waren 2 Kontrolluntersuchungen geplant (Visite 2 = Tag 4; Visite 3 = Tag 10/Ende der Behandlung).**

Die Untersuchung der Wirksamkeit der Studientherapie bei akuter Bronchitis erfolgte durch die tägliche Erfassung der tagsüber vom Patienten gezählten Hustenanfälle (manuelles Zählgerät), die tägliche Erfassung weiterer Symptome der akuten Bronchitis, und durch die bei jeder Visite vom Prüfarzt vorgenommene Beurteilung der wichtigsten Symptome einer akuten Bronchitis anhand des BSS.

Die Untersuchung der Verträglichkeit basierte auf der Erfassung von unerwünschten Ereignissen (UE), der Messung von Vitalzeichen sowie dem Patienten- und Prüfarzturteil zur Verträglichkeit am Ende der Studie.

Primärer Endpunkt war die Veränderung der Anzahl der Hustenanfälle tagsüber an den Tagen 7–9 gemäß der täglichen genauen Erfassung mit einem manuellen Zählgerät und Dokumentation durch den Patienten.

Die Behandlungseffekte wurden mit der Varianzanalyse (ANOVA) getestet, Zentrumseffekte wurden hierbei berücksichtigt. Aufgrund der signifikanten Abweichung von den „Verteilungsvoraussetzungen" der ANOVA wurde zusätzlich der Wilcoxon Test (stratifiziert nach Zentrum) durchgeführt.

Ergebnisse: **Die mittlere Reduktion der Hustenanfälle an den Tagen 7–9 relativ zum Ausgangswert betrug 68,7 % unter Thymian-Efeu-Kombination verglichen zu 47,6 % unter Plazebo ($p < 0{,}0001$). In der Thymian-Efeu-Kombinationsgruppe wurde eine 50%ige Reduktion der Hustenanfälle des Ausgangswertes 2 Tage früher erreicht als in der Plazebo-Gruppe. Die Symptome einer akuten Bronchitis (BSS) verbesserten sich rasch in beiden Gruppen, die Abnahme unter Thymian-Efeu-Kombination war im Vergleich zu Plazebo aber schneller und vollständiger, mit einer deutlich höheren Ansprechrate ($p < 0{,}0001$) bei Visite 2 (83,0 % vs 53,9 %) und bei Visite 3 (96,2 % vs 74,7 %).**

Die Behandlung war gut verträglich. Thymian-Efeu-Kombination und Plazebo unterschieden sich nicht in Häufigkeit und Schweregrad der UE. Schwere UEs wurden nicht berichtet.

Fazit: **Die orale Behandlung der akuten Bronchitis mit Thymian-Efeu-Kombination über ca. 11 Tage war Plazebo hinsichtlich der Wirksamkeit deutlich überlegen und war sicher und gut verträglich.**

1. Introduction

Acute bronchitis is predominantly caused by viral infections [1–5]. Therefore, the treatment of acute bronchitis should be symptomatical for most cases [5–6, 32]. Although antibiotics are widely used evidence for their efficacy in acute bronchitis is missing [2, 7–8]. The primary goal of the therapy of acute bronchitis is to improve coughing. In the case of a so-called dry or unproductive cough, the reduction in coughing is the primary aim, whereas in the case of a productive cough, the aim is to support expectoration and thereby to reduce coughing [9–10].

The fluid extract combination of thyme and ivy leaf, referred to as thyme-ivy combination[1)], is a combination of herbal extracts formulated to facilitate coughing up and thereby to reduce coughing frequency [11]. The primary active components of thyme are the volatile oils, especially thymol. These act locally on the lungs as they are eliminated from the body by the respiratory tract, disinfecting the airways, relaxing bronchial spasm and exerting a mucolytic action (decrease of the viscosity of mucus) [12]. Common ivy exerts an expectorant action on the respiratory tract. It does this by a reflex from irritative action on the stomach due to its saponin constituents [12, 14]. Ivy also has antispasmodic properties, helping to prevent and relieve coughing spasms. Both thyme and ivy are considered safe [13].

This clinical study was designed to evaluate the efficacy and the tolerability of thyme-ivy combination [5.4 ml three times daily (t.i.d.) for 11 days] compared to placebo in adult outpatients suffering from acute bronchitis with productive cough as the main symptom.

2. Patients, material and methods

The present clinical study was a randomised, double-blind, 11-day comparison in parallel groups of thyme-ivy combination and placebo in the management of patients suffering from acute bronchitis with productive cough. Twenty-eight centres in Germany (25 specialists for general or internal medicine and 3 research centres) participated in this prospective clinical phase IV trial which was conducted in accordance with the Declaration of Helsinki (amended version of 1996) and the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). The study protocol, the patient information and the informed consent form were approved by the ethics committee competent for the coordinating investigator ("Leiter Klinische Prüfung", LKP) according to German Drug

[1)] Bronchipret® Saft; pharmaceutical manufacturer: Bionorica AG, Neumarkt (Germany).

Law before enrolment of patients. Written informed consent was obtained from all patients prior to any study related measures. The clinical part of the study was conducted from October 2005 to February 2006.

Monitoring, data management and statistical evaluation were done in accordance with applicable ICH-Guidelines.

2.1. Patients

Adult male and female outpatients with a clinical diagnosis of acute bronchitis and recent onset (≤ 2 days) of bronchial mucus production with impaired ability to cough up were eligible for inclusion in the study if they were at least 18 years of age, had ≥ 10 coughing fits during the daytime on the last day prior to Visit 1 (according to patient's estimate), and a baseline Bronchitis Severity Score (BSS) ≥ 5 score points (of maximum 20 points) [5]. Diagnosis was based on medical history and physical examination, which included an evaluation of typical signs and symptoms according to BSS, i.e. cough, sputum, chest pain during coughing, dyspnoea and rales/rhonchi on auscultation of the lungs.

Standard exclusion criteria (including pregnancy, no contraception for women of child bearing age and lactation for females) were used, the principal ones being concomitant fever (> 39 °C), pneumonia, history of chronic bronchial or pulmonary disease such as chronic bronchitis, chronic obstructive pulmonary disease (including acute episode), bronchiectasis, bronchial asthma, mucoviscidosis, history of clinically relevant chronic cardiovascular, kidney, gastrointestinal or liver disease, known hypersensitivity to one or more of the active or inactive ingredients of the investigational product, malignant growth, or any severe somatopathic, neurologic and/or psychiatric disease.

Treatment with other drugs, such as immunosuppressives, systemic antibiotics and systemic or inhalation glucocorticosteroids (within 4 weeks prior to enrolment into the study and concomitantly), mucoactive substances other than the study medication (within 2 weeks prior to enrolment and concomitantly), antitussive drugs and other mucoactive measurements except for steam inhalation (concomitantly) were not allowed. Treatment with angiotensin converting enzyme (ACE) inhibitors was no reason for exclusion if started more than 4 weeks prior to Visit 1. Paracetamol could be taken in case of fever, other non-steroidal anti-inflammatory drugs were not allowed during the study.

2.2. Treatment

The study medication [thyme-ivy combination (Bronchipret® Saft) and placebo] was provided by the sponsor (Bionorica AG, Neumarkt, Germany). For use in this study, the marketed thyme-ivy combination syrup was repackaged to ensure blinding. Randomisation to thyme-ivy combination (batch no. 0502863) and placebo (batch no. 0503339) was made according to a parallel group model with a 1:1 allocation to the two treatment groups. The study medication supply for 11 days, including reserve, was handed over to the patient at Visit 1 = Day 0 (150 ml syrup) and at Visit 2 = Day 4 (200 ml syrup). 100.00 g thyme-ivy combination syrup contained 15.00 g fluid extract of thyme herb [1:2–2.5; extractant according to DAB (Deutsches Arzneibuch)] and 1.50 g fluid extract of ivy leaves DAC (Deutscher Arzneimittel Codex) (1:1; extractant: ethanol 70.0 volume percent). The placebo syrup did not contain any active ingredients. The double-blindness of the trial was ensured by identical appearance and aromatic flavour. The selected fixed-dose regimen (5.4 ml three times daily = 16.2 ml total daily dose for 11 days) followed the recommendation of the summary of product characteristics (SmPC) of the thyme-ivy combination medication for treatment of acute bronchitis in adults [11]. The investigator controlled patient's compliance by visual comparison of study medication remaining in the bottles. After study termination, the compliance was accurately checked by weighing the remaining content of each bottle returned.

2.3. Trial procedures

The individual treatment duration was 11 days, with a total of 3 visits to the investigator. Patients were randomised at Visit 1 (Day 0 = investigator's baseline assessments). Assessments made by the investigators were documented in the case report form (CRF) at each visit.

The change of symptoms of acute bronchitis was monitored by using a symptom diary (Day 0–Day 10) and by repeated clinical symptom assessment, including lung auscultation, to be performed after 4 days (Visit 2) and after 10 days of treatment (Visit 3).

The aim of confirmatory testing in this study was to show superiority of thyme-ivy combination treatment to placebo in the reduction of the frequency of coughing fits during the daytime recorded by a manual counter. A coughing fit was defined as at least 3 or more consecutive coughs without a discernible inspiration separating them. The patient was instructed to press the manual counter once for each coughing fit (starting with getting up in the morning and ending with bedtime).

2.4. Measurements

2.4.1. Efficacy

The primary outcome criterion was the change in mean frequency of coughing fits during the daytime of days 7 to 9 of the treatment period documented in the patient diary divided by the baseline value of Day 1 (standardised to the 1st day of precise recording with manual counter). The time window chosen for analysis (Day 7–9) was based on pharmacological considerations. Assuming that drugs with secretolytic properties (like thyme-ivy combination) have a delayed onset of effect on symptoms of acute bronchitis [3, 5] – contrary to cough blocking agents which cause a significant reduction in cough on the first day of treatment [15] – the period between Day 7 and Day 9 was determined to be relevant for evaluation of the primary efficacy outcome measure.

Secondary outcome criteria for the evaluation of treatment efficacy on coughing fits (calculated from diary records based on precise recording with manual counter) were:

- Reduction in coughing fits during daytime within 9 days of investigational treatment calculated as area under the curve [AUC]. This calculation summarises the treatment effect on coughing fits for the total observation period.
- Time to 50 % reduction in coughing fits during the day compared to Day 1. This parameter shows the benefit for the patient on the time axis.
- Proportion of patients with no coughing fits on Day 9. This parameter compares the cure rates regarding coughing fits achieved at the last day of the observation period.
- Relative reduction in mean frequency of coughing fits at Day 9. This parameter measures the change from baseline at the end of the observation period.

Further secondary outcome criteria for assessing the efficacy were:

- Response to treatment assessed by the investigator at Visits 2 and 3 when compared to Visit 1 using a verbal 4-point

rating scale (0 = no symptoms, 1 = symptoms improved, 2 = symptoms unchanged, 3 = symptoms deteriorated); patients with no or improved symptoms were classified as 'responders', patients whose symptoms were unchanged or deteriorated were classified as 'non-responders'.

- Change in mean BSS (addition of rating scores for cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnoea) at Visits 2 and 3 relative to the pre-treatment sumscore recorded at Visit 1 (Day 0) using a verbal 5-point rating scale ranging from 0 (absent) to 4 (very severe) [5]. Both the responder rates and the BSS measure the overall treatment effect on signs and symptoms associated with acute bronchitis.
- Change in the ability to cough up mucus during the daytime from Day 0 to Day 9 (calculated as AUC) using a verbal 5-point rating scale (0 = no mucus, 1 = no problem to cough up mucus, 2 = mild problems to cough up mucus, 3 = coughing up mucus was aggravated, 4 = coughing up mucus was very aggravated).
- Change in sleep disturbance induced by coughing from Day 0 to Day 10 (calculated as AUC) using a verbal 4-point rating scale with 0 indicating sleep not disturbed and 3 = sleep severely disturbed.
- Change in the patient's general well-being from Day 0 to Day 9 (calculated as AUC) using a verbal 4-point rating scale recorded in the diary from 0 (I am free of symptoms) to 3 (I feel very ill).

2.4.2. Tolerability

Adverse events (AEs) recorded at Visits 2 and 3 were assessed by the investigators for severity, duration, outcome, actions taken, pattern of occurrence and the causal relationship to treatment. Additional safety criteria were vital signs (blood pressure, heart rate, body temperature) at each study visit; temperature was recorded daily by the patient and the global judgement on tolerability was performed by investigator and patient at the end of treatment (Visit 3) using a 5-point verbal rating scale ranging from 0 (very good) to 4 (very poor).

2.5. Statistics

2.5.1. Sample size calculation

Sample size calculation was done under the assumption of a reduction in the primary endpoint to 0.54 under Placebo with a clinical relevant difference to thyme-ivy combination treatment of 20 % ($\Delta = 0.108$). The estimated standard deviation ($s = 0.354$) and limited error rates ($\alpha_{1\text{-sided}} = 0.025$; $\beta = 0.2$) led to a sample size estimation of 180 patients per group, when taking into account a drop out rate of about 5 %.

2.5.2. Statistical analyses

Analysis sets and handling of missing data

The Safety Evaluable Population (SEP) – for the analysis of the safety results – included all patients randomised with at least 1 documented application of the investigational drug and safety data.

The Full Analysis Set (FAS) – for the analyses of the efficacy variables – included all patients randomised with at least 1 documented application of the investigational drug and efficacy data.

Generally missing values (m. v.) were replaced by the "last observation carried forward" (LOCF) principle, except in case of premature termination of the study where data for Visit 2 were missing. In this case m. v. for Visit 2 were imputed by values of Visit 3. Another exception from the LOCF principle was applied when the number of coughing fits in the diary was not documented but additional data (BSS, diary data) showed the absence of coughing on this day. In this case the number of coughing fits was set to zero.

Statistical methods

Efficacy: The study – designed to test for statistical superiority of thyme-ivy combination over placebo – was conducted in a two-stage adaptive design in order to re-adjust the sample size calculation [16]. The pre-specified interim analysis of the primary endpoint included the data of 255 patients.

The primary endpoint (change in mean frequency of coughing fits during the daytime of Days 7 to 9 of the study period relative to Day 1 – documented in the patient diary) was tested on a significance level of alpha = 0.025 (one-sided) by ANOVA adjusted for centre effects. Due to significant deviation from the "preconditions" of the ANOVA, the Wilcoxon test (stratified by centre) was carried out additionally.

All hypotheses tests for the secondary endpoints were carried out descriptively on the 2-sided nominal level of an error probability (alpha) of 5 %. The Kaplan-Meier life-table methods and the Log-Rank test were used for time-dependent analysis.

Categorical data were analysed by the Chi-square test or the Cochran-Armitage Trend test.

The Wilcoxon test (stratified by centre) was also applied to all variables calculated by the AUC.

Safety: AEs were summarised descriptively by total number of AEs for each treatment group, and the number and percentage of patients reporting any AEs by the body system for the thyme-ivy combination versus the placebo group. The Wilcoxon test was used to compare differences between group means of vital signs (blood pressure, heart rate, body temperature). Differences between treatment groups regarding investigators' and patients' tolerability ratings were analysed using the Cochran-Armitage test for trend. Statistical analyses were done using SAS® version 8.2.

3. Results

3.1. Patient disposition

A total of 363 male and female outpatients (N = 182 thyme-ivy combination group; N = 181 placebo group) were included into the study. Two patients of the thyme-ivy combination group (N = 1: violation of an inclusion criterion; N = 1: subjective improvement) and 6 patients of the placebo group (N = 3: loss to follow up; N = 2: possibly or probably drug-related adverse event; N = 1: dislike to the taste of the medication) prematurely discontinued study participation. In addition, 6 patients under thyme-ivy combination and 4 patients under placebo prematurely discontinued treatment due to complete healing.

3.2. Analysis sets

Due to loss for follow up 2 patients of the placebo group were excluded from the SEP set. Therefore the SEP included 361/363 patients (N = 182/182 thyme-ivy combination group; N = 179/181 placebo-group). Of these, 1 placebo-treated patient had to be excluded from FAS because of missing post-baseline efficacy data. There-

fore the FAS comprised 360/363 patients (N = 182/182 thyme-ivy combination group; N = 178/181 placebo group).

A pre-planned interim analysis was carried out after data of 70 % of the planned patients (N = 255; N = 129 thyme-ivy combination group; N = 126 placebo group) had been validated.

3.3. Study duration and treatment compliance

The mean study duration was in accordance with the study protocol (mean: 11 days, maximum: 15 days in both treatment groups; FAS). Treatment compliance measured by the relation of actual medication intake/recommended medication intake was very good with similar mean values in both treatment groups (119.4 % in the thyme-ivy combination group and 119.5 % in the placebo group).

3.4. Demographics and baseline characteristics

Table 1 provides the demographics as well as baseline characteristics for the 360 patients included in the FAS (age range: 18–87 years). Treatment groups were comparable concerning demographics and baseline characteristics. The majority of patients in the thyme-ivy combination group and the placebo group were Caucasians (98.9 % vs 98.3 %).

3.5. Efficacy results

3.5.1. Coughing

In both treatment groups (FAS) the mean number of coughing fits continuously decreased from baseline to Day 9 (Fig. 1). The relative reduction in the mean frequency of coughing fits at Day 9 showed a distinct advantage of the herbal drug (thyme-ivy combination) compared to placebo (77.6 % vs 55.9 %; $p < 0.0001$; FAS). From Day 4 onwards, the reduction in coughing fits was more pronounced under thyme-ivy combination with superiority to placebo until the end of the period of observation, i.e., up to Day 9 (Fig. 1). The calculated AUC concerning the reduction of coughing fits confirmed that 9 days treatment with thyme-ivy combination was superior to placebo (4.7 ± 1.5 vs 5.7 ± 2.8; N = 360: $p < 0.0001$; FAS).

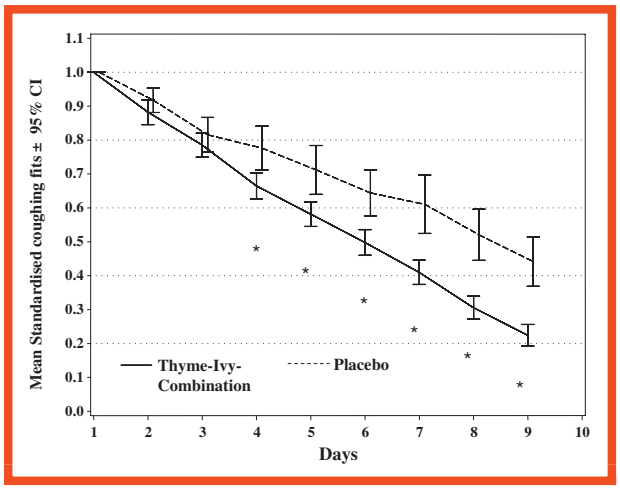

Fig. 1: Time course of coughing fits [standardised coughing fits ± 95 % confidence intervals (CI)] (FAS: N = 360). Significant difference on α-level = 0.05 (*) between thyme-ivy combination and placebo (WTC $p < 0.0001$).

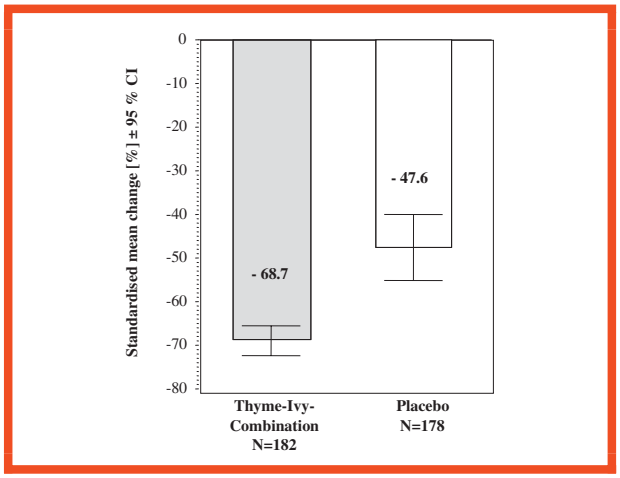

Fig. 2: Standardised mean change [%] in coughing fits on Day 7–9 ± 95 % CI (FAS: N = 360).

Table 1: Demographics and other baseline characteristics at Visit 1 (FAS).

Variable		Statistics	Thyme-ivy combination (N = 182)	Placebo (N=178)	p-value
Gender	Male Female	N (%) N (%)	87 (47.8) 95 (52.2)	81 (45.5) 97 (54.5)	Chi 0.6623
Age [years]		mean ± SD	43.4 ± 17.7	41.5 ± 17.3	W 0.2924
Height [cm]		mean ± SD	171.6 ± 9.0	171.3 ± 9.1	W 0.9640
Weight [kg]		mean ± SD	75.1 ± 13.7	74.0 ± 14.4	W 0.4362
Smoking habits	Smoker Non-smoker	N (%) N (%)	55 (30.2) 127 (69.8)	50 (28.1) 128 (71.9)	Chi 0.6567
Bronchitis Severity Score (BSS)[a]		mean ± SD	8.2 ± 2.0	8.3 ± 2.2	W 0.5896
Coughing fits [N/daytime]*		mean ± SD	25.8 ± 15.5	26.7 ± 16.3	W 0.6037

* Number of coughing fits according to patient's estimation for the previous day. SD = standard deviation of the mean. Chi = Chi-square test; W = Wilcoxon-two sample test, two-sided; [a] Bronchitis Severity Score = addition of rating scores for cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnoea using a verbal 5-point rating scale ranging from 0 (absent) to 4 (very severe).

At the time window chosen for analysis of the primary endpoint (Day 7 to Day 9), thyme-ivy combination treatment proved to be superior to placebo in the mean reduction of coughing fits relative to the baseline value (Fig. 2). The confirmatory analysis of the primary efficacy endpoint demonstrated superiority of thyme-ivy combination over placebo in the interim analysis (N = 255: $p < 0.0001$) which was confirmed again in the analysis of the FAS (N = 360: $p < 0.0001$).

The analysis of the treatment effect on the time axis showed that a successful (50 %) reduction in coughing fits from baseline was reached 2 days earlier (from Day 6 to study end = Day 10) under treatment with thyme-ivy combination compared to placebo (Fig. 3). Due to the distinct advantage of thyme-ivy combination treatment twice the percentage of patients in the verum group was free of coughing fits compared to the placebo group at Day 9 (28.6 % vs 14.6 %; $p = 0.0013$; FAS).

3.5.2. Responders and BSS

The advantage of thyme-ivy combination treatment over placebo was also demonstrated regarding the rates of responders and the improvements in the BSS. Treatment with thyme-ivy combination resulted in significantly higher responder rates compared to placebo treatment already after only 4 days' treatment/Visit 2 with a further increase up to study end/Visit 3 (Fig. 4). The average BSS decreased continuously in both treatment groups between baseline and the end of treatment, but the decrease was significantly more pronounced in the thyme-ivy combination group (–6.6 vs –3.3 points from Visit 1 to Visit 3; Fig. 5; for baseline values of BSS see Table 1).

3.5.3. Other symptom related parameters

Superiority of thyme-ivy combination treatment over placebo was also confirmed regarding the reduction in sleep disturbance induced by coughing and the improvement in the ability to cough up mucus during daytime and patient's general well-being (Table 2).

3.6. Safety results

Treatment with thyme-ivy combination for up to 15 days and a maximum cumulative exposure to 58.0 g fluid extract of thyme herb plus 5.8 g fluid extract of ivy leaves was well tolerated in 182 patients. With 9 adverse events (AEs) reported by 7/182 (3.8 %) patients in the thyme-ivy combination group, the occurrence of AEs was very low and similar to the placebo group in which 8 AEs were reported by 8/179 (4.5 %) patients. Most AEs were labelled as mild. All AEs had been resolved at study end. Severe or serious AEs were not reported in any treatment group.

At the end of the study (Visit 3), a 'very good' or 'good' tolerability was reported by 98.9 % vs 95.0 % of patients and by 100.0 % vs 97.8 % of investigators in the thyme-ivy combination group vs the placebo group, respectively.

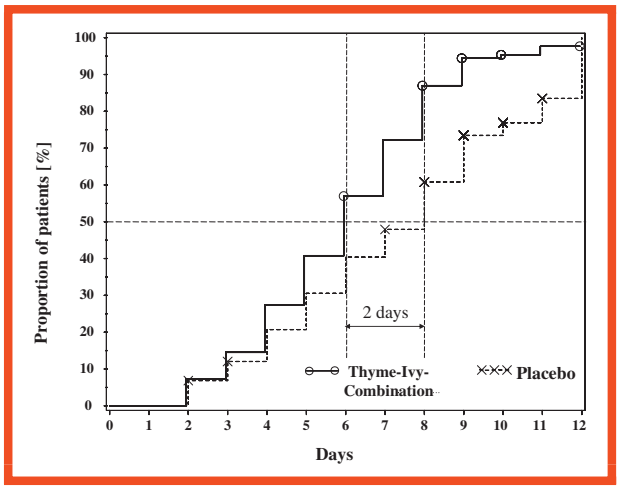

Fig. 3: Time to 50 % reduction in coughing fits [days] (FAS: N = 360). Significant difference between thyme-ivy combination and placebo (Log rank $p < 0.0001$). ○ – censored observations in the thyme-ivy combination group; × – censored observations in the placebo group.

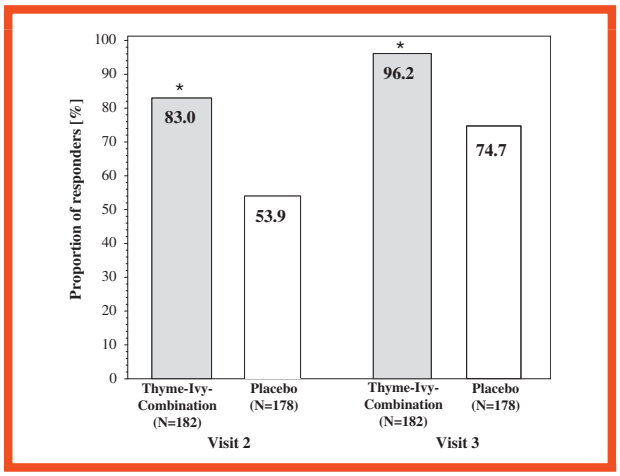

Fig. 4: Proportion of responders [%] at Visit 2 and Visit 3 (FAS: N = 360). Significant difference on α-level = 0.05 (*) between thyme-ivy combination and placebo at Visit 2 (Chi $p < 0.0001$) and Visit 3 (Chi $p < 0.0001$).

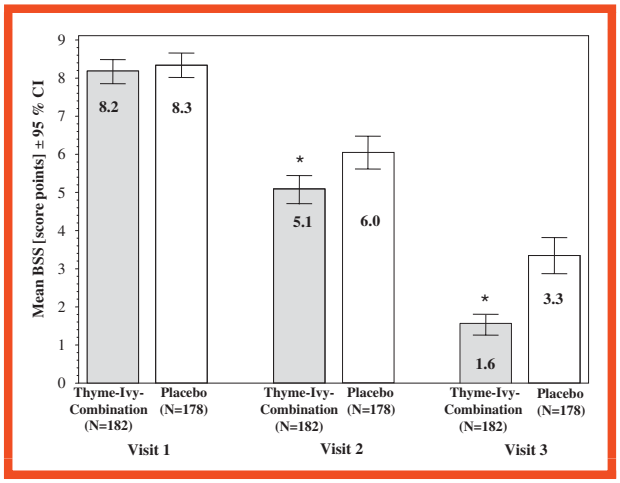

Fig. 5: Mean BSS [score points] ± 95 % CI (FAS: N = 360). Significant difference on α-level = 0.05 (*) between thyme-ivy combination and placebo at Visit 2 (WTC $p = 0.0009$) and Visit 3 (WTC $p < 0.0001$).

Table 2: 'Ability to cough up of mucus', 'sleep disturbance' and 'general well-being' – patient's daily assessments on verbal rating scales (FAS: N = 360).

Patients thyme-ivy combination/placebo	Secondary efficacy endpoint	Thyme-ivy combination mean ± SD [score points*days]	Placebo mean ± SD [score points*days]	p-value
181/178	Ability to cough up mucus during the daytime from Day 0 to Day 9 (AUC)$^{+)}$ [a]	15.6 ± 6.7	17.9 ± 8.0	^{WTC} < 0.0001
180/178	Sleep disturbance induced by coughing from Day 0 to Day 10 (AUC)$^{+)}$ [b]	10.4 ± 5.8	12.8 ± 6.9	^{WTC} < 0.0001
181/178	Patient's general well-being from Day 0 to Day 9 (AUC)$^{+)}$ [c]	12.3 ± 4.3	14.3 ± 5.2	^{WTC} < 0.0001

$^{+)}$ A lower AUC in the verum group denotes a greater symptom improvement compared to placebo. SD = standard deviation of the mean. ^{WTC} = Wilcoxon test adjusted for centres. [a] Verbal 5-point rating scale from 0 = no mucus to 4 = coughing up mucus was very aggravated; [b] verbal 4-point rating scale from 0 = sleep not disturbed to 3 = sleep severely disturbed; [c] verbal 4-point rating scale from 0 = I am free of symptoms to 3=I feel very ill.

In both treatment groups, means of blood pressure or heart rate did not show any clinically relevant changes from baseline. Under thyme-ivy combination an increase in body temperature (11/182 vs 18/179 patients) and concomitant use of paracetamol (2/11 vs 6/18 patients) was observed less frequently than under placebo.

4. Discussion

Acute bronchitis is usually a self-limited condition. In most cases, only symptomatic treatment is needed [6, 17, 32]. The value of antibiotics in the treatment of otherwise healthy subjects with acute bronchitis has not been established and the use of these agents is not recommended as a general practice according to present guidelines [18]. Several studies found no favourable therapeutic effect of antibiotics over placebo [19–22]. Evans et al. compared the use of azithromycin with vitamin C in 220 patients [23]. They found no difference in quality of life for both groups at the end of the study. A Cochrane meta-analysis for the effect of antibiotics in acute bronchitis including 9 trials with over 750 patients did not demonstrate a relevant advantage of antibiotics when compared to placebo [30].

In spite of current recommendations, antibiotics are widely used in uncomplicated upper and lower respiratory tract infections such as acute sinusitis and bronchitis [6, 24–25, 34]. Most clinicians prescribe antibiotics in spite of expert recommendation against this practice. The reasons for this continuing traditional practice of prescription are the pressure from the patients to receive antibiotics and the concern that patients may deteriorate if left untreated.

The present study found a significant and clinically relevant improvement in patients with acute bronchitis receiving oral treatment with a fluid extract combination of thyme and ivy leaves over placebo. This advantage could be demonstrated for the change in mean frequency of coughing fits during daytime of days 7 to 9 of the study period as the primary outcome as well as for secondary outcome parameters such as the severity and incidence of symptoms of acute bronchitis including cough, sputum, rales and rhonchi, chest pain and dyspnoea, expressed by the BSS. Other secondary parameters, that underscored the significant superiority of active treatment were ability to cough up mucus, sleep disturbance, general well-being and an earlier onset of the therapeutic activity by about 2 days.

By use of a manual counter for recording of coughing fits a reasonably objective method for the evaluation of efficacy was used for the first time. The precise recording of coughing fits is considered to be superior to patient's subjective rating of symptoms on verbal rating scales. Already from Day 4 onwards, the improvement of coughing fits was more pronounced under thyme-ivy combination, with a distinct advantage over placebo up to Day 9. At study end, twice the number of patients in the thyme-ivy combination group was free of coughing compared to the placebo group. These pronounced advantages were accompanied by a marked improvement in the ability to cough up mucus, and a less frequently increase in body temperature and concomitant use of paracetamol compared to placebo treatment. The observed significant improvement in severity and duration of symptoms is mirrored also in the significantly higher responder rates under the herbal treatment compared to placebo.

These positive results for the herbal medication correspond with the pharmacological actions of thyme and ivy. Thyme herb *(thymi herba)* has secretolytic, expectorant, bronchospasmolytic, antibacterial and antiphlogistic properties, whereas ivy leaves *(hederae helicis folium)* exert an expectorant and antispasmodic action on the respiratory tract [12, 14, 27–29]. The reduction of the frequency of coughing fits can be regarded as effect on bronchial inflammation and mucus viscosity, and on mucociliary clearance, which has been experimentally proven for thyme [31].

The results of this multicentre study proved the advantage of the treatment with the fixed fluid extract combination of thyme and ivy leaves in acute bronchitis that is evidently superior to placebo. Other herbal

medicinal products have been proven to be effective and safe in treatment of the symptoms of acute bronchitis which showed an onset of therapeutic activity after 3 to 5 days, too [3, 5, 33].

The tolerability of the herbal medication was very good and comparable to placebo. The nature of possibly or probably drug-related AEs [adverse drug reactions (ADRs) according to investigator's blinded assessment] was in accordance with the known side effect profile of thyme-ivy combination, i.e., mild gastrointestinal disorders in very few patients. The small amount of alcohol (7 Vol. %) in the study medication did not affect the tolerability of the thyme-ivy combination.

5. Conclusion

In patients with acute bronchitis with productive cough, treatment with the thyme-ivy combination resulted in a more rapid regression of symptoms particularly coughing, and responder rates compared to placebo were higher. The treatment with the thyme-ivy combination led to an earlier onset of the therapeutic activity by about 2 days.

It was safe and well tolerated. As compared to the common practice to treat most cases of uncomplicated acute bronchitis with antibiotics, the ivy-thyme combination seems to be a favourable alternative which may be associated with a superior benefit and a better tolerance. It is without the risk for the development of resistant pathogens in contrast to the frequent abuse of antibiotics for mild respiratory tract infections.

Responsibilities of authors and funding of the study

Bernd Kemmerich, MD habil, Specialist in Internal Medicine and Pneumology, was the coordinating investigator and scientific consultant ("Leiter der klinischen Prüfung" according to § 40 German Drug Law) of this multicentre study, and was responsible for the scientific advice for the writing of the manuscript.

Reinhild Eberhardt, MD, Specialist in Clinical Pharmacology, is Head of the Pharmalog Institute for Clinical Research, Munich/Germany, the independent contract research organisation (CRO) that was responsible for project management, and conduct of the study as well as for statistical analysis and reporting of study data.

Holger Stammer, MSc, (Pharmalog Institute for Clinical Research) was responsible for statistical analysis of the trial.

Carmen Martin, MD, Schondorf/Germany was responsible for writing the integrated study report and the manuscript.

Bionorica AG, Neumarkt (Germany), the pharmaceutical manufacturer of Bronchipret® Saft, sponsored this prospective multicentre study and was responsible for coordinating the publication of the study results and for the review and editing of the manuscript.

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References

[1] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): Leitlinie "Akute Bronchitis". July 1998; *www.uni-duesseldorf.de/WWW/AWMF/ii/ppneu-07.htm*

[2] Snow, V., Mottur-Pilson, C., Gonzales, R., Principles of appropriate antibiotic use for treatment of acute bronchitis in adults. Position paper. Clinical practice guideline. Part 1 of the American College of Physicians (ACP). Ann. Intern. Med. **134,** 518 (2001)

[3] Gruenwald, J., Graubaum, H.-J., Busch, R., Efficacy and tolerability of a fixed combination of thyme and primrose root in patients with acute bronchitis. Arzneim.-Forsch./Drug Res. **55,** 669 (2005)

[4] Matthys, H., de Mey, C., Carls, C. et al., Efficacy and tolerability of myrtol standardised in acute bronchitis. A multicentre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol. Arzneim.-Forsch./Drug Res. **50,** 700 (2000)

[5] Matthys, H., Eisebitt, R., Seith, B. et al., Efficacy and safety of an extract of Pelargonium sidoides (Eps 7630) in adults with acute bronchitis. A randomised, double-blind, placebo-controlled trial. Phytomedicine **10**, Suppl. IV, 7 (2003)

[6] Martinez, F. J, Acute bronchitis: state of the art diagnosis and therapy. Compr. Ther. **30, 5**5 (2004)

[7] Alberta Clinical Practice Guideline Working Group, Guideline for the management of acute bronchitis. December 2000, revised: November 2001; *www.albertadoctors.org*

[8] Vogel, F., Scholz, H., Al-Nawas, B. et al., Rationaler Einsatz oraler Antibiotika bei Erwachsenen. Med. Monatsschr. Pharm. **25,** 193 (2002)

[9] Irwin, R. S., Boulet, L.-P., Cloutier, M. M. et al., Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. Chest **114** (1998)

[10] Kardos, P. Cegla, U., Gillissen, A. et al., Leitlinie der Deutschen Gesellschaft für Pneumologie zur Diagnostik und Therapie von Patienten mit akutem und chronischem Husten. Pneumologie **58,** 570 (2004)

[11] Bionorica AG: Fachinformation [summary of product characteristics] Bronchipret® Saft; as of July 2002; Bundesverband der Pharmazeutischen Industrie e.V., Fachinfo-Service

[12] ESCOP Monograph, *Thymi herba* (Thyme). European Scientific Cooperation on Phytomedicine, Elburg (2003)

[13] Hagers Handbuch der pharmazeutischen Praxis, 5the ed., Springer, Berlin – Heidelberg etc. (1995)

[14] ESCOP Monograph, *Hedera helices folium* (Ivy Leaf). European Scientific Cooperation on Phytomedicine, Elburg (2003)

[15] Aliprandi, P. Cima, L., Carrara, M., Therapeutic use of levocloperastine as an antitussive agent. An overview of preclinical data and clinical trials in adults and children. Clin. Drug Invest. **22,** 209 (2002)

[16] Bauer, P., Köhne, K., Evaluation of experiments with adaptive interim analysis. Biometrics **50**, 10291 (1994)

[17] Fein, A., Grossmann, R., Ost, D. et al., Bronchitis. In: Diagnosis and management of pneumonia and other respiratory tract infections, 1st ed., pp 245–266, Professional Communication, USA (1999)

[18] Höffken, G., Lorenz, L., Kern, W. et al., S3-Leitlinie zu ambulant-erworbener Pneumonie und tiefen Atemwegsinfektionen. Pneumonologie **59,** 612 (2005)

[19] Fahey, T., Stocks, N., Thomas, T., Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. BMJ **316,** 906 (1998)

[20] Gonzales, R., Steiner, J. F., Sande, M. A., Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. JAMA **278,** 901 (1997)

[21] Gonzales, R., Steiner, J. F., Lum, A. et al., Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. JAMA **281**, 1512 (1999)

[22] Orr, P.H., Scherer, K., Macdonald, A. et al., Randomised placebo-controlled trials of antibiotics for acute bronchitis: A critical review of the literature. J. Fam. Pract. **36,** 507 (1993)

[23] Evans, A. T., Husain, S., Durairaj, L. et al., Azithromycin for acute bronchitis: a randomised, double blind, controlled trial. Lancet **359,** 1648 (2002)

[24] Raherison, C., Poirier, R., Daures, J. P. et al., Lower respiratory tract infections in adults: non-antibiotic prescriptions by GPs. Respir. Med. **97,** 995 (2003)

[25] Stocks, N. P., McElroy, H., Sayer, G. P. et al., Acute bronchitis in Australian general practice. A prescription too far? Aust. Fam. Physician **33,** 91 (2004)

[26] McIsaac, W. J., To, T., Antibiotics for lower respiratory tract infections. Still too frequently prescribed? Can. Fam. Physician **50,** 569 (2004)

[27] Curle, P. F., Fraibault, V., Prevot, A., The evaluation of five Bionorica drugs and bromhexine on tracheo-bronchial phenol red secretion in rats; Report. Batelle Europe, Geneva, Switzerland (1991)

[28] Haen, E., Pharmakologische Aktivitäten von Thymus vulgaris und Hedera helix. Proceedings of the 2nd Int. Congress on Phytomedicine. Sep. 11–14, 1996, Munich. Phytomedicine **3**, Suppl. I (1996/97)

[29] Leslie, G. B., A pharmacometric evaluation of nine biostrath herbal remedies. Medita **10**, 31 (1978)

[30] Smucny, J., Fahey, T., Becker, L. et al., Antibiotics for acute bronchitis. Cochrane database Syst Rev. **4**, CD000245 (2004)

[31] Verspohl, E. J., Press discussion "Virale Atemwegsinfekte: Vom Schnupfen bis zur Vogelgrippe" [Viral airway infections: From rhinitis to avian flu], Munich, 7 Dec. 2005; Komitee Forschung Naturmedizin, Munich

[32] Gillissen, A., Gessner, C., Hammerschmidt, S. et al., Acute bronchitis: when are antibiotics, and when is symptomatic treatment indicated? MMW Fortschr Med. **148,** 26 (2006)

[33] Goos, K. H., Albrecht, U., Schneider, B., Efficacy and safety profile of a herbal drug containing nasturtium herb and horseradish root in acute sinusitis, acute bronchitis and acute urinary tract infection in comparison with other treatments in the daily practice/results of a prospective cohort study. Arzneim.-Forsch./Drug Res. **56,** 249 (2006)

[34] Gill, J. M., Fleischut, P., Haas, S. et al., Use of antibiotics for adult upper respiratory infections in outpatient settings: a national ambulatory network study. Fam. Med. **38,** 349 (2006)