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 to 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.
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 combination1), 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 primary active components of thyme are the volatile 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 KV-Bezeichnung: Bronchipret® Saft; pharmazeutischer Hersteller: Bionorica AG, Neumarkt (Germany).
to Visit 1 (according to patient’s estimate), and a baseline Bron-chitis 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 contra-ception for women of child bearing age and lactation for fe-males) were used, the principal ones being concomitant fever (> 39 °C), pneumonia, history of chronic bronchial or pulmo-nary 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 dis-ease.

Treatment with other drugs, such as immunosuppressives, systemic antibiotics and systemic or inhalation glucocorticoste-roids (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 concomi-tantly), antitussive drugs and other mucoactive measurements (except for steam inhalation (concomitantly) were not allowed. Treatment with angiotensin converting enzyme (ACE) inhib-i-tors 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 blind-ing. 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 treat-ment groups. The study medication supply for 11 days, includ-ing 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 treat-ment (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 fre-quency 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 proper-ties (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 com-pared 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 ‘respond-
ers’, patients whose symptoms were unchanged or deterior-
ated 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 treat-
ment due to complete healing. Of these, 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) were included into the study. Two
patients of the thyme-ivy combination group (N = 2: possibly
or probably drug-related adverse event) prematurely discon-
tinued study participation. In addition, 6 patients under thyme-ivy combination and 4
patients under placebo prematurely discontinued treat-
due to complete healing.

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 effi-
cacy 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 prim-
ary 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 devi-
ation from the “preconditions” of the ANOVA, the Wilcoxon test
(stratified by centre) was carried out additionally.

All hypotheses tests for the secondary endpoints were car-
ried 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 percent-
age 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 temper-
ature). Differences between treatment groups regarding inves-
tigators’ and patients’ tolerability ratings were analysed using
the Cochran-Armitage Trend test. 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 addi-
tion, 6 patients under thyme-ivy combination and 4
patients under placebo prematurely discontinued treat-
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 in-
cluded 361/363 patients (N = 182/182 thyme-ivy combina-
tion 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-
Table 1: Demographics and other baseline characteristics at Visit 1 (FAS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistics</th>
<th>Thyme-ivy combination (N = 182)</th>
<th>Placebo (N = 178)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>Female N (%) 79 (47.8)</td>
<td>81 (45.5)</td>
<td>0.6623</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male N (%) 97 (52.2)</td>
<td>97 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>mean ± SD</td>
<td>43.4 ± 17.7</td>
<td>41.5 ± 17.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>95 (52.2)</td>
<td>171.3 ± 9.1</td>
<td></td>
</tr>
<tr>
<td>Height [cm]</td>
<td>mean ± SD</td>
<td>171.6 ± 9.0</td>
<td>174.0 ± 14.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>75.1 ± 13.7</td>
<td>74.0 ± 14.4</td>
<td></td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>mean ± SD</td>
<td>68.7 ± 13.7</td>
<td>70.1 ± 16.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>127 (69.8)</td>
<td>128 (71.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td>Smoker N (%) 55 (30.2)</td>
<td>50 (28.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-smoker N (%) 127 (69.8)</td>
<td>128 (71.9)</td>
<td></td>
</tr>
<tr>
<td>Bronchitis Severity Score</td>
<td>mean ± SD</td>
<td>8.2 ± 2.0</td>
<td>8.3 ± 2.2</td>
<td>0.5896</td>
</tr>
<tr>
<td>(RSS)</td>
<td></td>
<td>25.8 ± 15.5</td>
<td>26.7 ± 16.3</td>
<td>0.6037</td>
</tr>
</tbody>
</table>

* Number of coughing fits according to patient’s estimation for the previous day. SD = standard deviation of the mean. \( \chi^2 \) = Chi-square test; \( W \) = Wilcoxon-two sample test, two-sided. * 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.
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.

Reinhold 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


Antiallergika · Antiasthmatika · Antitussiva · Bronchodilatatoren · Bronchosekretolytika · Mukolytika