A Multi-centre, Randomised, Double-blind, Placebo-controlled Clinical Trial on the Efficacy and Tolerability of GeloMyrtol® forte in Acute Bronchitis

Authors
A. Gillissen[1], Th. Wittig[2], M. Ehmen[2], H. G. Krezdorn[3], C. de Mey[4]

Affiliations
[1] Department of Pulmonary Medicine, General Hospital Kassel, Kassel, Germany
[2] G. Pohl-Boskamp GmbH & Co. KG, Hohenlockstedt, Germany
[3] Internist, Munich, Germany
[4] ACPS-Network GmbH, Applied Clinical Pharmacology Services, Mainz-Kastel, Germany

Key words
- acute bronchitis
- clinical trial
- Myrtol®
- GeloMyrtol® forte

Abstract

GeloMyrtol® forte (Myrtol®) is a phytomedicine obtained by distillation from essential oils. The trial was conducted to confirm the efficacy of Myrtol® in the treatment of acute bronchitis.

Methods: Patients with acute bronchitis and without confounding co-morbidity or co-medication were randomly assigned to treatment with either Myrtol® 300 mg 4 times daily or matched placebo in double-blind, parallel-group fashion. Signs and symptoms were evaluated by the investigator at baseline and after 7, 10 and 14 days of treatment; intake of medication, wellbeing and symptoms were recorded daily by the patient in the patients' diaries.

Findings: 413 patients were enrolled and randomised (Myrtol®: 202; Placebo: 211); 398 had at least one on-treatment efficacy evaluation (Myrtol®: 196; Placebo: 202). The mean change in coughing fits from D01 (baseline) to D07-D09 (after about one week treatment) was 62.1% (95% CI: 57.6–66.6%) and 49.8% (95% CI: 44.6–55.0%) for treatment with Myrtol® and placebo, respectively ($p < 0.0001$). With Myrtol®, the median time to 50% reduction in coughing fits was statistically significantly shorter and there were more patients without day-time coughing fits; there also were statistically significantly less day-time coughing fits, less difficulty coughing up, less sleep disturbance due to night-time coughing; with Myrtol® there was less symptomatic impairment (composite bronchitis severity score and subscores) and significant more patients had a clinically satisfying response to the investigational treatment.

Both treatments were generally well tolerated.

Conclusions: Myrtol® is statistically significantly superior to placebo in treating acute bronchitis.

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Bibliography
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Correspondence
Dr. med. T. Wittig
G. Pohl-Boskamp GmbH & Co. KG
Kieler Str. 11 – D-25551 Hohenlockstedt
Tel.: +49/4826/59 240
Fax: +49/4826/59 213
t.wittig@pohl-boskamp.de

Introduction

Each year an episode of acute bronchitis is estimated to affect about 5% of the general population [1]. The majority of these patients seek medical attention, and this accounts for millions of office visits per year. The major reason for seeking care is for symptom relief particularly during the first week of illness. Respiratory viruses appear to be the most common cause of acute bronchitis (predominantly rhinovirus, influenza or parainfluenza virus, respiratory syncytial virus, coronavirus or adenovirus) [1,2] although the responsible germ is identified in clinical practice only rarely. Bacterial infections are thought to occur in fewer than 10% of all cases [1,2]; the most common bacteria in otherwise healthy individuals include Mycoplasma pneumoniae, Chlamydia pneumoniae and Bordetella pertussis [3]. According to the ACCP (American College of Chest Physicians) there is no causative treatment available and consequently symptomatic approach is the only recommended and remaining treatment option.

GeloMyrtol® forte [a,b] is a phytomedicine obtained by a highly defined multistep distillation process from essential oils; in the literature it is also denoted as Myrtol®[b]. Myrtol consists of many constituents. In-vitro and in-vivo, the major monoterpenes 1,8-cineole (CAS N° 470-82-6), d-limonene (CAS N° 5989-27-5) and (+) α-pinene (CAS N° 80-56-8) are used as biological marker substances, unlikely however to encompass the full scope of pharmacological active moieties. The quality of the essential oils is guaranteed by the relevant EMA-Guidelines for herbal medicinal products and a validated, standardised manufacturing process according to Good Agri-

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cultural Practice and Good Manufacturing Practice. This guarantees a consistent high quality. The active ingredient of GeloMyrtol® forte is produced out of plants of the Myrtaceae family and the Rutaceae family. The Myrtaceae oils are obtained by steam distillation whereas the Rutaceae oils are obtained by expression of the peels. The oils are then further processed and purified by subsequent distillation steps.

Myrtol is approved for the treatment of acute and chronic bronchitis and sinusitis in many European and non-European countries for several decades. Clinically, Myrtol has already been shown to be efficacious in the treatment of acute bronchitis, this also in comparison to active control medication like ambroxol and antibiotics [4]. For conditions such as acute bronchitis with a spontaneous recovery, a verification and confirmation relative to placebo is considered to be relevant and important. In this way the present study exemplifies continuing efforts to investigate and document the drug's therapeutic efficacy above and beyond the already existing documentation in patients with acute bronchitis.

Methods

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Ethical considerations

The study was performed in accordance with the Declaration of Helsinki and the Notes for Guidance on Good Clinical Practice. The study protocol, patient information and informed consent form were reviewed and approved by the competent central ethic committee of the Federal State of Bavaria which is competent for the country co-ordinating investigator in Germany, the local ethics committees of all investigators and the German Federal Institute for Drugs and Medical Devices (BfArM). Participation in the study was voluntary. Only subjects who were willing and able to provide informed consent were eligible.

Design

The study was conducted in a multi-centre, randomised, placebo-controlled, double-blind, parallel-group fashion. Eligible patients with acute bronchitis were randomly assigned 1:1 to a 2-week treatment with 4 daily doses of either 300 mg Myrtol or matched placebo capsules.

Preclinically, Myrtol was shown to enhance mucociliary clearance due to muco-secretomotoric actions and additionally, to have anti-inflammatory and anti-oxidant properties. Based on these actions and properties, Myrtol could be hypothesised to be of therapeutic value in the treatment of acute bronchitis by liquefying otherwise viscous secretions and facilitating their expectoration, reducing cough frequency and reducing coughing discomfort, while also avoiding impaction of secretions and preventing bacterial superinfection. This hypothesis has been tested and confirmed over the past decades for several secretomotoric/-mucolytic medications. In all such investigations, it is of prime importance to demonstrate whether and how such medication facilitates and accelerates the otherwise spontaneous recovery of the disease (as observed under placebo).

Since acute bronchitis is a condition characterised by a spontaneous regression [5, 6], patients assigned to treatment with placebo were not exposed to undue risk or inconvenience. The value of medication in the present study lies in a relevant reduction of symptoms and a more rapid and more complete recovery relative to the course under placebo.

There were no relevant on-study changes in the trial design.

Patients

400 patients with acute bronchitis were intended to be recruited in approximately 35 centres for ambulatory primary care in Germany. Eventually, 413 patients were recruited by 29 active study centres. Male and female patients were eligible if they met all of the following inclusion criteria: at least 18 years of age; Broca-index between 0.75 and 1.30; clinical diagnosis of acute bronchitis as characterised by: ≥ 10 coughing fits during the last day prior to the screening visit, a baseline Bronchitis Severity Score (BSS – see below) ≥ 5 points (of maximum 20 points), and an onset of first symptoms (bronchial mucus production with impaired ability to cough up) within 2 days before the start of the investigational treatment. Exclusion criteria were: history or presence of confounding respiratory disease (e.g. upper respiratory tract infection within the last 4 weeks, chronic bronchitis or COPD or acute exacerbations thereof (according to GOLD [3]) bronchiectasis, asthma, suspected pneumonia, cystic fibrosis, lung cancer); concomitant bacterial infection; elevated body temperature (> 39.5 °C rectally or > 39.0 °C axillary or otic); active cigarette smoking > one pack per day; hypersensitivity to the trial medication; inflammatory gastrointestinal or hepatic disease or inflammation of the gallbladder or bile duct; history or presence of clinically relevant cardiovascular, renal, metabolic, haematological, dermatologic, neurological, psychiatric, systemic or infectious disease; pregnancy or breastfeeding; women of childbearing potential without highly effective contraception (failure rate < 1 %); participation in a clinical research study within the last 6 weeks; previous participation in the trial; evidence or suspicion of non-compliance; inability to provide informed consent.

Prohibited co-medication were: antibiotics, systemic or inhalative glucocorticosteroids, angiotensin converting enzyme (ACE) inhibitors within the last 4 weeks, angiotensin-II-receptor antagonists, secretolytics, mucolytics, or antitussives (e.g. codeine or other morphine derivatives) within the last 2 days, inhalation and/or physical therapy of acute bronchitis, analgesics (except paracetamol), sedatives/hypnotics or sedating antihistamines, anti-arrhythmic (e.g. amiodarone), inhaled bronchodilators, inhaled chromoglycate). Any other concomitant medication was only allowed if it did not interfere with the eligibility criteria and the evaluation of the study endpoints.

The investigators were entitled to withdraw any patient prematurely if this was deemed to be in the patient's best interest (e.g. in the case of safety-limiting adverse events, relevant post-hoc con-compliance with the eligibility criteria, relevant intercurrent disease, need for or use of prohibited medication, etc.). Additionally, patients were to be discontinued prematurely if there was evidence of high fever (> 39.5 °C rectally or > 39.0 °C axillary or otic), evidence of pneumonia or if there was evidence relevant lack of efficacy of the investigational treatment.

Time schedule

The study lasted 2 weeks ± 2 days. It comprised 4 visits: visit V1: screening for eligibility, enrolment and randomisation – start of investigational treatment – dispensing of diary and medication for the first treatment week; visit V2 (study day D07 ± 1): evaluation after 1 week of treatment; evaluation of efficacy, tolerability, and compliance – dispensing of diary and medication for the second treatment week; visit V3 (study day D10 ± 2): evaluation after 10 days of treatment; evaluation of efficacy, tolerability, and compliance – continuation of the investigational treatment; visit V4 (study day D14 ± 2): end-of-trial evaluation.

Study Medication

Medication supplies of GeloMyrtol® forte and matched placebo capsules were provided by the sponsor. Individualised medication boxes solely identified by a randomly assigned treatment ID-number were dispensed. For each patient, medication boxes were distributed by treatment week. Care was taken that each patient was only treated with medication in accordance with his/her randomly set treatment assignment number.

Blinding

The investigators and the patients were blinded with regard to the nature of the medication assigned to each trial participant by using matched medication supplies for active and placebo medication (re. identical blisters, outer package, labelling, capsule size and outer appearance of the medication packs). Supplies were only identified by the respective treatment assignment number in accordance with the randomisation plan. Trial data were only unblinded after closure of the database.

Randomisation

Patients were assigned at random 1:1 to treatment with either Myrtol or matched placebo. The randomisation plan was generated by the data centre by means of RANCODE-Software by IDV. Randomization was carried out in blocks of 4 by trial site. Individual medication supplies were only identified by treatment assignment number and consisted of either Myrtol or placebo in accordance with the randomisation plan. At visit V1, eligible patients were assigned by the investigator to their subject/treatment number in order of entrance to the study starting with the lowest number first, and were then treated with the corresponding medication throughout.

Treatments

The first dose was applied at the end of V1; otherwise, the patients took the medications themselves at home. Each intake was recorded in a diary. Patient compliance (drug accountability and documentation in the diary) was checked by the investigator at each visit (V2, V3, V4). According to the approved dosage recommendations of GeloMyrtol® forte for acute bronchitis the patients were instructed to take 4 capsules per day for 2 weeks: 1 capsule in the morning (30 min before breakfast), 1 capsule midday (30 min before lunch), 1 capsule in the evening (30 min before dinner), and 1 capsule late in the evening at bedtime [7]. The capsules were to be taken with sufficient cold water.

Study criteria and methods – efficacy

The evaluation of efficacy was based a) on the patients' daily records in weekly diaries and b) the investigators' assessment of the patients' condition at the scheduled visits. The validation of the used parameters frequency of day-time coughing fits and Bronchitis Severity Score is based on several clinical studies on acute bronchitis [8–12] in which they were defined as important tools for the evaluation of the efficacy of the study medication. Furthermore, the significance and value of these 2 parameters is confirmed by the guideline for acute and chronic cough of the German Society of Pneumology [13].

- Frequency of day-time coughing fits (defined as a single coughing event of 3 or more consecutive coughs) counted using a manual counter from waking up to bedtime and recorded daily in the diary at bedtime; the number of coughing fits on day D01 was set as baseline.
- Response to treatment: at each on-/post-treatment visit, response to treatment was scored by the investigator by means of a verbal rating scale (VRS: 0 = symptoms healed [cured], 1 = symptoms improved compared to baseline, 2 = symptoms unchanged compared to baseline, 3 = symptoms deteriorated compared to baseline); patients with scores 0 or 1 were defined as "responders"; patients with scores 2 or score 3 were defined as "non-responders".
- Bronchitis Severity Score (BSS): at each visit, the investigator scored the intensity for each lead sign/symptom (cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnoea) using a 5-point VRS (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The BSS was calculated as the sum of these scores; in order to be eligible, the patients had to have a baseline BSS of at least 5/20 points.
- Difficulty to cough-up mucus during the day: at baseline (V1; CRF-record) and in the evening of D01–D13 (diary records), the presence ("yes"/ "no") of day-time and night-time cough and the difficulty of expectoration on coughing – if present – was scored (VRS: 0 = no problem to cough up mucus, 1 = mild problems to cough up mucus, 2 = coughing-up mucus is impaired, 3 = coughing-up mucus is very impaired).
- Sleep disturbance due to coughing at night: at baseline (V1; CRF-record) and in the morning of D01–D14 (diary records), the patient rated his/her sleep disturbance during the preceding night (VRS: 0 = "I cannot remember waking up due to coughing", 1 = "I slept well although I can remember coughing during the night", 2 = I woke up due to at least one severe coughing fit, but I fell asleep again", 3 = "I hardly slept because of many severe coughing fits").
- Work incapacitation: at the last scheduled visit (V4), the investigator was to score the patients' work incapacitation to acute bronchitis (total number of days until Day D14).
- Diary data: coughing fits during the day, disturbance of sleep by cough, type of cough (sputum consistence) and general wellbeing as recorded daily by the patient on categorised verbal rating scales (VRS).
- Visit data: at each visit, the investigator recorded body temperature, findings of lung auscultation ("normal" or "abnormal"; if abnormal, the findings were to be specified acc. to predefined categories) and the 1 s Forced Expiratory Volume (FEV_1); additionally, at each visit, the absence/presence of bronchial hyperreactivity (characterised by coughing when exposed to cold/change of temperature, during exercise and/or when exposed to noxious substances), acute rhinitis, sore throat, difficulty swallowing, hoarseness, headache, pain in limbs and joints, fatigue, others (with specification) were recorded.

Study criteria and methods – safety and tolerability

Safety and tolerability were evaluated with regard to the following

- Safety: the presence of adverse events (AE) and changes in general well-being was recorded throughout, at each visit and at the telephone contact on Day 3.
- Vital signs: at each visit, the patients' blood pressure (mmHg) and pulse rate (bpm) was measured using an automated oscillometric device after 5 min rest each time using the same arm.

- Body temperature: at baseline (V1 – CRF-record) and in the evening of Day D0–Day 13 (diary records), body temperature [°C] was to be measured either from the axilla, the ear or rectally. The patient was to contact the investigator if the body temperature exceeded 39°C. Diaries were checked for elevated body temperature. The use of any antipyretic medication (e.g. paracetamol) was recorded.

Statistical analysis – Criteria for comparison of the investigational treatments

- Primary criterion: ratio of the mean frequency of day-time coughing fits on days D07-D09 to the baseline frequency on D01.
- Secondary criteria: for the daily day-time coughing fits, difficulty of coughing-up, sleep disturbance due to night-time coughing, and impairment of general wellbeing, the course of the data was summarised by the trapezoidal area under the course of the respective data (AUD) from baseline (D01) to the respective endpoint.

Statistical analysis – Datasets

- SEP (Safety Evaluable Population): all patients who took the assigned trial medication at least once and for whom at least one post-/on-treatment safety evaluation was available.
- FAS (Full Analysis Set): all patients who took the assigned trial medication at least once and for whom at least one post-/on-treatment efficacy evaluation was available.
- PP (Per-Protocol Set for sensitivity analysis): FAS-patients without relevant protocol deviation(s) and with efficacy data (number of coughing fits) for at least D07, D08, and D09; patients who terminated the study prematurely due to insufficient efficacy (incl. elevated body temperature or evidence of pneumonia) were not excluded from the PP.

Statistical analysis – Sample size estimates

The size of the study sample had been set *a priori* assuming a 50% reduction of the mean frequency of day-time coughing fits on days D07-D09 from baseline for the placebo group and an additional 10% reduction under active treatment. Assuming the standard deviation of the baseline-normalised frequency of coughing fits to be 0.35 and setting the type-I error rate to 2.5% 1-sided and the statistical power to 80% yielded an estimate of 194 patients per treatment group using the t-test approach (program StudySize version 1.09). Assuming a rate of approximately 3% non-evaluable patients, 200 patients had been scheduled to be enrolled in each of the 2 treatment groups (total N = 400).

Statistical analysis – Interim analysis

After completion of 262 patients, a protocol-defined blinded interim analysis was carried-out in order to verify whether the estimate of the standard deviation of the baseline-normalised frequency of coughing fits had been appropriate. The estimate was confirmed and the sample size was kept as originally planned.

Statistical analysis – Handling of missing information

In the FAS dataset, completely missing diaries were not imputed by any procedure. If only baseline data were available, these data were not used for imputation of proceeding values (no "Baseline-value" carried forward). Otherwise, missing data were imputed according to a Last Observation Carried Forward [LOCF] method that was fixed at the Blinded Review Meeting and Valid Statement depending on the criterion and the kind of data loss. In the PP dataset, LOCF was only carried-out for those missing data in the CRF that resulted from non-efficacy of the investigational trial medication (premature study termination because of lack of efficacy incl. high fever or evidence of pneumonia).

Statistical analysis – Treatment contrasts

Baseline values were considered to be the most important confounder with an impact on the study results; accordingly, baseline adjustment was performed either by defining variables relative to baseline (e.g. for the primary endpoint) or by adjusting baseline effects by the statistical method afterwards (e.g. ANOVA or ANCOVA). As indicated, treatments were contrasted by analysis of variance with 'Treatment' as fixed effect and 'Centre' as a random effect; in the event that the ANOVA-residuals revealed significant non-normality, a Wilcoxon-Mann-Whitney test stratified by centre was performed instead (Van Elteren test). For the time to 50% reduction in coughing fits, the treatments were contrasted by means of a Log-Rank test.

Results

Patient disposition

The study was carried out in 29 trial sites including 29 investigators from all over Germany in the period from January 2011 to May 2011. Only investigators qualified according ICH E6 Guideline for GCP were involved in the study; these practice-based physicians consisted of 7 internists and 22 specialists in general medicine.

A total of 413 patients provided informed consent and was investigated in terms of their eligibility. No subject was discontinued at this stage. All screened patients were enrolled, randomised and treated at least once (SEP: 413; Myrtol: 202; Placebo: 211). 398 patients had at least one on-treatment efficacy evaluation (FAS: 398; Myrtol: 196; Placebo: 202); 350 patients were retained in the PP dataset (Myrtol: 172; Placebo: 178).

Premature discontinuations

37/413 treated patients were discontinued prematurely (16/202 [7.9%] and 21/211 [10.0%] patients treated with Myrtol and placebo, respectively) – see **Fig. 1**. In the Myrtol group, the most common reasons for premature study discontinuation were withdrawal of consent and lost-to-follow-up (4/16 dropouts each). Other reasons were AEs (n = 3) and insufficient efficacy (n = 3). In the placebo group, dropout reasons were insufficient efficacy (7 from 21 discontinuations), AEs (n = 6) and withdrawal of consent (n = 4).

Demography

The FAS of 398 patients consisted of 217 [54.5%] females and 181 [45.5%] males (see **Table 1**); 96.7% were Caucasians; mean age: 42 ± 16 years (range: 18–83 years); mean height: 171 ± 9 cm (range 153–194 cm); mean body weight: 75 ± 13 kg (range: 47–117 kg). There were no relevant differences between the datasets and between the treatment groups within each dataset in this regard.

Baseline features – Diagnosis and disease severity

All patients had an acute bronchitis of recent onset (≤ 2 days). At study start, all patients suffered from cough, of which the intensity was severe in 142 patients (35.7%), and even very severe in 60 patients (15.1%). 92% of all patients felt subjectively poor or

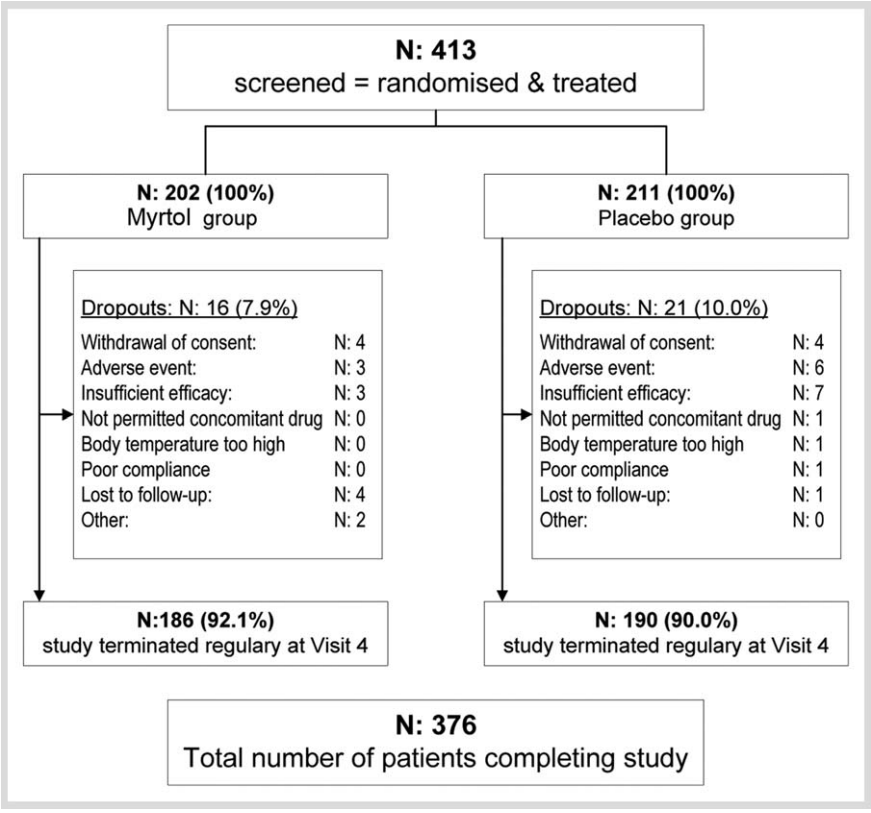

Fig. 1 Study subject disposition: number of subjects enrolled, number of subjects treated, number of subjects who discontinued from the trial prematurely, and number of subjects who completed the trial regularly after 14 days of investigational treatment (visit V4). Note: all screened subjects were enrolled.

Table 1 Demographic data.

Variable	Myrtol	Placebo	Total	p-value [1]
N	196	202	398	
Gender				
Men	88 (44.9%)	93 (46.0%)	181 (45.5%)	0.82
Women	108 (55.1%)	109 (54.0%)	217 (54.5%)	
Age (yrs)				
Mean	42.5	41.1	41.8	0.26
SD	15.5	16.4	15.9	
Range	18–81	18–83	18–83	
Height (cm)				
Mean	171.4	171.4	171.4	0.87
SD	8.9	8.2	8.6	
Range	153–194	154–193	153–194	
Weight (kg)				
Mean	75.3	74.5	74.9	0.66
SD	13.7	12.4	13.9	
Range	47–117	48–109	47–117	

[1]Test for difference between groups (2-sided)

very poor and 86% of all patients had pathological auscultation findings. There were no relevant differences between the study groups with regard to the disease intensity at baseline.

Baseline features – Co-morbidity

For 128/202 [63.4%] patients of the Myrtol-group and 134/211 [63.5%] of the Placebo-group (SEP dataset) past or present (co-) morbidity was reported (mainly back pain and hypertension).

Baseline features – Co-medication

For 113/202 [55.9%] patients of the Myrtol-group and 116/211 [55.0%] of the Placebo-group (SEP dataset) past or present use of (co-) medication was reported at baseline: mainly sex hormones [28.1%], thyroid supplements [8.2%], beta-adrenoceptor blockers [7.0%], non-specific gynaecological medications [5.1%], antidiabetic medications [3.9%], and lipid-lowering agents [5.8%].

Compliance

Based on the diary records including Day D09, patients' mean adherence to study medication was almost 100% in both treatment groups (Myrtol: 62.0–100.0%, mean 98.1±5.3%; placebo 73.0–100%, mean 98.2±4.5%). 5 patients were excluded due to low treatment adherence (=protocol violation).

Efficacy

Treatment with Myrtol proved consistently superior to Placebo with regard to primary and secondary outcome parameters:

- There was a significantly lower mean frequency of day-time coughing fits for days D07–D09 from (expressed as ratio of the baseline frequency on Day D01) for treatment with Myrtol: this corresponds to a mean change in coughing fits of 62.1% (95% CI: 57.6–66.6%) under Myrtol treatment compared to 49.8% (95% CI: 44.6–55.0%) under placebo ($p<0.0001$; **Fig. 2**).

For the secondary outcome criteria, treatment with Myrtol proved superior to placebo on several accounts; in patients treated with Myrtol compared to those treated with placebo, there were following relevant differences

- a larger relative reduction in mean frequency of coughing fits (FAS, $p<0.001$ and $p<0.0001$; **Fig. 3**),
- a larger reduction in daily coughing fits (FAS, $p<0.0001$; **Table 2**),
- the time to 50% reduction in coughing fits was shorter (FAS, $p=0.0002$; **Table 2**),
- more patients achieved a condition without coughing fits (FAS, $p=0.0012$; **Table 2**),
- it proved easier to cough up mucus during the day (FAS, $p=0.0004$; **Table 2**) and

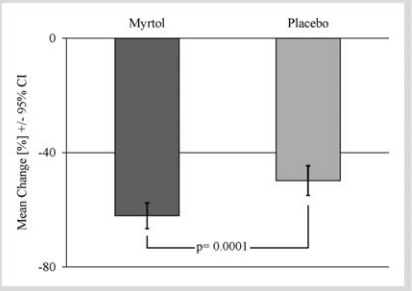

Fig. 2 Change in the mean frequency of day-time coughing fits on Day D07-D09 (standardised for the baseline frequency on Day D01) for the patients treated with Myrtol and Placebo.

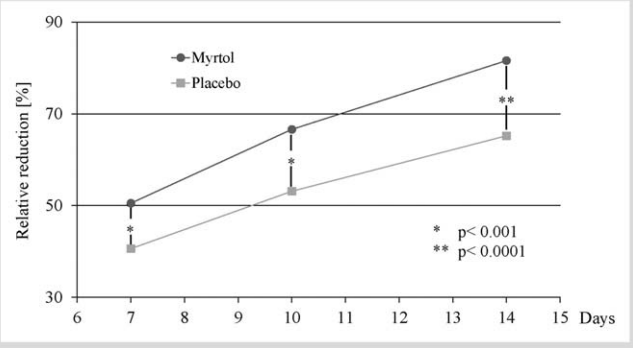

Fig. 3 Relative reduction in mean frequency of coughing fits of investigational treatment with either Myrtol or Placebo.

Table 2 Descriptive statistics of the main cough-related efficacy criteria for the full analysis data set (FAS): means (± standard deviation) or N of patients (and %) by criterion and treatment (Myrtol and Placebo) along with the p-value for the difference between the treatments.

Endpoint	Myrtol	Placebo	p-value (2-sided)
N	196	202	
Reduction in daily coughing fits[1]	5.8 ± 3.1	7.1 ± 3.8	<0.0001
Time to 50% reduction in coughing fits [2]	5 (5–6)	6 (6–8)	0.0002
No coughing fits [3]	88 (44.9%)	59 (29.2%)	0.0012
Difficulty to cough up mucus during the day [4]	11.2 ± 7.2	14.1 ± 9.3	0.0004
Sleep disturbance induced by coughing at night [4]	10.8 ± 7.2	13.7 ± 9.0	0.0007

[1] Mean ± SD (coughing fits x days), [2] Median (min.–max.) in [days], [3] N of patients (%), [4] Mean ± SD (score points × days)

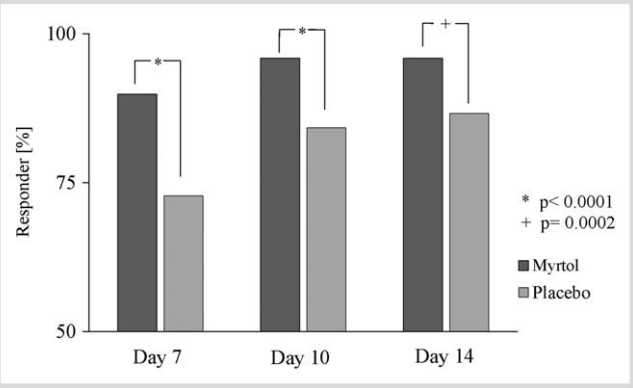

Fig. 4 Responder rates after 7, 10, and 14 days of investigational treatment with either Myrtol or Placebo.

- there was less sleep disturbance due to night-time coughing (FAS, p = 0.0007; **Table 2**).

Additionally, Myrtol proved superior to Placebo also with regard to responder and non-responder rates:

- Already in the second treatment week more than 90% of the patients of the Myrtol-group could be considered "responders" (healed/cured or improved), distinctly and statistically significantly more than for the Placebo treatment (Day D07: p < 0.0001, D10: p < 0.0001, D14: p = 0.0002; **Fig. 4**),
- This corresponds to a very low non-responder rate in the Myrtol-group (8% after 1 week, 3% after 2 weeks) in contrast to the Placebo treatment (Day D07: p < 0.0001, D10: p < 0.0001, D14: p = 0.0002; **Fig. 5**).

Also, treatment with Myrtol proved superior to Placebo also in terms of the Bronchitis Severity Score (BSS):

- The mean BSS has been about the same for both treatment groups at baseline; at each on-treatment visit, the mean BSS was distinctly lower in the Myrtol-group than in the patients treated with Placebo. Accordingly, the mean changes in BSS from baseline were larger at each on-treatment visit in the patients treated with Myrtol than in the patients treated with Placebo; at all visits, the treatment difference was statistically significant (p < 0.0001; **Fig. 6**).
- For the BSS-Subscores (cough, sputum, rales/ rhonchi, chest pain on coughing, and dyspnoea) a similarly beneficial effect of the Myrtol-treatment relative to the Placebo-treatment was seen; on Day D10, the mean changes from baseline for all subscores were statistically significantly lower for the Myrtol-group than for the Placebo-group (**Fig. 7**); on Day D14, this also applied except for 'chest pain on coughing' and 'dyspnoea', for which there was little difference between the 2 treatments (**Fig. 8**).

Safety and tolerability

39 AEs were reported (32/413 = 7.7%): 21 AEs in 16/202 patients of the Myrtol-group (7.9%) and 18 AEs in 16/211 patients of the placebo-group (7.6%). In the Myrtol group, the investigators classified 10 AEs in 8 patients as at least possibly drug related. In the placebo group, 2 AEs in 2 patients had a reasonable causal relationship to the test medication. Most of these adverse drug reactions (ADR) were of mild-to-moderate intensity including eructation, nausea or mild diarrhoea in the Myrtol-group and moderate abdominal pain in the placebo-group.

All events resolved without sequelae within the protocol-defined observation and follow-up time. In the Myrtol-group, 5 ADRs led to premature discontinuation of 3 patients from the trial. In the placebo-group, 2 ADRs led to premature discontinuation of 2 patients.

The present study was conducted with Myrtol and its new coating as test medication. The incidence rate of gastro-intestinal disorders was 0.035. In a previous randomised, placebo and actively controlled, double-blind clinical trial Myrtol was administered with its old coating, resulting in a higher incidence rate of gastro-intestinal disorders of 0.083. This corresponds to a relative risk reduction (RRR) of 58%.

Discussion

Acute bronchitis is mostly of viral origin but later bacterial superinfect infection might occur [14]; nevertheless, it is still quite often treated with antibiotics [1,5,6,14–16]. The natural

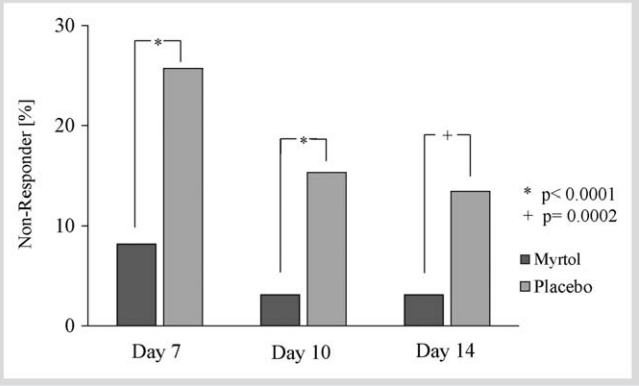

Fig. 5 Non-Responder rates after 7, 10, and 14 days of investigational treatment with either Myrtol or Placebo.

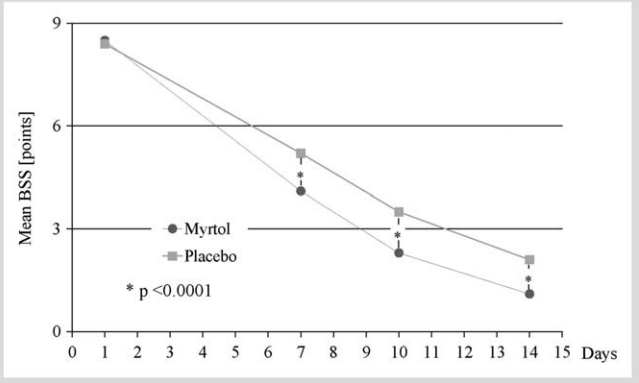

Fig. 6 Course of the means of the composite Bronchitis Symptom Score (BSS) over the course of the study with evaluation at baseline (Day D01) and after 7, 10, and 14 days of investigational treatment with either Myrtol or Placebo.

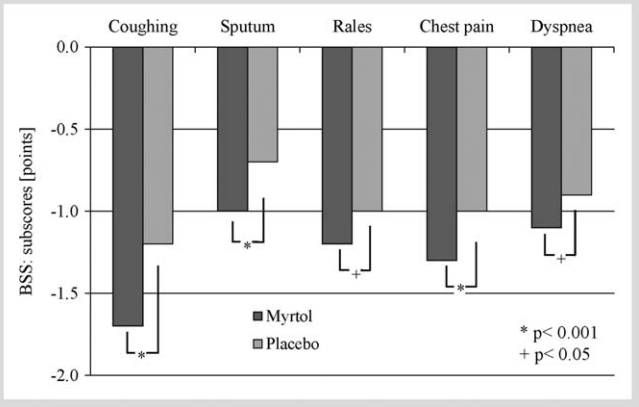

Fig. 7 Means of the BSS-Subscores after 10 days of investigational treatment with either Myrtol or Placebo.

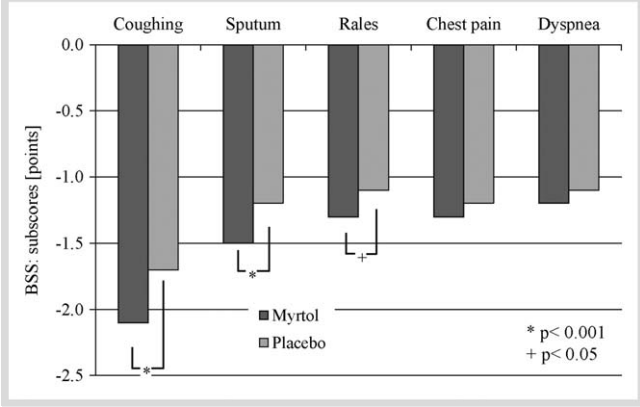

Fig. 8 Means of the BSS-Subscores after 14 days of investigational treatment with either Myrtol or Placebo.

course of an acute bronchitis mainly in terms of cough generally lasts 4 weeks on average until complete recovery [17]. Cough is the most commonly observed symptom of acute bronchitis beginning within 2 days of initial infection in up to 85% of all cases. Most patients have a cough for less than 2 weeks although many are still coughing after 2 weeks, and a few cough for up to 6–8 weeks or longer [1,18]. The diagnosis of acute bronchitis is mainly clinical, with cough as main symptom [19]. Microscopic examination or culture of sputum in the healthy adult with acute bronchitis generally is not helpful. Since most cases of acute bronchitis are caused by viruses, cultures are usually negative or exhibit normal respiratory flora [20]. Moreover, it recommend to limit the testing of the pathogens only to special cases, e.g. in case of already existing bronchopulmonary diseases and in hospitalized patients [20–22].

The benefit of antibiotics is small [23,24] in relation to the risk of promoting bacterial resistance [17,25–27]. In spite of many efforts little change in the prescribing habits in this indication has yet been reached. This often is explained by the patients' pressure and expectations [28–30]. These are likely to result from the substantial symptomatic discomfort that acute bronchitis causes in spite of its otherwise benign natural course and from the concern about bacterial (super-) infection. This is particularly the case when coughing is pronounced and regresses more slowly. Therefore, there is an urgent need for an effective treatment alternative. Tussisedatives may help the patient symptomatically, but they carry the risk a) of suppressing the body's protective mechanism for airway clearance and this might delay healing, and b) in promoting drug dependency when using opioid derivatives. Mucolytic i.e., secretolytic and secretomotoric agents such as in Myrtol may therefore be better suited, but generally their therapeutic positioning needs to be endorsed by more and better evidence of their efficacy and safety.

Myrtol has been shown to be efficacious in the treatment of lower respiratory tract diseases like acute [4] and chronic [31] bronchitis as well of upper respiratory tract diseases like acute [32] and chronic sinusitis [33] in well-designed, GCP-compliant, prospective, randomised, double-blind, Placebo- and actively-controlled, parallel-group trials. This is explained by its secretomucolytic, secretomotoric, and mucociliary clearance enhancing properties [33–40]; further pharmacological properties contribute as well, anti-inflammatory [41–43] and anti-oxidant actions [44,45], in particular; furthermore bacteriostatic properties were demonstrated in in-vitro studies [33,46]. The large therapeutic margin and excellent safety of Myrtol is supported by a full panel of toxicological studies required by pertinent European guidelines [47]. Currently the scientific documentation of Myrtol contains around 100 preclinical and 27 clinical studies [33].

The findings of the present study are in agreement with an earlier randomised, double-blind, placebo-controlled study, which also evidenced the superiority of Myrtol 4 times daily over placebo [4]. In this earlier trial, the non-responder rate was much higher in the placebo group (20.9% after 1 week treatment)

when compared with Myrtol (5.3%). Even after 2 weeks of treatment the efficacy ratio remained about the same (p: 0.001). After 2 weeks, 50% of the Myrtol patients but only about 30% in the placebo group where cough free during the day. Also, the overall efficacy was rated as very good or good after one treatment week in 86% of the patients of the Myrtol group, but only for 47% of the placebo patients.

The present study confirms these findings. Since GeloMyrtol® forte is commonly used in the country where this study was conducted, the participating physicians and patients were to be expected to be well familiar with this medication. For this reason, the true nature of the investigational medication was not disclosed. Nevertheless the study has some limitations. Here a strict distinction between common cold, bacterial or viral induced acute bronchitis was not promoted. On the other side acute bronchitis is normally diagnosed clinically and as mentioned above most patients suffering from acute bronchitis are not tested.

Myrtol has many additional characteristics besides containing a compound with mere mucolytic characteristics. Begrow et al. [39] and Kwok et al. [40] demonstrated that Myrtol in pharmacologically doses stimulates ciliary beat frequency and thus increases mucociliary clearance in the lower as well as in the upper respiratory tract in vivo. It could further be demonstrated that Myrtol inhibits pro-inflammatory effects of activated alveolar macrophages derived from patients with chronic obstructive pulmonary disease (COPD) [41]. All these effects not only promotes the mucociliary clearance in the human bronchi but also reduces the exaggerated inflammation and therefore promotes an enhanced elimination of bacteria including the clearance of pseudomonas aeruginosa as demonstrated by Cao et al. [37] in COPD-rat model. Therefore it can presumed, that the positive effect we found in our trial is the result of these drug characteristics. We further could demonstrate that Myrtol was well tolerated and that there was no significant difference compared with placebo. Interestingly, for Myrtol with the new coating there is a 58% reduction in the risk of gastro-intestinal disorders compared to Myrtol with the previous coating [4].

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Conflict of Interest

There are no competing interests to declare. The trial reported in the present publication was sponsored by G. Pohl-Boskamp GmbH & Co. KG, Hohenlockstedt, Germany. Dr. C. de Mey was responsible for the design of the trial, the evaluation of the data and the present publication. Prof. Dr. A. Gillissen was the responsible scientific study expert overseeing the entire trial including the final publication. Both Prof. Dr. A. Gillissen and Dr. C. de Mey were remunerated by the sponsor for their services provided with regard to the orderly conduct and reporting of the trials. Dr. Krezdorn was investigator and also co-ordinating investigator of the trial. Dr. Th. Wittig is an employee of the sponsor who provided important contributions to the design and interpretation of the trial. Martina Ehmen is also an employee of the sponsor and was as sponsor's drug safety officer. At no time the sponsor took undue influence on the data presented here and the conclusions drawn from them.

References

1 *Wenzel RP*, *Fowler AA*. Acute bronchitis. N Engl J Med 2006; 355: 2125–2130
2 *Kroening-Roche JC*, *Soroudi A*, *Castillo EM et al.* Antibiotic and Bronchodilator Prescribing for Acute Bronchitis in the Emergency Department. J Emerg Med Aug 2012; 43 (2): 221–227
3 *Roisin RR*, *Vestbo J*. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2011;Available from: http://www.goldcopd.org/
4 *Matthys H*, *de Mey C*, *Carls C et al.* Efficacy and Tolerability of Standardized in Acute Bronchitis. A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol. Arzneim-Forsch/Drug Res 2000; 50 (II): 8 700–711
5 *Verheij TJM*, *Kaptein AA*, *Mulder JD*. Acute bronchitis: aetiology, symptoms and treatment. Fam Pract 1989; 6: 66–69
6 *Braman SS*. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1): 95S–103S
7 German Summary of Product Characteristics (Fachinformation) GeloMyrtol®/GeloMyrtol® forte Aug 2010;
8 *Kemmerich B*, *Eberhardt R*, *Stammer H*. 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. Arzneim.-Forsch./Drug Res 2006; 56 (9): 652–660
9 *Kemmerich B*. Evaluation of efficacy and tolerability of a fixed combination of dry extracts of thyme herb and primrose root in adults suffering from acute bronchitis with productive cough. A prospective, double-blind, placebo-controlled multicentre clinical trial. Arzneim -Forsch/Drug Res 2007; 57 (9): 607–615
10 *Matthys H*, *Heger M*. Treatment of acute bronchitis with a liquid herbal drug preparation from Pelargonium sidoides (EP 7630): a randomised, double-blind, placebo-controlled, multicenter study. Current Medical research and Opinions 2007; 23 (2): 323–331
11 *Gruenwald J*, *Graubaum HJ*, *Busch R*. Efficacy and tolerability of a fixed combination of thyme and primrose root in patients with acute bronchitis. Arzneim.-Forsch./Drug Res 2005; 55 (11): 669–676
12 *Gruenwald J*, *Graubaum HJ*, *Busch R*. Evaluation of the Non-inferiority of a Fixed Combination of Thyme Fluid- and Primrose Root Extract in Comparison to a Fixed Combination of Thyme Fluid Extract and Primrose Root Tincture in Patients with Acute Bronchitis. Arzneim -Forsch/Drug Res 2006; 56 (No. 8): 574–581
13 *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 2004; 58: 570–602
14 *Gillissen A*. Akute Bronchitis. In *Reuter P*, Hrsg. Springer Lexikon Diagnose & Therapie. 1. AuflageSpringer, Berlin Heidelberg: 2006; Part 1, Part 2, Seiten 165–174
15 *Macfarlane JT*, *Holmes WF*, *Macfarlane RM et al.* Contemporary use of antibiotics in 1089 adults presenting with acute lower respiratory tract illness in primary care in the UK: implications for developing management guidelines. Respir Med 1997; 91: 427–434
16 *Macfarlane J*, *Holmes W*, *Macfarlane R et al.* Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. BMJ 1997; 315: 1211–1214
17 *Kardos P*, *Berck H*, *Fuchs KH et al.* Leitlinie der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin zur Diagnostik und Therapie von erwachsenen Patienten mit akutem und chronischem Husten. Pneumologie 2010; 64: 336–373
18 *Knutson D*, *Braun C*. Diagnosis and Management of Acute Bronchitis. Am Fam Physician 2002; 65: 2039–2045
19 *Gwaltney JM Jr*. Acute bronchitis. In: Mandell GL, Bennett JE, Dolin R (eds.). Principles and practice of infectious diseases. 4th ed. New York: Churchill Livingstone, 1995; 606–608
20 *Hueston WJ*, *Mainous AG IIIrd*. Acute Bronchitis. Am Fam Physician Mar 15 1998; 57 (6): 1270–1276, 1281–1282
21 *Adam D*, *Bodmann KF*, *Elies W et al.* Praxisorientierte Empfehlungen zur kalkulierten Initialtherapie bakterieller Erkrankungen der Atemwege und des HNO-Bereichs bei Erwachsenen. Arzneimitteltherapie 2005; 23: 247–255
22 Arzneimittelkommission der deutschen Ärzteschaft: Handlungsleitlinie Atemwegsinfektionen aus Empfehlungen zur Therapie akuter Atemwegsinfektionen Arzneiverordnung in der Praxis, Sonderheft, 2. Auflage; 2002

23 *Vogel F*, *Worth H*, *Adam D et al.* Rationale Therapie bakterieller Atemwegsinfektionen. Chemotherapie Journal 2000; 9 (1): 3–23
24 *Orr PH*, *Scherer K*, *Macdonald A et al.* Randomized Placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. J Fam Pract 1993; 36: 507–512
25 *Smith SM*, *Fahey T*, *Smucny J et al.* Editorial Group: Cochrane Acute Respiratory Infections Group Antibiotics for acute bronchitis. 2009 Jan 21: CD000245
26 *Belongia EA*, *Schwartz B.* Strategies for promoting judicious use of antibiotics by doctors and patients. BMJ 1998; 317: 668–671
27 *Huovinen P*, *Cars O.* Editorials – Control of antimicrobial resistance: time for action. BMJ 1998; 317: 613–614
28 *Wise R*, *Hart T*, *Cars O et al.* Antimicrobial resistance is a major threat to public health. BMJ 1998; 317: 609–610
29 *Webb S*, *Lloyd M.* Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. Br J Gen Pract 1994; 44: 165–169
30 *Rapaport J.* Patients' expectations and intention to self medicate. J R Coll Gen Pract 1979; 29: 468–472
31 *Meister R*, *Wittig Th*, *Beuscher N et al.* Wirksamkeit und Verträglichkeit von Myrtol standardisiert bei der Langzeitbehandlung der chronischen Bronchitis, Arzneim.-Forsch./Drug Res. 1999; 49 (I): 4: 351–358
32 *Federspil P*, *Wulkow R*, *Zimmermann Th et al.* Efficacy of Myrtol Standardized in the Therapy of Acute Sinusitis – Results of a Double-Blind, Randomized, Placebo-Controlled, Multicentric Study. Laryngo-Rhino-Otol 2000; 79: 1–5
33 *Wittig Th.* Myrtol standardisiert – Eine klinische Dokumentation, Ergebnisse Verlag. 5. Auflage 2010;
34 *Behrbohm H*, *Kaschke O*, *Sydow K.* Der Einfluß des pflanzlichen Sekretolytikums Gelomyrtol® forte auf die mukoziliäre Clearance der Kieferhöhle. Laryngo-Rhino-Otol 1995; 74: 733–737
35 *App EM.* Stellenwert der Mukusclearance für das Bronchialsystem – Pathophysiologie und therapeutische Ansätze. in: *Meister R.* Entzündliche Erkrankungen des Bronchialsystems. Springer Verlag, 1st Edition2000; 27–53
36 *Behrbohm H*, *Kaschke O*, *Sydow K.* The influence of a secretolytic drug on mucociliary clearance of the maxillary sinus. J Rhinol 1997; 4 (1): 29–33
37 *Cao L*, *Chen Y*, *Zhao Y et al.* Effect of Myrtol standardized on mucus hypersecretion and clearance of Pseudomonas aeruginosa in a rat model of chronic obstructive pulmonary disease. Arzneim Forsch/Drug Research 2011; 61 (12): 685–692
38 *Dorow P*, *Th Weiss*, *Felix R et al.* Einfluß eines Sekretolytikums und einer Kombination von Pinen, Limonen und Cineol auf die mukoziliare Clearance bei Patienten mit chronisch obstruktiver Atemwegserkrankung. Arzneim Forsch/Drug Research 1987; 37 (11): 1378–1381
39 *Begrow F*, *Böckenholt C*, *Ehmen M et al.* Effect of Myrtol Standardized and Other Substances on the Respiratory Tract: Ciliary Beat Frequency and Mucociliary Clearance as Parameters. Adv Ther 2012
40 *Kwok RP.* The effects of Gelomyrtol forte® on human ciliary beat frequency and intracellular cyclic adenosine monophosphate in vitro. Dissertation for the degree of Master of Research in Medicine. Division of Respiratory Medicine, Department of Medicine, Queen Mary Hospital, Hong Kong: 2007
41 *Rantzsch U*, *Vacca G*, *Dück R et al.* Anti-inflammatory effects of Myrtol standardized and other essential oils on alveolar macrophages from patients with chronic obstructive pulmonary disease. Eur J Med Res 2009; 14: (Suppl 4): 205–209
42 *Juergens UR*, *Stöber M*, *Vetter H.* Steroidartige Hemmung des monozytären Arachidonsäuremetabolismus und der IL-1ß-Produktion durch 1.8-Cineol. Atemw-Lungenkrkh 1998; 24: 3–11
43 *Beuscher N*, *Kietzmann M*, *Bien E et al.* Interference of Myrtol standardised with inflammatory and allergic mediators. Arzneim-Forsch/Drug Res 1998; 48 (I): 985–989
44 *Beuscher N*, *Bien E*, *Elstner EF et al.* Myrtol standardized in treatment of sinusitis and bronchitis – Pharmacodynamics and pharmacokinetics, Zeitschrift für Phytotherapie. Abstractband, Kongress der Gesellschaft für Phytotherapie 1997; 9–10
45 *Graßmann J*, *Hippeli S*, *Dornisch K et al.* Antioxidant Properties of Essential Oils. Arzneim-Forsch/Drug Res 2000; 50 (I): 135–139
46 *Christoph F*, *Kaulfers P-M*, *Stahl-Biskup E.* In vitro evaluation of the antibacterial activity of β-triketones admixed to Melaleuca oils. Planta Medica 2001; 67 (8): 768–771
47 *Beuscher N*, *Bien E*, *Vierling TH.* Myrtol standardized in treatment of sinusitis and bronchitis – Safety and Toxicology. Zeitschrift für Phytotherapie, Abstract Volume, Congress of the Gesellschaft für Phytotherapie 1997; 7–8