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Original article

Efficacy and safety of a combination herbal medicinal product containing *Tropaeoli majoris herba* and *Armoraciae rusticanae radix* for the prophylactic treatment of patients with respiratory tract diseases: a randomised, prospective, double-blind, placebo-controlled phase III trial

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Abstract

Objective:
The aim of this ICH-GCP study was to investigate the efficacy and safety of a prophylactic administration of a combination herbal medicinal product (CHMP) in two dosages compared to placebo with respect to the incidence of new occurring infections of the respiratory tract (RTI). Clinical experience of prophylactic treatment of respiratory tract infections with the marketed CHMP containing horseradish root (*Armoraciae rusticanae radix*) and nasturtium (*Tropaeoli majoris herba*) has existed for decades.

Methods:
The study was performed as a phase III, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group trial. All groups received two film coated tablets three times a day. Group 1 received the CHMP tablets 3 × 2 per day, group 2 the CHMP tablets 2 × 2 and placebo tablets 2 × 1 per day and group 3 received placebo tablets 3 × 2 per day. Maximum duration of treatment was 84 days. The primary efficacy criterion was the comparison of the incidences of new occurring RTIs between the treatment groups during the prophylactic treatment. In addition the character of occurring infections, number of sick days and severity of infections were compared. Further criteria were subjects' well being, the satisfaction of subjects with the respective treatments and severity and incidence of the observed adverse events (AE) and serious adverse events (SAE) during the study period.

Trial registration:
EudraCT No. 2010-023227-26.

Results:
From 371 subjects screened, a total of 351 subjects of both sexes from 18 to 75 years were randomly allocated to one of the three groups. In order to achieve scientifically and medically impeccable results it was necessary to address acute infections of the respiratory tract occurring during the normal incubation period. Early infections (≤day 7) were excluded from the data set in a sensitivity analysis. In the intention to treat (ITT) population excluding early infections ≤day 7 ($n = 344$) the infection rates were 13.3% for CHMP 3 × 2 ($n = 113$), 18.4% for CHMP 2 × 2 ($n = 114$) and 25.6% for placebo ($n = 117$). The statistical trend test showed significant results ($p = 0.0171$). For the per protocol (PP) population – also excluding

infections ≤day 7 ($n=334$) – infection rates were: CHMP 3 × 2 ($n=110$) 12.7%, CHMP 2 × 2 ($n=113$) 18.6% and placebo ($n=111$) 24.3% ($p=0.0266$). Secondary parameters of infections (infection diagnosis, intensity, duration) showed no relevant differences between the treatment groups. The study medication was well tolerated.

Limitations:

This was the first clinical ICH-GCP study with the CHMP conducted in this indication and with a sufficient number of subjects. The study population comprised subjects from 18 to 75 years and covered different diagnoses of RTIs. The results show a benefit when using 3 × 2 film tablets of CHMP for prophylaxis of RTIs. However, no data are available on use of the CHMP in this indication in children, adolescents and the elderly (over 75 years).

Conclusion:

This trial demonstrates the efficacy and safety of the combination herbal medicinal product as the treatment of first choice in the prophylactic treatment of episodes of respiratory tract infections. Clinical experience was confirmed in an ICH-GCP study.

Introduction

The combination herbal medicinal product (CHMP) chosen for this study has been available on the German market for decades and its composition has not been changed since 1994. Experience in the prophylactic treatment of respiratory tract infections exists from many years of clinical application of CHMP. However, to date no ICH-GCP study covering this indication or data verifying the clinical evidence required from a regulatory point of view has been available. Protection of vulnerable patients with a safe medicinal product is of a paramount importance. In addition, respiratory tract infections also pose the risk of an economical burden, as sufferers experience a progressive deterioration in capacity to work and to undertake day-to-day activities[1]. Respiratory infections have a remarkable variety ranging from mild and self-limiting recurrent respiratory tract infections (rRTIs) of the nasal cavity, larynx, pharynx and glands, such as common cold, influenza and sinusitis, up to life-threatening conditions such as bacterial pneumonia. Upper respiratory tract infections (URTIs) including nasopharyngitis, pharyngitis, tonsillitis and otitis media comprise close to 90% of the total episodes of respiratory tract infections. Lower respiratory tract infections comprise pneumonia, laryngotracheobronchitis, bronchitis, and bronchiolitis. Most respiratory tract infections are caused by viruses such as rhinovirus, corona virus and influenza virus[2]. For initial infection, a viral particle enters the nasal cavity via contaminated fingers or droplet. Even tiny amounts (1–30 viral particles) are sufficient to cause an infection. Clinical symptoms of disease begin to display after 10–12 hours with a peak at 36–72 hours[3]. 'Common cold' is a localized viral infection of the nose, also affecting the sinuses, ears and bronchial tubes, producing typical symptoms of sneezing, runny nose, nasal congestion, sore throat, cough, hoarseness, headache, and sometimes fever, tremors, chills, fatigue and a massive negative impact on the well-being in general. Children (depending on age and exposure) are highly vulnerable and suffer between 6–10 episodes of respiratory diseases/year, in contrast to adults (about 2–3 times/year). Due to these circumstances the number of sick days is also an important aspect of any prophylactic treatment. Influenza, caused by influenza virus (type A or B), is a severe manifestation of common cold, characterized by symptoms of common cold along with muscle pain and forceful coughing. In some patients viral infection of the respiratory tract may lead to secondary bacterial infection. Primary infections with bacteria are less common[2]. Infections with *Hemophilus influenzae* and *Streptococcus pneumoniae* make patients susceptible to developing sinusitis (2–3 times/year or more). During an inflammation of the nasal mucosa e.g. caused by a viral infection, the mucous membrane of the ducts of the paranasal sinuses swells. The mucus accumulates in sinuses and serves as a breeding ground for bacteria. Prolonged episodes of colds, lasting longer than 2–3 weeks, display a discoloration of the initially glassy or whitish mucus to the yellow/greenish colour, resulting in a purulent form[4].

Antibiotics are the usual choice for treatment of respiratory infections, although viruses are involved in most cases of disease, associated with drawbacks such as limited therapeutic window and emergence of resistance[4]. However, many pre-clinical and clinical studies demonstrate a successful prophylactic approach using plant-derived herbal medicines or their combinations[5–8]. Therefore, a preventive well tolerated herbal medicine against acute RTIs is desired and also actively requested by the patients. In addition, well tolerated and safe prophylactic measures would be advantageous for all immunocompromised patients.

Therefore this study was focussed on the confirmation of clinical experience of the efficacy and safety of an approved combination herbal medicinal product (CHMP) for the prophylactic treatment of respiratory tract infections (RTIs). The CHMP is available as film tablet with 80 mg horseradish root (*Armoraciae rusticanae radix*) and 200 mg nasturtium (*Tropaeoli majoris herba*) as the active ingredients. Both plants contain different isothiocyanates (mustard oils), which are responsible for the clinical efficacy of the CHMP. Whereas in horseradish root the relevant mustard oils are allylisothiocyanate and phenylethylisothiocyanate, in nasturtium it is benzylisothiocyanate. In several investigations an antimicrobial activity of these two isothiocyanates-based active ingredients has been proved[9–12]. This was also confirmed in a most recent in-vitro investigation conducted by the investigators[12]. A broad antibacterial activity against clinically relevant pathogens covering both gram-positive and gram-negative organisms was detected. This investigation also

demonstrated that the combination of the two active ingredients leads to a synergistic activity[12]. Antiviral activity against influenza virus (H1N1) has also been recently described[13]. These results prove that there is a rationale for treatment of both RTIs and chronic recurrent urinary tract diseases (rUTIs) with the medicinal product. It is important to emphasize that no resistance against isothiocyanates has yet been observed. The efficacy and safety of the CHMP, consisting of horseradish root and nasturtium, was demonstrated in observational cohort studies versus standard antibiotics and placebo, in the therapy of acute bronchitis, sinusitis and cystitis[14–16]. The current placebo-controlled clinical trial, however, was focussed on the review of the efficacy and safety of investigational CHMP in the prophylaxis of RTIs. An important objective was to investigate the efficacy of different dosages of 2 × 2 tablets/day versus 3 × 2 tablets/day versus placebo in terms of the incidence of acute occurring new episodes of respiratory tract infections during the prophylactic treatment, the number of infection days and severity of infection. The secondary objectives focussed on safety assessment and tolerance of CHMP, on recording the severity and number of observed adverse events (AE) and serious adverse events (SAE) and the overall rate of treatment satisfaction.

Methods

Study design

The study was designed as a phase III, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group study with three treatment groups involving twelve centres in Germany. Throughout the study, group 1 and group 2 received the CHMP in two different dosages, while group 3 received placebo. The study medication was manufactured in a double-dummy technique in order to maintain blinding for physicians and study participants. The study was conducted according to the standards of ICH-GCP. The study protocol was approved by the Federal Higher Authority (BfArM), the independent leading Ethics Committee (EC) and the ECs responsible for each respective investigator/study site. The study was registered under EudraCT number 2010-023227-26. The subjects were insured against any potential harm, according to the German Drug Law. The subjects were randomly allocated to one of the three treatment groups into permuted blocks size of 18 generated by an independent statistician. Packaging and allocation of the treatment numbers to the medication was carried out by the manufacturer according to the randomisation list. The subjects received the study drugs in boxes pre-numbered in consecutive order according to the time of their enrolment into the study, always using the lowest number available. Both investigators and subjects remained blinded regarding treatment and group details. Subjects could always be de-blinded in the event of an emergency. All other study staff including monitor, biometrician, principal investigator and the sponsor remained blinded throughout the study. The blinding was maintained during review of the complete database for subject's validity and allocation to the populations of statistical analysis. After a Blinded Data Review Meeting the database was frozen and the code was broken for statistical evaluation of the study.

Subjects

A total of 371 subjects were screened at 12 active centres across Germany, of whom 351 were randomised and received the planned treatment. The study population comprised adults of both genders aged from 18 years up to 75 years, with a medical history of at least two acute respiratory tract infections in the last cold season, according to the physician records. For safety reasons females of childbearing potential had a pregnancy test and were instructed to employ a safe contraception method during the course of the study. The subjects were required to sign an informed consent form approved by the responsible Ethics Committee prior to any study procedure. Subjects with chronic disorders or obstruction of the respiratory tract (e.g. COPD), chronic infections (e.g. chronic rhinitis, sinusitis, bronchitis), medical history of reaction to one of the components of the study medication or ethanol, drug abuse or administration of anti-influenza or anti-pneumonia vaccines after inclusion in the study (screening visit) were excluded. In order to ensure that the prophylactic effect originates from the CHMP treatment, no influenza and pneumonia vaccination was permitted during the study period. Administration of influenza or pneumonia vaccines led to exclusion.

Treatment

All groups received two film coated tablets three times a day for a treatment period of 84 days. Each group comprised 117 subjects. Group 1 (CHMP 3 × 2) received two CHMP film coated tablets three times a day, comprising a total of 1200 mg nasturtium herb and 480 mg horseradish root. Group 2 (CHMP 2 × 2) received two CHMP film coated tablets two times a day (morning, evening), comprising 800 mg nasturtium herb and 320 mg horseradish root, and two placebo film tablets once a day (noon). Group 3 (Placebo) received two placebo film tablets three times a day. Compliance was assessed via drug accountability and subject's diary.

Treatment with study medication was initiated at visit 1 (day 0) after the subject has been randomised into one of the three groups. The duration of the treatment period was

84 days (12 weeks). During the treatment period a total of five visits were conducted on days 0 (visit 1), 21 (visit 2), 42 (visit 3), 63 (visit 4) and 84 (visit 5). For subjects who reported an occurrence of an acute infection between the scheduled visits, an extra visit was carried out. In case the acute infection was confirmed, the administration of study medication was stopped. The subject was treated according to physician's decision and an exit visit was scheduled 10 (±2) days after the confirmation of an acute infection.

Study medication

Film coated tablets of the active study medication and placebo were supplied by Repha GmbH, Langenhagen, Germany. They contained a combination of horseradish root (*Armoraciae rusticanae radix*) and nasturtium herb (*Tropaeoli majoris herba*). One coated tablet contained as active ingredients 80 mg horseradish root powder and 200 mg nasturtium herb powder. Placebo tablets contained the inactive ingredients and were identical in appearance to the active drug tablets. The study medication was primarily packed into blisters in a double-dummy technique. One box (containing the appropriate number of blisters of the study medication) was supplied to each subject at the start of the treatment (visit 1) and thereafter at visits 2, 3 and 4 for the respective intervals of 3 weeks each. The subjects were asked to take the tablets after the meal with some fluid. The study medication was manufactured and packaged according to GMP guidelines.

Procedures

Subjects were informed and checked for inclusion into the study, and concomitant diseases were recorded during screening and randomisation visits. Informed consent and information regarding demography, medical history, and a blood sample were obtained from potential subjects during screening. Subjects were randomised during the first visit. A pregnancy test (in women of childbearing potential) was performed. The following examinations and procedures were conducted throughout the treatment period (visit 1 – visit 5): concomitant medication, concomitant therapy, complaints/symptoms in terms of a respiratory tract infection (recorded in subject's diaries, electronic Case Report Forms [eCRFs]) and adverse events (AEs)/serious adverse events (SAEs) were recorded, vital signs checked and auscultation of the respiratory tract conducted. Both the study medication and subjects' diaries were given to the subjects on the day of the visit, starting from visit 1 (day 0) to visit 4 (day 63). These were returned completed to the investigator during the respective next visit (from visit 2 to visit 5) and again provided for until the next time point. This procedure was followed until the exit visit. Study medication packages (empty, full or unused) were returned to the investigator at the next visit to the study site (visits 2, 3, 4 and 5). Subjects were asked to assess and report tolerance of the study medication and compliance in their diaries during visits 2, 3, 4 and 5. A regular exit visit scheduled at visit 5 (day 84) included a pregnancy test (female subjects of child-bearing potential) and blood check-up for measuring the haematological and clinical chemistry. Subjects were asked to assess the overall satisfaction (satisfied/not satisfied) with the study medication. The physicians assessed and reported the rating for displaying the efficacy of study medication. The prophylactic treatment with study medication ended after 84 days.

If a subject visited the study site with an acute episode of RTI between the scheduled visits, an extra visit was carried out. The remainder of study medication was returned to the study site. The infection was confirmed and the subject treated according to the decision of the physician. An exit visit was carried out 10 (±2) days after treatment.

Assessment

The primary efficacy criterion was the comparison of the incidences of newly occurring RTIs between the treatment groups during the prophylactic treatment. Secondary efficacy criteria were the character of occurring infections, number of sick days and severity of infections. In order to identify a respiratory tract infection the subjects had been questioned by the physician about the following complaints/symptoms: coughing, chest pains, nasal congestion, runny nose, pain and/or scratchy throat, hoarseness, shivering, fever, headache, malaise and/or pain in the limbs. The symptoms were rated with no, low, moderate or severe intensity. Furthermore, auscultation of the respiratory system (normal, abnormal) was conducted.

Physicians rated the efficacy of the study medication by means of a scale (very good, good, moderate, not satisfactory, no efficacy). Monitored safety variables were general well-being during the study, frequency and severity of reported adverse events (AE) and serious adverse events (SAE), clinical signs, as well as vital parameters, which were recorded at each visit. Safety laboratory data were checked on visit 0 and visit 5 (blood picture, CRP, creatinine, AST, ALT and γ-GT).

Statistical analysis

Sample size calculation and statistical analysis were carried out in accordance with ICH-GCP guidelines at Institut für angewandte Statistik GmbH, Bielefeld, Germany. For sample size calculation a decrease of infection frequency of ≥20% when treated with the active substance compared to placebo was assumed. Worst case scenario was a decrease of infection rates about 60% (placebo) and

40% (active substance). To detect a decrease in infection rates between groups with a two-sided 5% significance level, a power of 80% and an assumed dropout rate of 10%, a sample size of 108 subjects per group (total 324 subjects) was necessary.

The statistical methods comprised descriptive statistics, Fisher's exact test, χ^2-test, Kruskal–Wallis test, *F* test (ANOVA), *U* test, Log rank test, Kaplan–Meier plot, Cochran–Armitage trend test, Jonckheere–Terpstra test, Mantel–Haenszel estimation for odds ratios, Cochran–Mantel–Haenszel test and Breslow–Day test. The level of significance was set at $\alpha = 0.05$ two-tailed.

Due to the decision of the study steering group a post hoc exclusion of early occurring infections became necessary as acute infections of the respiratory tract show an incubation phase in the range from 24 h to a number of days. Therefore the infections in question may – with a high degree of certainty – already have been existing infections without signs and symptoms by the time of the randomisation according to the study protocol. This would have had a twofold impact on the study as early infections which could not be influenced by prophylactic treatment would lead to a decreased discriminatory power of the study and a bias in the comparison of treatment groups. It was therefore decided to focus on the analysis for the sets of subjects (PP and ITT) with an onset of a new episode of an infection from day 7 onwards. Figure 1 shows the number of subjects in the respective sets.

Results

The majority of the included subjects were females (59.8% group 1, 60.7% group 2 and 62.4% in group 3) with median ages (males and females) of 43.0 years in groups 1 and 2 and 41.0 years in group 3. Most of the subjects were Caucasians. The median body mass index value was 25.4 kg/m^2 in group 1, 26.1 kg/m^2 in group 2 and 25.6 kg/m^2 in group 3. The median number of RTIs during the past 1.5 years before study inclusion was 2 for all groups. The most frequent diagnoses of RTIs in medical history were bronchitis (47.6%), acute sinusitis (41.0%), acute upper respiratory infections of multiple and unspecified sites (39.3%), acute nasopharyngitis (22.8%) and acute pharyngitis (17.7%). The median duration of an infection was 15 days in group 1, 20 days in group 2 and 17 days in group 3. For days between healing and randomisation an average of 294 days (group 1: 293 days, group 2: 303 days, group 3: 293 days) was recorded. The infection was treated with medication in 75.2% (group 1), 73.5% (group 2) and 73.5% (group 3) of the subjects. Consequently a homogenous subject population was investigated in this clinical study.

A total of 7 subjects were excluded from the efficacy analysis because of an occurrence of an early infection during the first 7 days of the treatment. Those were 4 subjects from group 1 (CHMP 3 × 2) and 3 subjects from group 2 (CHMP 2 × 2). Infection was confirmed on treatment days 1, 2 and 5 in group 1 and on days 3 and 4 in group 2.

Intent-to-treat population

The infection rate displayed a significant monotonic trend ($p = 0.0171$) for CHMP 3 × 2 ($n = 113$) 13.3%, CHMP 2 × 2 ($n = 114$) 18.4% and placebo ($n = 117$) 25.6% during the study period, using the Cochran–Armitage test.

Fisher's exact and χ^2 tests were used for pair-wise comparison of the groups. The results of pair-wise comparison displayed significant differences ($p = 0.0203$ and $p = 0.0181$, respectively) between the CHMP 3 × 2 group and the placebo group, demonstrating significantly fewer re-infections in the CHMP 3 × 2 group during the study period.

The difference of the medians of time point of infection in the CHMP 3 × 2 group (44 days) and the CHMP placebo group (35.5 days) were calculated to be nonsignificant by the Kruskal–Wallis test. However, a significant temporal trend was observed in the pair-wise comparisons of the time point of infection between the CHMP 3 × 2 and placebo groups ($p = 0.0160$). Investigation of the CHMP 3 × 2 and placebo groups regarding the time-points of infections in the ITT cohort demonstrated striking statistical significance in the primary endpoints, using Kaplan–Meier plot/log rank test (Figure 2).

Per-protocol population

The infection rates displayed a significant monotonic trend ($p = 0.0266$) where CHMP 3 × 2 and CHMP 2 × 2 groups showed 12.7% and 18.6% re-infections respectively and the placebo group displayed 24.3% incidence of infection (Cochran–Armitage test).

The results of pair-wise comparison using Fisher's exact and χ^2 tests displayed a significant difference ($p = 0.0371$ and $p = 0.0266$, respectively) between the CHMP 3 × 2 and the placebo group. This further strengthens the concept that treatment with CHMP 3 × 2 significantly decreases the probability of re-infection compared to placebo.

The difference of the medians of time point of infection during treatment in CHMP 3 × 2 (36 days), CHMP 2 × 2 (42 days) and placebo group (35 days) were calculated to be nonsignificant by the Kruskal-Wallis test.

However, a significant temporal trend was observed with the log rank test in terms of the time points of infection between CHMP 3 × 2 and placebo groups ($p = 0.0258$), also seen in the Kaplan–Meier plot (Figure 3).

It was evident from the analysis of efficacy that treatment of CHMP 3 × 2 was superior to that of CHMP 2 × 2.

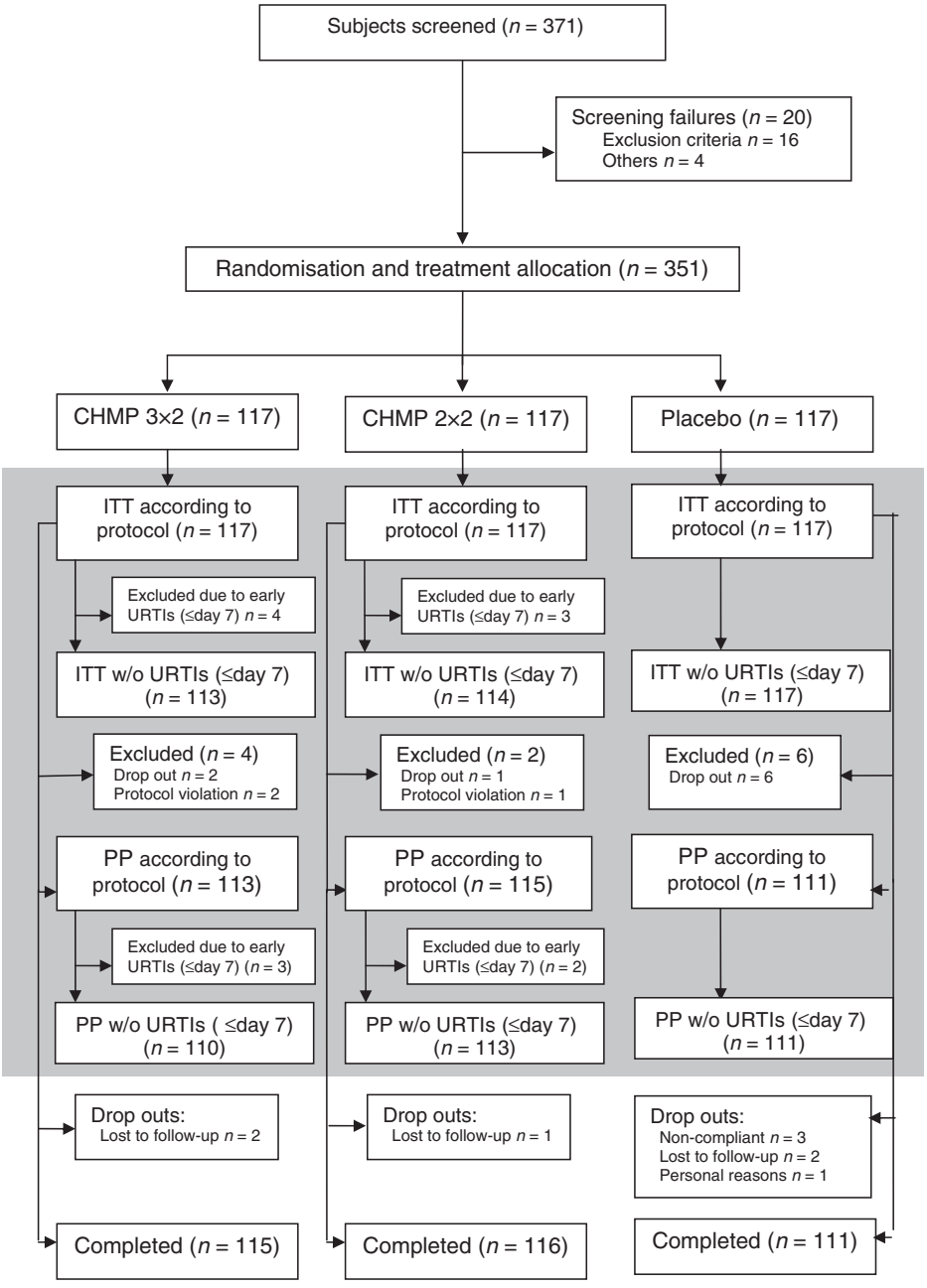

Figure 1. Chart of patient flow.

Kaplan–Meier plot/log rank test after a pair-wise comparison yielded nonsignificant but superior results for the CHMP 3 × 2 group in the ITT ($p = 0.2929$) and PP cohorts ($p = 0.2426$). However, both treatment groups CHMP 3 × 2 and CHMP 2 × 2 were found to have superior efficacy compared to placebo group. During treatment infection rates were always found to be lower in the CHMP 3 × 2 group in comparison to the CHMP 2 × 2 group, indicating the superiority of the former over the latter, in both ITT and PP cohorts. Both dosages of CHMP were determined to be superior to placebo treatment.

Secondary variables

Secondary parameters subjected to evaluation included diagnosis of cold episodes and their duration, intensity and type of medication received against the episodes.

The diagnosis of episodes of acute rhinopharyngitis, sinusitis, laryngitis and tracheitis showed no significant difference in either ITT or PP cohorts as tested by χ^2 test ($p \leq 0.15$). The median duration of the cold episode was 10 days for both CHMP 3 × 2 and placebo groups (nonsignificant result by Kruskal–Wallis test) in the

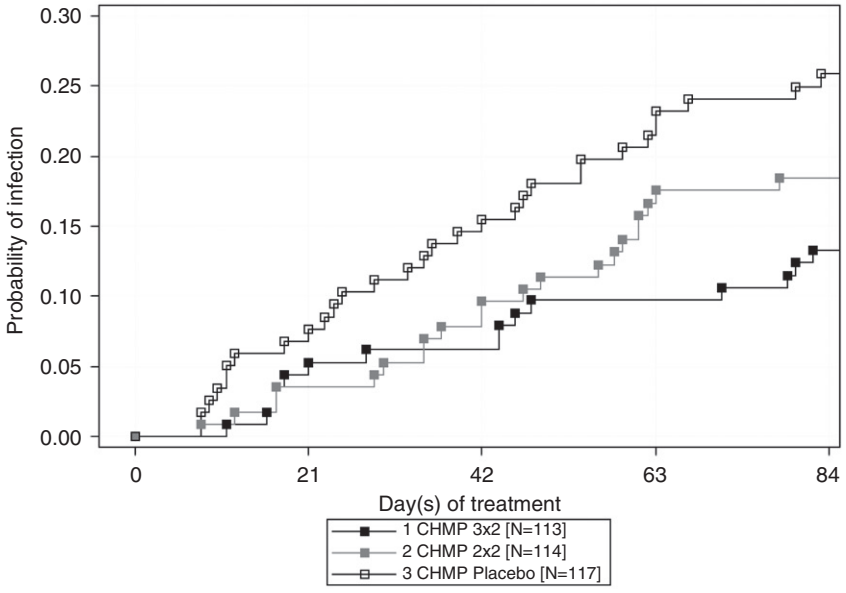

Figure 2. Kaplan–Meier plot showing the probability of infection against time (between randomisation and start of common cold episode), after exclusion of early infections of the airways (≤day 7): CHMP 3 × 2, CHMP 2 × 2 and placebo groups (ITT cohort). Results of the log rank test: CHMP 3 × 2 versus placebo group: $p = 0.0160$, CHMP 3 × 2 versus CHMP 2 × 2 group: $p = 0.2929$, CHMP 2 × 2 versus placebo group: $p = 0.1584$.

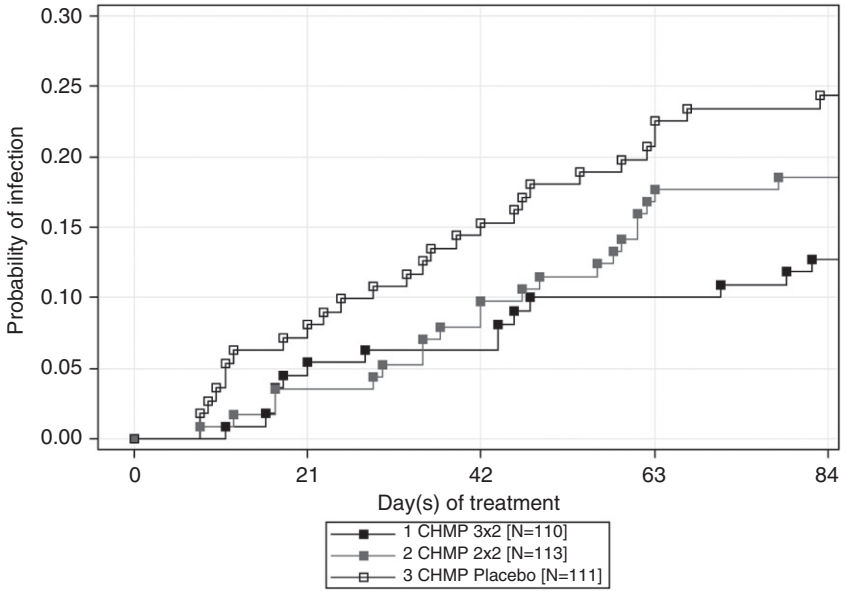

Figure 3. Kaplan–Meier plot of the time between randomisation and start of common cold episode after exclusion of early infections of the airways (≤day 7): CHMP 3 × 2, CHMP 2 × 2 and placebo groups (PP cohort). Results of the log rank test: CHMP 3 × 2 versus placebo group: $p = 0.0258$, CHMP 3 × 2 versus CHMP 2 × 2 group: $p = 0.2426$, CHMP 2 × 2 versus placebo group: $p = 0.2616$.

ITT population. The intensity of infection was predominantly classified as moderate (CHMP 3 × 2: 80.0% and placebo: 83.3%). In approximately 80% of infections the subjects chose a drug therapy against common cold.

Overall the secondary parameters of the infections (infection diagnosis, intensity, duration) do not display any significant differences as regards to treatment groups.

Efficacy

Intent-to-treat population

A simultaneous analysis of the judgement on efficacy with the Jonckheere–Terpstra test on a monotonic trend shows a significant monotonic trend of the three treatment groups ($p = 0.0173$). The judgements with regard to

efficacy show a significant difference using the Mann-Whitney U test, with better assessments for CHMP 3 × 2 especially compared with placebo but also for CHMP 3 × 2 compared with CHMP 2 × 2 ($p = 0.0205$ and $p = 0.0609$ respectively; U-test).

Per-protocol population

According to the Jonckheere–Terpstra test there is also a significant trend ($p = 0.0238$) as regards differences between CHMP 3 × 2 and placebo ($p = 0.0278$, U test). The difference between CHMP 3 × 2 and CHMP 2 × 2 is statistically noticeable ($p = 0.0742$, U test).

Safety

The study medication was well tolerated. Adverse drug reactions (ADRs) ($p = 0.6013$) were observed in only 2 subjects of the CHMP 3 × 2 group, 1 of the CHMP 2 × 2 group and 3 subjects of the placebo group. No statistically significant differences were observed with regard to the occurrence of ADRs between the treatment groups ($p = 0.2509$).

Fourteen subjects from the CHMP 3 × 2 group (12.0%) and 9 from the CHMP 2 × 2 group (7.7%) reported adverse events (AEs). This was in contrast to 17 subjects from the placebo group with 14.5% (22 events) reporting AEs.

One serious adverse event (SAE) was recorded in one subject in the CHMP 3 × 2 group where a subject complained about back pain. A relationship to the study medication was excluded.

Discussion

Prophylactic treatment with the CHMP against respiratory tract infections has been used for decades in daily practice, but lacked proof with regard to up-to-date scientific methods and required studies. Therefore, it was our aim to verify the clinical experience in an ICH-GCP clinical study.

Recent in vitro studies supported the assumption of a successful outcome of the trial. These confirmed the excellent antibacterial and antiviral efficacy of the active ingredients of the combination herbal medicinal product (CHMP)[12,13]. The mustard oils from horseradish root (allylisothiocyanate and phenylethylisothiocyanate) and the corresponding mustard oil contained in nasturtium (benzylisothiocyanate) revealed broad antibacterial activities against clinically relevant pathogens. The in-vitro study demonstrated that the combination of the two active ingredients leads to a synergistic activity[12]. Therefore it was also important to verify these results in a clinical study. The primary efficacy criterion – the comparison of the number of new occurring infections over the study period – was chosen in order to prove the efficacy of the medicinal product in a defined subject population.

Median incubation periods for respiratory tract infection range from half a day to 12 days[17]. Therefore, an infection which occurred during the first five to seven days of the prophylactic treatment might have already existed before randomisation and start of the treatment without displaying the signs and symptoms defined by the protocol. The Study Steering Group agreed in the light of medical and scientific considerations to focus on newly occurring episodes of RTIs from study day 7 onwards as otherwise those patients already suffering from a new infection by start of intake of the prophylactic treatment may jeopardise outcome of the prophylactic treatment.

In the analysis of efficacy it was shown that CHMP 3 × 2 was superior to CHMP 2 × 2. Kaplan–Meier plot/log rank test – after a pair-wise comparison – yielded non-significant but superior results for the CHMP 3 × 2 group in the ITT ($p = 0.2929$) and PP cohorts ($p = 0.2426$). CHMP 3 × 2 and CHMP 2 × 2 were found to have superior efficacy compared to placebo. Infection rates during treatment in the CHMP 3 × 2 group were always found to be lower in comparison to the CHMP 2 × 2 group, indicating the superiority of the former over the latter, in both ITT and PP cohorts. Both dosages of CHMP were determined to be superior to placebo treatment.

The CHMP has proven to be well tolerated: adverse drug reactions (ADRs) were observed for CHMP 3 × 2: $n = 2$ (1.7%), CHMP 2 × 2: $n = 1$ (0.9%), placebo: $n = 3$ (2.6%) ($p = 0.6013$).

This was the first clinical ICH-GCP study conducted with the CHMP in this indication and with a sufficient number of subjects. The study population comprised subjects from 18 to 75 years and covered different diagnoses of RTIs. The results show a benefit when using 3 × 2 film tablets of CHMP for prophylaxis of RTIs. However, no data are available on use of the CHMP in this indication in children, adolescents and the elderly (over 75 years).

Clinical experience was confirmed with data obtained from an ICH-GCP study regarding clinical efficacy and safety of the CHMP. The product was proven to be a prophylactic treatment of first choice against infections of the respiratory tract for instance associated with the common cold, sinusitis and influenza.

Conclusions

In a state of the art and ICH-GCP study a combination herbal medicinal product (CHMP) administered in doses 3 × 2/day and 2 × 2/day over a period of up to 84 days was compared to placebo in a multicentre, prospective, double-

blind, parallel-group, randomised trial. The data from this study for efficacy and safety, showing a statistically significant superior efficacy of the CHMP associated with an excellent safety profile in favour of the CHMP, have confirmed clinical experience existing over decades. The data support the fact that this medicinal product is a treatment of first choice for prophylactic treatment of respiratory tract infections – being most beneficial to be administered in the period of higher infection rates in the winter period. Safety parameters with an extremely low number of adverse events and adverse drug reactions allow for administration in all age groups and over a longer period of time. Elderly patients, being at a higher risk of suffering from such infections, may especially benefit from the treatment. Moreover, subjects reported over 90% satisfaction with the use of this combination herbal medicinal product and therefore subjects' compliance is expected to be high. Data suggest that the recommended daily dose for prophylactic treatment of RTIs is three times two film coated tablets of the combination herbal medicinal product. Further studies in different study populations will be needed to confirm the data. Based on these results the therapy may serve for physicians and patients as an excellent therapy for a medical problem with limited treatment options.

Transparency

Declaration of funding

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Declaration of financial/other relationships

The statistical analysis was conducted by J.S., who received remuneration from Repha GmbH for his services. V.F., U.A. and G.S. have disclosed that they have served as consultants/advisors to the sponsor Repha GmbH.

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Notice of Correction

The version of this article published online ahead of print on 31 October 2012 contained two minor typographical errors. These have been corrected for this version

