Report Synopsis

Confidentiality statement:

Study title:
Efficacy, safety and tolerability of two weeks treatment with SIA capsules in acute bronchitis.

Study Identifier:
P1001GF (Pohl-Boskamp)

EudraCT number: 2010-022819-19

Co-ordinating investigator:
Dr. Krezdorn, specialist in internal medicine, Munich

Study centres:
Thirty-three (33) principal investigators in Germany (specialists in internal medicine and general practitioners)

Publication:
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Studied period:		**Clinical phase:**
First subject enrolled:	20-JAN-2011	Phase IIIb
Last subject completed:	29-MAY-2011	

Objectives:
The primary objective of this study was to investigate the effect of SIA capsules versus placebo during a 2-week treatment period in adult patients with acute bronchitis.
The secondary objective was to assess the safety and tolerability of SIA capsules and placebo.

Methodology:
Female and male adult outpatients presenting with clinical signs and symptoms of acute bronchitis (cough, sputum, chest pain during coughing, shortness of breath (dyspnoea) and abnormal breath sounds (rales / rhonchi) on lung auscultation were screened for study participation at the trial site. The individual study duration was 14 ± 2 days. There was no run-in or post-treatment period.
At Visit 1, eligible patients who signed informed consent form and fulfilled all eligibility criteria were randomly allocated to 1 of the 2 parallel treatment groups. Treatment with the blinded investigational medication (SIA capsules) started at Visit 1 at the study site (doctor's practice).
The effect of study treatment on acute bronchitis was evaluated by the patient's daily counting of coughing fits during the day (manual counter), assessment of acute bronchitis related symptoms (ability to cough up, sleep disturbance), and by the investigator's assessment of the most important

symptoms of acute bronchitis using the Bronchitis Severity Score (summation of ratings for cough, sputum, chest pain during coughing, dyspnoea and rales / rhonchi on auscultation of the lungs), and patient's response to treatment compared to baseline and work incapacitation due to illness.
Safety and tolerability of study treatment were evaluated based upon adverse event monitoring, review of concomitant medication, general physical examinations including cardiopulmonary auscultation, measurement of vital signs (blood pressure, pulse rate, body temperature), as well as patient's daily ratings of general well-being.

Number of subjects:
Planned: 400, randomised: 413 (SIA 202, Plc 211), safety set: 413 subjects, full analysis set: 398 (SIA 196, Plc 202) subjects.

Diagnosis and main criteria for inclusion:
Clinical diagnosis of acute bronchitis (ICD-10: J20). Characteristic signs and symptoms include cough, sputum, chest pain during coughing, shortness of breath (dyspnoea) and abnormal breath sounds (rales / rhonchi) on lung auscultation.

Test product, dose and mode of administration, batch number:
SIA capsules, containing 300 mg SIA obtained by distillation of a mixture of plants of the Myrtaceae family and the Rutaceae family, test product was administered orally, batch number: 212319.

Duration of treatment: The individual study duration was 14 ± 2 days.

Reference therapy, dose and mode of administration, batch number:
Matched placebo. The placebo capsules were administered orally, batch number: 212345.

Criteria of evaluation:
Efficacy:
Primary Efficacy Endpoint: Mean in coughing fits (Day 7, Day 8, ay 9) / Coughing fits (Day 1). The primary outcome criterion was the mean frequency of coughing fits during the day of Days 7 to 9 of the treatment period documented in the diaries divided by the baseline value of Day 1 (standardized to the first day of patient's precise recording with a manual counter).
Secondary Efficacy Endpoints: reduction in coughing fits during the day calculated as Area Under The Curve [AUC] from Day 1 to Day 13 (diary data); time to 50% reduction in coughing fits during the day compared to Day 1 (diary data); proportion of patients with no coughing fits after 7, 10 and 14 days treatment (diary data); relative reduction in the mean frequency of coughing fits after 7, 10 and 14 days treatment (diary data); response to treatment assessed at Visit 2, Visit 3 and Visit 4 when compared to Visit 1 (CRF data) based on investigator's ratings on VRS-4.
Patients with no or improved symptoms / signs were classified as "Responders", patients whose symptoms / signs were unchanged or deteriorated were classified as "Non-responders". Change in the mean BSS at visit 2, visit 3 and visit 4 when compared to visit 1 (CRF data) based on investigator's ratings on a VRS-5. Also the change from visit 2, visit 3 and visit 4 to baseline (visit 1) for each of the 5 single BSS item scores was evaluated; change in the ability to cough up mucus

during the day based on patient's ratings on a VRS-4; change in sleep disturbance induced by coughing at night calculated as AUC from Day 0 to Day 14 (diary data) based on patient's ratings on a VRS-4; change in general well-being calculated as AUC from Day 0 to Day 13 (diary data) based on patient's ratings on a VRS-4; mean number of days of work incapacitation at Day 14 (CRF data).

Safety:
Safety variables were: Treatment compliance, Frequency and intensity of adverse events (AE), Change in results of physical examination from Visit 1 to Visit 4, Change in vital signs from Visit 1 to Visit 4.

Statistical methods:
The confirmatory analysis of the primary endpoint was based on the FAS. An additional evaluation with the PP data set was carried out for the primary endpoint to support the results of the primary analysis. For the PP population, the Last Observation Carried Forward [LOCF] method was done for those missing data which were definitely generated by the efficacy / non-efficacy of the study medication.
All secondary endpoints were tested for difference between treatment groups and were evaluated for the FAS (primary analysis) and the PP data set (sensitivity analysis). These analyses were performed only for explorative purpose.
Non-categorical data were summarised per treatment group using suitable descriptive measures (number of observations, arithmetic mean, standard deviation, minimum, 1st quartile [Q1], median, 3rd quartile [Q3], and maximum). Categorical data were presented by frequencies and percentages by treatment group and total.
Baseline values were compared between treatment groups and tested by Mann-Whitney-Wilcoxon test (numerical variables) or Chi-square test (categorical variables).
For secondary endpoints, changes in percentages (responders, patients without coughing fits) were calculated by the Chi-Square test or Cochran-Armitage trend test. Time-to-effect variables were evaluated by the Kaplan-Meier Method and analysed by the log-rank test.
Other secondary endpoints were evaluated by the of ANnalysis Of VAriance [ANOVA] or Analysis of COVAriance [ANCOVA] with 'treatment' as fixed effect, 'centre' as random effect and 'baseline' as covariate (only for ANCOVA). In case of significant non-normality of the ANOVA or ANCOVA residuals, the Wilcoxon Mann-Whitney test stratified by centre (Van Elteren test) was calculated in addition (primary and secondary endpoints). All p-values were 2-sided.
A blinded interim analysis was performed on the primary outcome measure 'mean in Coughing fits (Day 7, Day 8, Day 9) / Coughing fits (Day 1)' to prove the assumed variation of the primary endpoint and to increase the sample size in case of an underestimation of the standard deviation. .

Summary - conclusions:

Efficacy:
Treatment with SIA capsules 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 to 66.6 %) under SIA capsules treatment compared to 49.8 % (95 % CI: 44.6 to 55.0 %) under placebo ($p< 0.0001$).
For the secondary outcome criteria, treatment with SIA capsules proved superior to placebo on several accounts; in patients treated with SIA capsules 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 $p<0.0001$;), a larger reduction in daily coughing fits (FAS, $p< 0.0001$), the time to 50% reduction in coughing fits was shorter (FAS, $p= 0.0002$), more patients achieved a condition without coughing fits (FAS, $p= 0.0012$), it proved easier to cough up mucus during the day (FAS, $p= 0.0004$) and there was less sleep disturbance due to night-time coughing (FAS, $p= 0.0007$).
Additionally, SIA capsules proved superior to Placebo also with regard to responder and nonresponder rates: Already in the second treatment week more than 90% of the patients of the SIA-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: $p= 0.0002$). This corresponds to a very low non-responder rate in the SIA-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: $p= 0.0002$).
Also, treatment with SIA capsules 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 SIA-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 SIA capsules than in the patients treated with Placebo; at all visits, the treatment difference was statistically significant ($p <0.0001$).
For the BSS-Subscores (cough, sputum, rales / rhonchi, chest pain on coughing, and dyspnoea) a similarly beneficial effect of the SIA-treatment relative to the Placebotreatment was seen; on Day D10, the mean changes from baseline for all subscores were statistically significantly lower for the SIA-group than for the Placebo-group; on Day D14, this also applied except for 'chest pain on coughing' and 'dyspnoea', for which there was little difference between the two treatments.

Safety:
Thirty-nine AEs were reported (32/413 = 7.7%): 21 AEs in 16/202 patients of the SIA group (7.9%) and 18 AEs in 16/211 patients of the placebo-group (7.6%). In the SIA group, the investigators classified 10 AEs in 8 patients as at least possibly drug related. In the placebo group, 2 AEs in two 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 SIA-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 SIA-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.

Conclusions:
The results of the trial show that SIA is superior to placebo in patients with acute bronchitis. Oral treatment with SIA capsules (1200 mg / day) for about two weeks was safe and well tolerated, and the treatment regimen (300 mg q.i.d) was well accepted.