

Synopsis

Title of study: "Efficacy and tolerability of Bronchipret® Saft for the treatment of acute bronchitis in adults" - A randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase IV study – Protocol and its amendments: There is no amendment to the original Clinical Trial Protocol (CTP), Final Version dated 05 AUG 2005.			
Co-ordinating investigator (LKP according to §40 German Drug Law): Bernd Kemmerich, MD habil, Specialist in Pulmonary Medicine, Munich (Germany) Investigators: In addition to the co-ordinating investigator, further 27 investigators were active (26 specialists in general and internal medicine and 1 physician without specialisation)			
Study centres: 28 out of 30 initiated study centres participated (25 doctor's practices and 3 research centres)			
Medical Specialist	Postal Code	City / Rural District	Country
General Practitioner	14057	Berlin	Germany
General Practitioner	80634	München	Germany
Internal Medicine	134XX	Berlin	Germany
Internal Medicine	813XX	München	Germany
General Practitioner	82152	Planegg	Germany
General Practitioner	87600	Kaufbeuren	Germany
General Practitioner	82061	Neuried	Germany
Internal Medicine	80802	München	Germany
Internal Medicine	803XX	München	Germany
General Practitioner	80339	München	Germany
General Practitioner	81379	München	Germany
Internal Medicine	819XX	München	Germany
General Practitioner	876XX	Görisried	Germany
Internal Medicine	80331	München	Germany
General Practitioner	80634	München	Germany
General Practitioner	917XX	Ornbau	Germany
General Practitioner	83527	Haag	Germany
General Practitioner	82166	Lochham	Germany
Internal Medicine	84453	Mühdorf	Germany
General Practitioner	972XX	Ipesheim	Germany
General Practitioner	80997	München	Germany
n/a (research center)	106XX	Berlin	Germany
Internal Medicine	103XX	Berlin	Germany
Internal Medicine	121XX	Berlin	Germany
Pneumologist	109XX	Berlin	Germany
General Practitioner	14478	Potsdam	Germany
General Practitioner	16547	Birkenwerder	Germany
Internal Medicine	14612	Falkensee	Germany
Publication (reference): None			
Studied period: approx. 3.5 months (clinical part) Date of first enrolment: 19 OCT 2005 (first patient first visit) Date of last completed: 03 FEB 2006 (last patient last visit)		Phase of development: IV	
Objectives: - To assess the efficacy and tolerability of 10 days' treatment with a herbal medicinal product, Bronchipret® Saft, for treatment of acute bronchitis with productive cough as the main symptom in adult patients in comparison to placebo. - To conduct a prospective controlled clinical study with Bronchipret® Saft according to current scientific standards, which meets the requirements of ICH-GCP.			
Methodology (according to final study protocol of 5 AUG 2005):			

Male and female adult outpatients with acute bronchitis were screened for study participation from October 2005 to January 2006 (autumn/winter). The individual study and treatment duration was 10 days, with a total of 3 visits and a patient diary (no run-in or post-treatment period).

- Double-blind treatment with Bronchipret® Saft (a mucoactive herbal syrup) or placebo

At Visit 1 (V1) eligible patients who had given their written informed consent were randomised to 1 of the 2 parallel treatment groups. Treatment with the blinded study medication (Bronchipret® Saft or placebo) started on Day 0 (before the next meal following V1). Patients were instructed to continue taking the medication 3 times daily (t.i.d.) before meals until Day 10, always at the same time of the day (5.4 ml syrup in the morning, at noon, and in the evening).

- Evaluation of efficacy and tolerability (study visits and patient diary)

The efficacy of study treatment (Bronchipret® Saft or placebo) on acute bronchitis was evaluated by patient's daily records of coughing fits¹⁾ during daytime [manual counter] and daily assessment of his/her ability to cough up during daytime, sleep disturbance due to coughing in the night and general well-being [rating scales], and by investigator's assessment of most important symptoms of acute bronchitis, namely cough, sputum, rales/rhonchi, chest pain during coughing, dyspnoea (Bronchitis Severity Score), patient's response to treatment, and by visual control of sputum quality at each study visit [rating scales].

The tolerability of study treatment was evaluated based on adverse events (i.e. both subjectively perceived undesired concomitant symptoms and objectively detected signs of disease), measurement of vital signs (blood pressure, heart rate, body temperature) and by patient's and investigator's global judgement of tolerability at study end.

- The following data were recorded in the CRF at V1 (Day 0), V2 (Day 4), V3 (Day 10) and daily in the diary (Day 0-Day 10):

V1		- written informed consent - inclusion diagnosis, inclusion/exclusion criteria - demographic data incl. body weight and height, smoking [yes/no], previous medication - baseline complaints, clinical relevant findings - randomisation
V1, V2, V3		- Bronchitis Severity Score (BSS): cough, sputum, rales/rhonchi, chest pain during coughing, dyspnoea [5-point-rating scale] - sputum quality [4-point-rating scale] - concomitant disease(s) and concomitant therapy - blood pressure [mmHg] and heart rate [beats per minute=bpm]
V1, V2, V3	Day 1-9 (evening)	- body temperature [°C]
V1	Day 0-10 (morning)	- sleep disturbance due to coughing during the night [4-point rating scale]
V1*	Day 1-9 (evening)**	- number of coughing fits during daytime [N]
	Day 0-9 (evening)	- drug administration [frequency]
V1	Day 0-9 (evening)	- ability to cough up during daytime [4-point rating scale]
V1	Day 0-9 (evening)	- general well-being [4-point rating scale]
V2, V3		- frequency and intensity of adverse events (AEs) - drug compliance (check of content of bottle) - response to treatment [4-point rating scale]
V3		- investigator's and patient's global judgement of tolerability [5-point rating scale]

*Coughing fits during the day before V1 (patient's estimation). **Coughing fits recorded with manual counter.

Number of patients:

- Study plan:

According to sample size calculation, 170 evaluable patients per group were needed to detect an effect size of approximately 30%. Assuming a drop out rate of 5%, about 180 patients per group (total N=360) were to be randomised.

- Patient disposition:

	CORRECTLY RANDOMISED	DROP OUTS	COMPLETED	Interim analysis Efficacy*		ANALYSED All patients		
				I-FAS	I-PP	A-FAS	A-PP	safety SEP
Bronchipret® Saft	182	2	180	129	113	182	156	182
Placebo	181	6	175	126	109	178	152	179
Total	363	8	355	255	222	360	308	361

*confirmatory analysis of efficacy

Diagnosis:

Acute bronchitis (ICD-10: J20) with productive cough as the main symptom.

¹⁾ A fit of coughing was defined as 3 or more consecutive coughs without a discernible inspiration separating them.

Inclusion criteria:

- Written informed consent obtained
- Males and females aged ≥ 18 years
- Diagnosis of acute bronchitis with productive cough requiring all of the following criteria:
 - ≥ 10 coughing fits during daytime (according to the patient's estimate)
 - onset of bronchial mucus production with impaired ability to cough up for a maximum of 2 days prior to Visit 1
 - BSS ≥ 5 points (of maximum 20 points)

Test product (IMP):

Bronchipret® Saft (syrup)

Active ingredients: 100 g syrup contain 15.0 g liquid extract of thyme herb (1:2-2.5) and 1.5 g liquid extract of ivy leaves (1:1)

Mode of administration: peroral

Dose regimen: 5.4 ml t.i.d. (16.2 ml total daily dose) for 10 days

Batch number: 0502863 (blinded batch number: 05098631)

Expiry date: JUL 2008

Reference product:

Placebo (syrup)

Active ingredients: none

Mode of administration: peroral

Dose regimen: 5.4 ml t.i.d. (16.2 ml total daily dose) for 10 days

Batch Numbers: 0503339 (blinded batch number: 05098631)

Expiry Date: JUL 2008

Duration of treatment:

- 10 days (first intake: Day 0)

Patients were asked to take the investigational product (syrup) in the morning, at noon and in the evening (before meals). First intake of study medication started at the day of Visit 1 (Day 0).

Criteria for evaluation:
Efficacy
Primary endpoint [units]

- Change in mean frequency of coughing fits during daytime: mean in coughing fits_(Day 7, Day 8, Day 9) /coughing fits_(Day 1).

The primary endpoint of this study was the change in mean frequency of coughing fits during daytime documented in the patient diary (starting with getting up in the morning and ending with bedtime) relative to the baseline value of Day 1.

The primary endpoint was calculated by the number of coughing fits measured on Day 7, Day 8 and Day 9, documented in the diary, divided by the number of observed days (3 days). Due to the need to adjust for the influence of the baseline value (higher baseline values lead with a high probability to higher values on Day 7, Day 8 and Day 9), this mean value was divided by the baseline value (Day 1) for each patient. Contrary to cough blocking agents, the drugs with secretolytic properties (like Bronchipret® Saft) have a delayed onset of effect on coughing. Therefore, the period between Day 7 and Day 9 was determined to be relevant for evaluation of the primary efficacy outcome measure.

Secondary endpoints

1. Reduction in coughing fits during daytime [units]
2. Time to 50% reduction in coughing fits during daytime compared to Day 1 [days]
3. Proportion of patients with no coughing fits on Day 9 [%]
4. First day coughing fits were reduced by $\geq 75\%$ and totalled < 10 [day]
5. Response to treatment [N/%]
6. Bronchitis Severity Score (BSS) [score points]
7. BSS-subscores [score points]
8. Sputum quality [score points] rated by investigator
9. Ability to cough up during daytime [score points*days]
10. Sleep disturbance due to coughing during the night [score points*days]
11. General well-being [score points*days]

Safety:

1. Frequency and intensity of adverse events (AEs) [N/%]
2. Change in vital signs: blood pressure [mmHg], heart rate [bpm], body temperature [°C]
3. Investigator's and patient's global judgements of tolerability at V3 [score points]

Statistical methods:
Interim analysis on the primary efficacy endpoint

 On 25 JAN 2006, a pre-planned adaptive interim analysis was performed on the primary outcome measure „mean in coughing fits_(Day 7, Day 8, Day 9) /coughing fits_(Day 1)” of 255 patients from 21 investigational centres. The interim analysis

was done by the Bauer-Köhne approach and included an early stopping rule, if the one-sided test of the primary endpoint revealed a p-value of $p \leq p_0$ (significance) or $p > p_1$ (negative result), or a sample size recalculation in case of a p-value between $p_0 \leq p < p_1$. 6 centres recruited fewer than 5 patients and were pooled. Therefore, 15 centres and 1 pooled centre were used for interim analysis.

Final analysis

The analyses of the primary and secondary endpoints were performed using the full analysis set of the interim analysis (I-FAS) and the FAS of all patients (A-FAS: patients included in the interim analysis plus overrunning patients). The analysis of the per-protocol set (PP) was performed additionally as a sensitivity analysis to determine the effects of the patients excluded from the 2 PP cohorts (I-PP and A-PP). Means, standard deviations, Minima, 25%-quantiles, Median, 75%-quantiles and Maxima were calculated for continuous data. Otherwise, frequency tables were used. Confidence intervals were calculated for selected variables.

- Confirmatory and explorative analyses of the primary efficacy endpoint

The change in mean frequency of coughing fits during daytime “mean in coughing fits_(Day 7, Day 8, Day 9) /coughing fits_(Day 1)” was tested on a significance level of $\alpha=0.025$ (1-sided). Evidence of efficacy was obtained if the response to 10 days’ oral treatment with Bronchipret® Saft (IMP) was superior to 10 days’ treatment with placebo (reference therapy). Treatment effects were analysed by ANOVA adjusted for centre effects. In case of a significant deviation from the “Normal distribution” of the ANOVA residuals, the Mann-Whitney-Wilcoxon test (stratified by centre) was carried out additionally. The confirmatory test on superiority was performed using the I-FAS. Additional explorative tests were performed in the I-PP, the A-FAS and the A-PP.

- Descriptive, explorative analyses of the secondary efficacy endpoints

All hypotheses tests for the secondary endpoints were carried out at the 2-sided nominal level of an error probability (α) of 5%. The p-values were valid for explorative interpretation.

The following tests were used to test the results of the secondary endpoints for differences between groups:

- the Log-Rank test for “time to 50% reduction of coughing fits during daytime compared to Day 1” and “first day coughing fits were reduced by $\geq 75\%$ and totalled <10 ” analysed by the Kaplan-Meier life-table methods (survival curve);
- the Chi-square test for the individual response to treatment (responder, non-responder), “proportion of patients with no coughing fits on Day 9”, the “BSS-subscores” and the change in “sputum quality”. The Cochran-Armitage Trend test was performed additionally in case of categorical variables with more than 2 ordered categories (BSS-subscores, sputum quality)
- the analysis of variance (ANOVA, adjusted for centre effects) for the “reduction in coughing fits during daytime”.
- the analysis of covariance (ANCOVA, adjusted for centre effects and baseline as covariate) for the changes in “BSS”, “ability to cough up during daytime”, “sleep disturbance due to coughing during the night” and “patient’s general well-being”.

- Safety analyses

AEs (coded as preferred terms) were tabulated for each treatment group by system organ class according to MedDRA 9.0 coding. The basic displays of AEs in defined categories (frequency, severity, time of onset, pattern of occurrence, outcome, actions taken and investigator’s causality assessment) were used to compare the AE rates between treatment groups.

The changes in vital signs (blood pressure, heart rate, body temperature) from baseline to study termination were described and tested for differences between treatment groups using the WILCOXON test.

The Cochran-Armitage-Trend test was used to test the results for differences between groups regarding the safety endpoint “investigator’s and patient’s global judgement of tolerability”.

- Handling of drop outs or missing data

Patients who did not provide any follow-up efficacy data were excluded from the efficacy evaluation.

With regard to the primary endpoint, each missing value was imputed using the following procedure, assuming that the diary was available and at least 1 post-baseline value was documented (FAS and PP):

- If the patient did not record the number of coughing fits in the diary but additional records* in the diary and/or CRF revealed that the patient had stopped coughing, the number of coughing fits was set to “0” for the respective day(s).

* Additional records documenting “no cough”:

- Priority 1: Question “Any cough (during daytime or the night)? answered “no” (diary)
- Priority 2: BSS-subscore for cough=0 (absent), available on V2, V3 (CRF)
- Priority 3: Premature discontinuation due to “healing” and date of discontinuation recorded (CRF).

- In case of contradictory data, the information with the highest priority was relevant for the imputation decision.

Otherwise, and for all other parameters in the FAS (but not in the PP set), missing values were replaced according to the “last observation carried forward (LOCF)” method, where the last available value was used for imputation of a missing value.

If the patient withdrew from the study for reasons associated with the study medication, such as an unexpected worsening of disease/condition during study or lack of efficacy or unknown reasons (patient lost to follow-up), the worst category was used for the global judgement of tolerability by patient and investigator.

Summary – Conclusions:

Efficacy results

- Coughing fits

From Day 4 onwards, the reduction in coughing fits was more pronounced under Bronchipret® Saft with a distinct advantage over placebo until the end of the period of observation (i.e., up to Day 9). After 1 week's treatment with Bronchipret® Saft, the average number of coughing fits calculated for 3 days (Day 7 to Day 9) was reduced to 29.8% of the baseline value compared to only 49.6% in the placebo group (primary efficacy endpoint, I-FAS: $p < 0.0001$). Proof of superiority of Bronchipret® Saft over placebo regarding the primary outcome measure was demonstrated in the analysis of variance model (ANOVA - mixed effects model with factors "treatment" and "centre") and in the non-parametric Mann-Whitney-Wilcoxon test with stratification by centre.

The inclusion of overrunning patients (A-FAS) led to the same conclusions. Only minor differences in efficacy were observed between the 2 data sets, and thus the interim analysis results were confirmed to be reliable when all randomised and evaluable patients were analysed.

From Day 6 onwards, the time to 50% reduction in coughing fits during daytime was consistently shortened by 2 days when compared to placebo (A-FAS: $p < 0.0001$). At Day 9, twice the percentage of patients in the Bronchipret group was free of coughing fits compared to the placebo group: 28.6% (N=52/182) vs 14.6% (N=26/178) respectively (A-FAS: $p = 0.0013$).

Coughing fits (patient's recording by manual counter) and derived endpoints (I-FAS, A-FAS)					
Patients Bronchipret/ Placebo	Coughing fits	Statistics [unit]	Bronchipret	Placebo	p-value
129/126	Mean frequency of coughing fits on Day 7-9 [standardised to baseline value] (I-FAS: primary endpoint)	Mean % [fits/day]	29.8	49.6	^{WTC} <0.0001
179/175	(A-FAS: sensitivity analysis)	Mean % [fits/day]	31.3	52.4	^{WTC} <0.0001
181/175	Reduction in coughing fits during daytime: AUC _{(Day 1-Day 9)/Day 1 +} (A-FAS)	Mean ±SD [fits/day]	4.7 ±1.5	5.7 ±2.8	^{WTC} <0.0001
182/178	Time to 50% reduction (A-FAS)	Median [day]	6	8	^{Log} <0.0001
182/178	Proportion of patients with no coughing fits on Day 9 (A-FAS)	% [patients]	28.6	14.6	^{CHI} 0.0013
179/175	First day coughing fits reduced by ≥ 75% and <10 fits/day (A-FAS; combined endpoint)	Mean [day]	9.4 ±3.4	11.1 ±3.6	^W <0.0001

^{CHI} = Chi-square test; ^{Log} = Log-Rank test; ^W = Wilcoxon 2-sample test, 2-sided; ^{WTC} = Wilcoxon test adjusted for centres

+ The smaller AUC in the Bronchipret group denotes a greater improvement compared to placebo.

- Overall efficacy outcome (responders, BSS, general well-being, sleep disturbance)

Therapeutic intervention with Bronchipret® Saft resulted in significantly higher responder rates compared to placebo treatment already after only 4 days' treatment (Visit 2: 83.0% vs 53.9%; A-FAS: $p < 0.0001$) with a further increase up to study end (Visit 3: 96.2% vs 74.7%; A-FAS: $p < 0.0001$).

The average Bronchitis Severity Score (BSS) decreased continuously in both treatment groups between baseline and treatment end, but the decrease was much more pronounced in the Bronchipret group (from 8.2 to 1.6 score points = -6.6 score points; A-FAS) than in the placebo group (from 8.3 to 3.3 score points = -5.0 score points; A-FAS). The mean inter-group difference for decrease in BSS between baseline and the 2nd examination after 4 days, as well as between baseline and the 3rd examination after 10 days showed a significant superiority of Bronchipret® Saft compared to

placebo (Δ Visit 2 - Visit 1: $p=0.0009$ and Δ Visit 3 - Visit 1: $p<0.0001$; A-FAS).

Superiority of treatment with Bronchipret® Saft over placebo was also confirmed regarding patients' general well-being evaluated from Day 0 to Day 10 (mean AUC: 12.3 ± 4.3 vs 14.3 ± 5.2 ; A-FAS: $p<0.0001$) and reduction in sleep disturbance induced by coughing evaluated from Day 0 to Day 10 (mean AUC: 10.4 ± 5.8 vs 12.8 ± 6.9 ; A-FAS: $p<0.0001$).

Overall efficacy outcome measures according to the investigator's or patients' assessments on rating scales (A-FAS)

Patients Bronchipret/ Placebo	Variable	Statistics [unit]	Bronchipret	Placebo	p-value
182/178	Responder				
	Visit 2	%	83.0	53.9	CHI <0.0001
	Visit 3	%	96.2	74.7	CHI <0.0001
182/178	Bronchitis Severity Score				
	Δ Visit 2-Visit 1	Mean $\pm$ SD [score points]	- 3.1 $\pm$ 2.7	- 2.3 $\pm$ 2.5	WTC 0.0009
	Δ Visit 3-Visit 1	Mean $\pm$ SD [score points]	- 6.6 $\pm$ 2.6	- 5.0 $\pm$ 3.3	WTC <0.0001
181/178	General well-being AUC _{Day 0-Day 9 +}	Mean $\pm$ SD [score points*days]	12.3 $\pm$ 4.3	14.3 $\pm$ 5.2	WTC <0.0001
180/178	Sleep disturbance due to coughing AUC _{Day 0-Day 10 +}	Mean $\pm$ SD [score points*days]	10.4 $\pm$ 5.8	12.8 $\pm$ 6.9	WTC <0.0001

CHI =Chi-square test; WTC =Wilcoxon test adjusted for centres

+ The smaller AUC in the Bronchipret group denotes a greater improvement compared to placebo.

- Sputum quality

There was a similar change over time in both treatment groups with improvements in sputum quality recorded mainly at study end. Under Bronchipret® Saft, improvement rates were more extensive than under placebo at Visit 2 (19.3% vs 10.2) and Visit 3 (70.9% vs 55.7% respectively). The "Cochrane-Armitage Trend Test", designated to detect a trend towards improvement showed statistical significance in favour of Bronchipret® Saft at Visit 3 ($p=0.0263$) but not at Visit 2 ($p=0.2817$).

- Ability to cough-up during daytime

The improvement in patients' ability to cough up mucus was more pronounced under Bronchipret® Saft with a distinct advantage over placebo from Day 0 to Day 9 (mean AUC: 15.6 ± 6.7 vs 17.9 ± 8.0 ; FAS: $p<0.0001$).

Safety results:

- Adverse events

Treatment with Bronchipret® Saft up to 15 days and a maximum cumulative exposure to 58.0 g fluid extract of thyme herb plus 5.8 g fluid extract of ivy leaves was well tolerated in 182 patients randomised to the Bronchipret group. With 9 AEs reported by 7/182 (3.8%) patients in the Bronchipret group, the occurrence of AEs was very low and similar to the placebo group in which 8 AEs were reported by 8/179 (4.5%) patients. AEs observed under Bronchipret® Saft were labelled most commonly as mild (77.8% AEs vs 62.5% mild AEs in the placebo group), and treatment was not required for the majority of AEs (77.8% AEs vs 50% of AEs requiring no treatment in the placebo group). None of the patients reporting an AE under Bronchipret® Saft discontinued the study prematurely compared to 2 patients with AEs in the placebo group. Severe or serious AEs were not reported in any treatment group and all AEs had resolved by study end (patient recovered).

The nature of possibly or probably drug-related AEs (ADRs according to investigator's blinded assessment) was in accordance with the known side effect profile of Bronchipret® Saft, namely gastric complaints reported by 1 patient (mild gastric disorder and frequent bowel movements) and mild or moderate nausea reported by 2 patients. Transient moderate erythema, a further ADR reported by 1 patient resolved without treatment 4 days before regular stop of Bronchipret® Saft. All 5 ADRs reported by 4 patients in the Bronchipret group resolved spontaneously without any

treatment, whereas the 2 ADRs (moderate flatulence, mild dermatitis allergic) reported by 2 patients in the placebo group resulted in premature drug discontinuation.

- **Vital signs**

Group means of blood pressure or heart rate did not show any clinically relevant changes from baseline, neither under Bronchipret® Saft nor under placebo. No AE was reported indicating a relevant individual increase or decrease of blood pressure or heart rate during the treatment period in any patient. An increase in body temperature and the administration of remission medication (antipyretics/analgesics) was reported for fewer patients under Bronchipret® Saft compared to placebo treatment. A temporary increase above 39 °C between visits was recorded in the diary of 1 patient of the Bronchipret group (maximum: 39.2 °C) and of 3 patients of the placebo group (maximum: 40.1 °C).

- **Global judgements of tolerability**

Patient's ratings on global tolerability of the investigational medication were in agreement with the corresponding ratings of the investigators with an advantage of Bronchipret® Saft over placebo regarding patients' tolerability ratings ($p=0.0236$), but not regarding investigators' tolerability ratings ($p=0.1269$). At the end of the study (Visit 3), a 'very good' or 'good' tolerability was reported by 98.9% vs 95.0% of patients and by 100.0% vs 97.8% of investigators in the Bronchipret group vs the placebo group respectively.

Compliance:

Mean compliance values of 119.4 % in the verum group and 119.5% in the placebo group indicate that a considerable number of patients administered more than the recommended daily dose of 16.2 ml or didn't fill the remaining study medication back into the bottle after taking an overdose. Loss of medication due to spilling of the syrup is a further explanation.

Conclusion

Oral treatment with fluid extract combination of thyme and ivy leaves for about 2 weeks was safe, well tolerated and therefore comparable to placebo treatment but evidently superior in terms of efficacy.

In patients with acute bronchitis with productive cough, treatment with the ivy-thyme combination resulted in a more rapid and more complete recovery from symptoms, particularly coughing and sputum, and shortened the average duration of acute bronchitis, e.g. of coughing fits by nearly 2 days.

Date of the report: 27 JUN 2006 (final version)