3 SYNOPSIS

Name of Sponsor/Company: **Engelhard Arzneimittel GmbH & Co. KG**	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Prospan®	**Volume:**	
Name of Active Ingredients: Ivy leaves dry extract ([5 - 7.5:1] 35 mg in 5 mL, extraction solvent: ethanol 30 % (m/m))	**Page:**	
Title of Study: Randomized, placebo-controlled, double-blind, multi-center trial to evaluate the efficacy and safety of 2 Prospan® posologies (2x7.5 mL/day and 3x5 mL/day) in the treatment of acute bronchitis		
[redacted]		
Trial centers: Three General Practitioners (GPs) and two ear, nose and throat (ENT) specialist in Germany		
Publication (Reference): Planned		
Study Period (Months): 7 **Date of first enrolment:** 18 Nov 2016 **Date of last completed:** 26 Jun 2017		**Phase of Development:** III

Objectives:

Primary objective:

To evaluate the efficacy of ivy leaves cough liquid either applied 3x5 mL or 2x7.5 mL daily compared with placebo in subjects with acute bronchitis, in particular with regard to cough severity (CS).

The primary efficacy outcome was the change of CS assessed by the Bronchitis Severity Score (BSS) between V1 and V5 with regard to pooled vera vs. pooled placebo.

Secondary objectives:

The secondary outcomes were assessed by:

- Difference of the BSS assessed over the whole observation period (between V1 and each of the visits V2, V3, V4, V5, and V6).
- Difference of the BSS between V1 and V5 with regard to ivy leaves cough liquid vs. placebo each in the dosing scheme 3x5 mL.
- Difference of the BSS between V1 and V5 with regard to ivy leaves cough liquid vs. placebo each in the dosing scheme 2x7.5 mL.
- Difference of the BSS between V1 and V5 with regard to verum applied 3x5 mL vs. verum applied 2x7.5 mL daily.
- CS assessed on Visual Analogue Scale (VAS) over the whole treatment period (AUC over 7 days, V1, V2, V3, V4, and V5).

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- Difference of the CS assessed by the Verbal Category Descriptive Score (VCD) over the whole observation period (between V1 and each of the visits V2, V3, V4, V5, and V6).
- Change of spirometrical values (FEV1, FVC, FEV1/FVC%) between V1 and each of the visits V2, V5 and V6.
- Global efficacy assessments (GEA) at V5 and V6.
- Safety of ivy leaves cough liquid compared with placebo over the whole treatment period (7 days, V1, V2, V3, V4 and V5).

Other aims:

- Change of MEF_{25}, MEF_{50} and MEF_{75} between V1 and each of the visits V2, V5 and V6.

Methodology: Double-blind, randomized, multi-center, placebo-controlled, Phase III study (parallel group design).

Number of Subjects:
Planned: n=210 [n=180 evaluable] (n=120 ivy leaves cough liquid, n=60 placebo)
Analyzed: n=209 (n=139 ivy leaves cough liquid, n=70 placebo)

Diagnosis and Main Criteria for Inclusion:

Subjects eligible for inclusion in this trial had to fulfil all of the following criteria:

1) Acute bronchitis with symptoms lasting 48 to 72 hours prior to treatment.

2) Men or women of any ethnic origin.

3) Age: 18 to 75 years.

4) Subjects who were able to understand and were willing to comply to trial instructions.

5) Having given written informed consent.

6) Satisfactory health except for the bronchitis as determined by the investigator based on medical history and physical examination.

7) CS score of at least 50 mm on a 100 mm VAS at V1.

8) BSS of at least 10 points at V1.

9) VCD score of at least 2 points at V1.

Subjects eligible for inclusion in this trial were not allowed to fulfil any of the following criteria:

1) Allergic bronchial asthma, bronchial hyperreactivity, chronic bronchitis, other chronic or inherited lung disease.

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2) History of hypersensitivity to any excipient of the applied drugs.

3) History of drug hypersensitivity, asthma, urticaria, or other severe allergic diathesis as well as current hay fever.

4) History of chronic gastritis or peptic ulcers.

5) Any gastrointestinal complaints within 7 days before V1.

6) Participation in a clinical trial within 30 days prior to the treatment phase of this study or concomitantly.

7) Treatment with corticoids, beta-2 agonists (e.g. salbutamol, fenoterol), expectorants, theophylline, antitussives, anaesthetics, acetylsalicylic acid (e.g. aspirin) or other non-steroidal anti-inflammatory drugs, leukotriene inhibitors, ACE inhibitors, antiviral drugs or antibiotics, antihistamines, immunosuppressants, isoprenaline, atropine, sodium cromoglycate or homeopathic drugs against common cold within 7 days before V1.

8) Drug or alcohol abuse in the opinion of the investigator.

9) Pregnant or nursing (lactating) women.

10) Body temperature >38.3°C.

11) Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) who are not using an acceptable method of contraception defined as:

- Surgical sterilization
- Hormonal contraception
- IUD
- Double barrier method
- Total abstinence throughout the trial at the discretion of the investigator.

Periodic abstinence is NOT an acceptable method of contraception. An acceptable method of contraception must be maintained throughout the trial.

A woman who is post-menopausal must have a negative urine pregnancy test at screening but will not need to comply with an acceptable method of contraception. Women are considered post-menopausal and not of child-bearing potential if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman

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has been confirmed by follow up hormone level assessment.

12) Subjects with significant diseases, defined as a disease which, in the opinion of the investigator, may either put the subject at risk because of participation in the trial or a disease which may influence the results of the trial or the subject's ability to participate in the trial; includes subjects with a history of gastrointestinal bleeding, significant cardiovascular, liver or renal disease.

13) Subjects directly or indirectly involved in the execution of this protocol, including employees of the CRO and persons related to them.

Test Product, dose and mode of administration, batch number:

Active ingredient: ivy leaves dry extract ((5 - 7.5:1) extraction solvent: ethanol 30 % (m/m)), oral liquid, 35 mg in 5 mL, bottle containing 200 mL in total, 5 mL liquid t.i.d or 7.5 mL liquid b.i.d. Batch No. 16H086B.

Duration of Treatment: 7 days (±1 day).
Duration of Observation: 14 days (±1 day).

Reference therapy, dose, mode of administration, batch number:

Placebo did not contain the active ingredient but was indistinguishable in its final formulation from the investigational drug, oral liquid, bottle containing 200 mL in total, 5 mL liquid t.i.d or 7.5 mL liquid b.i.d. Batch No. 16H086B.

Criteria for Evaluation:
Efficacy: assessed on the following scales:

- BSS,
- VAS,
- VCD score,
- Global efficacy assessments ((GEA), 5-point Likert scale),
- Spirometry.

Safety: assessed by adverse events, vital signs, physical examinations, pregnancy test, and global safety assessments at V5 and V6.

Statistical Methods:
The primary efficacy variable BSS change from V1 (Baseline) to V5 was compared between pooled treatment groups using an analysis of covariance (ANCOVA) model with treatment group and center as fixed effects and baseline BSS as a covariate.
The secondary efficacy variable BSS change from V1 (Baseline) to V5 was compared between ivy leaves cough liquid and placebo in the dosing scheme 3x5 mL and in the dosing scheme 2x7.5 mL using an ANCOVA model with treatment group and center as fixed effects and baseline BSS as a covariate.
The secondary efficacy variable BSS change from V1 (Baseline) to V5 was compared between ivy leaves cough liquid applied 3x5 mL and ivy leaves cough liquid applied 2x7.5 mL by means of a t-test with one-sided α-level of 2.5 %. The treatment effect was estimated by means of the mean treatment difference and a one-sided 97.5 %

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confidence interval was determined. Non-inferiority had to be concluded if the one-sided 95 % confidence interval was within the region of non-inferiority (-1 to ∞).
As a sensitivity analysis for the primary efficacy variable, an additional model was run that contained a term for the treatment*center interaction. The treatment by center interaction effect was assessed for significance and the least square mean comparisons between treatments within each center were presented. Further secondary efficacy variables were analyzed descriptively by means of Mann-Whitney tests and Cochran-Mantel-Haenszel tests (CMH), respectively.

The incidence of all treatment-emergent AEs (TEAEs) was tabulated after grouping by System Organ Class (SOC) and Preferred Term (PT). For each PT and summarized over each SOC overall, the table presented the number of subjects in each treatment group in whom the event occurred and the rate (%) of occurrence. The incidence of all potentially attributable events, i.e., those whose causal relationship to the IMP, according to the local investigator, was not related, unlikely, possible, probably, or certain was tabulated similarly. The incidence of all serious AEs and potentially attributable events were tabulated similarly.

SUMMARY AND CONCLUSIONS

EFFICACY:

A total of 209 subjects with acute bronchitis was randomly assigned to double-blind treatment (ivy leaves cough liquid [pooled]: n=139; placebo [pooled]: n=70; ivy leaves cough liquid (3x5 mL/d): n=69; placebo: n=35) and (ivy leaves cough liquid (2x7.5 mL/d): n=70; placebo: n=35). For efficacy all subjects were evaluated as the Full Analysis Set (FAS) and also analysed for Safety (SAF). The results for the Per Protocol population (PP) did not differ from those of the FAS population.

The cough severity (CS) assessed by Bronchitis Severity Score (BSS) across all algometry assessments in the five key symptoms of bronchitis and the severity of each symptom change between V1 and V5 was the primary efficacy outcome; the total BSS was calculated as the sum of individual scores. There was a significant ($p<0.0001$) difference between the two pooled treatment groups with regard to the primary efficacy outcome.

Superiority of the ivy leaves cough liquid versus placebo was also demonstrated as change of from baseline in cough severity assessed by the BSS between V1 and V5 for patients treated with 3x5 mL dosing scheme ($p<0.0029$) and 2x7.5 mL dosing scheme ($p<0.0033$), respectively. There were no significant differences between the two dosing schemes and non-inferiority could be concluded as the corresponding confidence interval was completely within the limits of (-1 to ∞).

Furthermore, the extent of CS in both treatment groups was evaluated as change of from baseline assessed by Visual Analogue Scale (VAS) over the treatment period of 7

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days at Visit 5 (VAS AUC_{0-7d}), that was significantly lower (less cough) for ivy leaves cough liquid compared to placebo ($p<0.0001$). Moreover, the CS measured on Verbal Category Descriptive (VCD) Score showed significant treatment differences in favor of ivy leaves cough liquid. There were no significant differences between the two dosing schemes.

For the spirometry assessment, no statistically significant treatment differences were observed. Due to lack of quality in the majority of measurements, no conclusion can be made to the different treatments.

The ivy leaves cough liquid was effective in the treatment of acute bronchitis. Subjects treated with ivy leaves cough liquid had significant reductions in cough severity (rate, number, type, and extent), severity of symptoms associated with cough and bronchitis, and global assessments of subjects and investigators compared to the placebo groups. The results confirmed that the ivy leaves cough liquid had a favorable impact on the outcome of subjects suffering from acute bronchitis.

SAFETY RESULTS:

All 209 subjects enrolled with acute bronchitis who received at least one dose of the trial medication were included in the safety population.

A total of 28 subjects had at least one adverse event during the clinical trial. A total of 29 adverse events (ivy leaves cough liquid: n=20 (14.4 %), placebo: n=9 (12.9 %)) were documented. Twenty-two AEs were attributable to a worsening of the CS measured on VAS based on the protocol requirement that worsening of greater than 5 mm on VAS should be recorded as AE. The adverse events were relatively well-balanced between the treatment groups.

Beside those 22 AEs that were evaluated as worsening of CS measured on VAS, a total of 7 patients (ivy leaves cough liquid: n=6 (4.3 %), placebo: n=1 (1.4 %)) had one adverse event (AE) during the course of the clinical trial. All AEs in this clinical trial were non-serious and of mild or moderate severity and for all these AEs, except of one, a causal relationship had been excluded. The only AE with suspected causal relationship occurred in the ivy leaves cough liquid group (2x7.5 mL/d) and represented abdominal pain upper which is expected according to the package insert of ivy leaves extract.

There was no pattern indicating any specific adverse effect related to the study drug or specifically affecting one of the study subjects. The ivy leaves cough liquid was a safe option for the treatment of acute bronchitis.

CONCLUSION:

This report presents the data collected during a Phase III study to evaluate the efficacy and safety of 3x5 mL and 2x7.5 mL dosing scheme ivy leaves cough liquid in subjects

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with acute bronchitis in comparison to placebo. Measurements for cough severity were obtained by VAS evaluation, VCD, and BSS scores.

The results of the PP analysis for the primary variable did not differ from those of the FAS analysis.

Superiority of the ivy leaves cough liquid was demonstrated as change of from baseline in the BSS across all algometry assessments in the five key symptoms of bronchitis and the severity of each symptom between V1 and V5. The BSS showed significant treatment differences in favor of ivy leaves cough liquid compared to placebo. There were no significant differences in efficacy between the two dosing schemes. The extent of cough severity assessed by VAS over 0-7 days at Visit 5 (AUC_{0-7d}) was significantly lower (less cough) for the ivy leaves cough liquid group compared to placebo.

The analysis of adverse events did not lead to any significant difference between the treatment groups.

In the centerwise subgroup analysis, a potential qualitative interaction was detected. Center 3 showed in contrast to the other four centers an ‘effect reversal’ (i. e. the placebo seemed to be superior) between the two pooled treatment groups. However, the Gail-Simon test for qualitative interaction (Gail M. and Simon R., 1985) showed no significant interaction (p=0.3706). Moreover, the probability that in a multi-center trial with 5 centers at least one of the centers shows an ‘effect reversal’ is greater than 40 % (Senn S., 1997).

For the spirometry assessment, no statistically significant treatment differences were observed. Due to lack of quality in the majority of measurements, no conclusion can be made to the different treatments.

An ivy leaves cough liquid in the dosing scheme of 3x5 mL formerly compared with placebo in a randomized, double-blind, multi-center, parallel group study to evaluate the efficacy and tolerability in patients with acute bronchitis showed consistent superiority of the ivy leaves cough liquid treatment versus placebo in all clinically relevant variables (rate, number, and type of observed acute bronchitis, severity of cough symptoms, and global assessments of subjects and investigators).

Both formulations of the ivy leaves cough liquid were effective and safe in the treatment of acute bronchitis and there were no differences between the two dosing schemes. The results confirm that the ivy leaves cough liquid has a favorable impact on the outcome of subjects suffering from acute bronchitis.

Date of report: 15 Mar 2018