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, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of a liquid containing ivy leaves dry extract vs. Placebo in the treatment of acute cough		
[redacted]		
Trial sites: Four General Practitioners (GPs) and one ear, nose and throat (ENT) specialist in Germany		
Publication (Reference): None		
Study Period (Months): 4.5 **Date of first enrolment:** 28 Jan 2015 (FSFV) **Date of last completed:** 16 Jun 2015 (LSLV)		**Phase of Development:** II

Objectives:

Primary objective:

To evaluate the efficacy of Ivy leaves Cough Liquid compared with Placebo applied three times a day in subjects with acute cough, in particular with regard to cough severity (CS).

- The primary efficacy outcome was CS assessed by Visual Analogue Scale (VAS) over the whole treatment period (area-under-the-curve ($AUC_{0\text{-}168\ h}$) over 7 days, Visits V1, V2, V3, V4 and V5).

Secondary objectives:

The secondary outcomes were assessed by:

- Difference of the Bronchitis Severity Score (BSS) assessed between V1 and each of the visits V2, V3, V4 and V5.
- CS on VAS over the whole observation period (AUC over 14 days, V1, V2, V3, V4, V5 and V6).
- CS on Verbal Category Descriptive Score (VCD) over the whole treatment period (AUC over 7 days, V1, V2, V3, V4 and V5).

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- Global efficacy assessment at V5 and V6.
- Safety of Ivy leaves Cough Liquid compared with Placebo applied three times a day over the whole treatment period (7 days, V1, V2, V3, V4, and V5).

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

Number of Subjects:
Planned: n=180 (n= 90 Ivy leaves Cough Liquid, n=90 Placebo)
Analyzed: n=181 (n=89 Ivy leaves Cough Liquid, n=92 Placebo)

Diagnosis and Main Criteria for Inclusion:

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

- Acute cough with symptoms lasting 2-3 days prior to treatment.
- Men or women of any ethnic origin.
- Age: 18 to 75 years.
- Subjects who are able to understand and are willing to comply to trial instructions.
- Having given written informed consent.
- Satisfactory health except for the cough as determined by the investigator based on medical history and physical examination.
- Cough Severity (CS) score of at least 50 mm on a 100 mm VAS at V1.
- Acute BSS of at least 10 points at V1.
- VCD score of at least 2 points at V1.

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

- Allergic bronchial asthma, bronchial hyperreactivity, chronic bronchitis, other chronic or inherited lung disease.
- History of hypersensitivity to any excipient of the applied drugs.
- History of drug hypersensitivity, asthma, urticaria, or other severe allergic diathesis as well as current hay fever.
- History of chronic gastritis or peptic ulcers.
- Any gastrointestinal complaints within 7 days before V1.

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- Participation in a clinical trial within 30 days prior to the treatment phase of this study or concomitantly.
- 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.
- Drug or alcohol abuse in the opinion of the investigator.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) who were not using an acceptable method of contraception.
- 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 might influence the results of the trial or the subject's ability to participate in the trial; included subjects with a history of gastrointestinal bleeding, significant cardiovascular, liver or renal disease.
- Subjects directly or indirectly involved in the execution of the 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. Batch No. 14N019B.

Duration of Treatment: 7 days.

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. Batch No. 14N019B.

Criteria for Evaluation:

Efficacy: The primary efficacy outcome was CS assessed by Visual Analogue Scale (VAS) over the whole treatment period (area under the curve ($AUC_{0\text{-}168\ h}$) over 7 days, visits V1, V2, V3, V4, and V5).

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Secondary efficacy outcomes were:

- Difference of the Bronchitis Severity Score (BSS) assessed between V1 and each of the visits V2, V3, V4, and V5.
- CS on VAS over the whole observation period (AUC over 14 days, V1, V2, V3, V4, V5, and V6).
- CS on Verbal Category Descriptive Score (VCD) over the whole treatment period (AUC over 7 days, V1, V2, V3, V4 and V5).
- Global efficacy assessments (GEA) at V5 and V6.

Safety:

- Safety of Ivy leaves Cough Liquid compared with Placebo applied t.i.d. over the whole treatment period (7 days, V1, V2, V3, V4, and V5).
- Safety assessed by adverse events, vital signs, physical examinations, and global safety assessments at V5 and V6.

Statistical Methods:
The primary efficacy variable AUC of CS was compared between treatment groups using an ANCOVA model with treatment group and site as main effects and baseline value as a covariate. As a sensitivity analysis, an additional model was carried out that contained a term for the treatment by site interaction. The treatment by site interaction effect was assessed for significance and the least square mean comparisons between treatments within each site were presented. Secondary efficacy variables were analyzed by means of Mann-Whitney tests and Cochran-Mantel-Haenszel tests (CMH), respectively.

The incidence of all treatment-emergent AEs 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 suspected-drug-related AEs was tabulated similarly. The incidence of all treatment-emergent AEs was also tabulated by severity categories.

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SUMMARY AND CONCLUSIONS

EFFICACY:

A total of 181 subjects with acute cough was randomly assigned to double-blind treatment (Ivy leaves Cough Liquid: n=89; Placebo: n=92). 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 (Ivy leaves Cough Liquid: n=88; placebo: n=90) did not differ from those of the FAS population.

In all clinically relevant variables (rate, number, and type of observed acute cough, severity of cough symptoms, and global assessments of subjects and investigators) there was a consistent superiority of the Ivy leaves Cough Liquid treatment versus Placebo confirming the robustness of the observations made. The primary efficacy outcome cough severity assessed by Visual Analogue Scale over the treatment period of 7 days (area-under-the-curve $AUC_{0\text{-}168\ h}$) indicated a higher efficacy of Ivy leaves Cough Liquid group compared to Placebo ($p < 0.0001$). Also, the rate of cough severity assessed by Verbal Category Descriptive (VCD) and the rate of Bronchitis Severity Score (BSS) showed the same trend, a distinct and statistically significant reduction in the Ivy leaves Cough Liquid group compared to Placebo at all follow-up visits in the FAS population ($p < 0.0001$).

After a treatment period of 7 days (Visit 5) and seven days later (Visit 6), the treatment efficacy of the Ivy leaves Cough Liquid and Placebo was assessed globally (GEA) by the subjects and investigators using a 5-point rating scale. At all time-points there was significant evidence that the subjects and the investigators rated the Ivy leaves Cough Liquid more efficacious than Placebo ($p<0.0001$).

The results indicate a positive effect of Ivy leaves Cough Liquid treatment compared to Placebo in subjects with acute cough. In this context a remarkable early onset of efficacy (after 48 h) was observed. The safety findings presented in this clinical trial suggest that the benefit-risk balance of treatment with Ivy leaves Cough Liquid remains unchanged also for elderly patients included in the study (> 65 years of age).

The Ivy leaves Cough Liquid was effective in the treatment of acute cough. 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 group.

SAFETY RESULTS:

All 181 subjects enrolled with acute cough who received at least one dose of the study medication were included in the safety population.

A total of 21 subjects (Ivy leaves Cough Liquid: n=9, Placebo: n=12) had at least one adverse event (AE), of these, 18 subjects had one single adverse event, 1 subject in the

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Ivy leaves Cough Liquid group had 2 adverse events and 1 subject in the Placebo group had 2 adverse events and another subject in the Placebo group had 4 AEs. All AEs in this clinical trial were non-serious and of mild or moderate severity. No drug-related adverse events were recorded.

The adverse events were relatively well-balanced between the treatment groups. The reported AEs stand partly in close connection to the underlying disease as cough ("worsening of cough"), middle ear effusion, swollen tongue, and sinusitis. It was mainly at Site 4 where the investigator evaluated slight worsenings of 2 to 5 mm on VAS in the cough assessment as adverse events; mainly the scores stay at a same level. It is obvious that Site 4 had a different opinion on when to record the data, because all other sites did not rate such minimal changes of little millimeters on the perpendicular line of the VAS as adverse events named "worsening of cough".

A small group of subjects aged > 65 years (n=5 for Ivy Leaves Cough Liquid, n=3 for Placebo) had been included in the study. The safety profile in this subgroup gives no hints for a reduced safety of Ivy leaves Cough Liquid in comparison to Placebo in patients between 65 and 75 years of age, baring in mind that the number of patients in both groups is too small for statistical testing.

There was no pattern indicating any specific adverse event related to the study drug or specifically affecting one of the study subjects. The Ivy leaves Cough Liquid is a safe option for the treatment of acute cough.

CONCLUSION:

This report presents the data collected during a Phase II study to evaluate the efficacy and safety of Ivy leaves Cough Liquid in subjects with acute cough in comparison to Placebo. Measurements for cough severity were obtained by VAS evaluation, VCD, and BSS scores.

A total of 181 subjects were included and completed up to seven days of treatment with trial medication of Ivy leaves Cough Liquid and Placebo, followed by a seven day follow-up period. VAS values differed significantly between Ivy leaves Cough Liquid and Placebo.

Subjects treated with Ivy leaves Cough Liquid had statistically significant and clinically relevant 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 group. The results confirm that the Ivy leaves Cough Liquid has a favorable impact on the outcome of subjects suffering from acute cough compared to Placebo. Significantly more subjects in the Ivy leaves Cough Liquid group reached a higher level of satisfaction for the active treatment compared to the Placebo group, as seen from the results of the global assessment of efficacy. The patients in the Ivy leaves Cough Liquid group experienced a significantly

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faster reduction of symptoms vs. Placebo (already after 48 hours). The excellent risk/benefit ratio was also observed in elderly patients (65-75 years) included in the study.

There was no pattern indicating any specific adverse event related to the study drug or specifically affecting any one of the study subjects. Overall, the safety evaluation did not reveal any additional risks and confirmed the good safety profile of the Ivy leaves Cough Liquid.

The results of this clinical trial are clear-cut and consistent across all objectives of efficacy and safety variables. For the treatment of subjects with acute cough, the Ivy leaves Cough Liquid is an effective and safe option.

Date of report: 12 January 2016