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Medizentrum Essen-Borbeck[1], Essen, Germany; Engelhard Arzneimittel GmbH & Co. KG[2], Niederdorfelden, Germany; Clinsearch GmbH[3], Zug, Switzerland; CRM Biometrics GmbH[4], Rheinbach, Germany

A randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of a liquid containing ivy leaves dry extract (EA 575®) vs. placebo in the treatment of adults with acute cough

A. Schaefer[1], M.S. Kehr[2], B.M. Giannetti[3], M. Bulitta[4], C. Staiger[2]

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Melanie S. Kehr, Engelhard Arzneimittel GmbH & Co. KG, Herzbergstr. 3, 61138 Niederdorfelden, Germany
m.kehr@engelhard.de

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This randomized, placebo-controlled, double-blind trial was conducted to assess the efficacy and safety of ivy leaves cough liquid in the treatment of acute cough. A total of 181 adult patients with acute cough were treated with either ivy leaves cough liquid containing EA 575® or with placebo three times a day for one week. The primary efficacy outcome was cough severity (CS) assessed by Visual Analogue Scale (VAS) over the whole treatment period (area-under-the-curve ($AUC_{0\text{-}168\ h}$) over 7 days (visit (V)1, V2, V3, V4, and V5). The secondary endpoints were defined as the CS assessed by VAS over the whole observation period (V1 – V6) and by Bronchitis Severity Score (BSS) and Verbal Category Descriptive (VCD) score. The evaluation of the VAS, BSS and VCD score revealed that subjects treated with ivy leaves cough liquid showed statistically significant and clinically relevant reductions in CS, severity of symptoms associated with cough and bronchitis compared to the placebo group. Furthermore, a remarkable early onset of efficacy was observed as significant reductions of cough severity were detected within 48 hours after the first drug intake. At all following visits and even 7 days after the end of treatment (V6) this significant treatment advantage was detected in comparison to placebo. All adverse events (AEs) in this clinical trial were non-serious, mild or of moderate severity and not drug-related. This clinical trial proved consistent superiority of the ivy leaves cough liquid treatment versus placebo and confirmed the EA 575® preparation to be a safe and efficacious option for the treatment of acute cough.

1. Introduction

Cough is one of the lead symptoms of respiratory illnesses and one of the most frequently reported disorders in medical practice, in children as well as in adults. Its most common causes are upper respiratory tract infections (URTIs) and acute bronchitis. These illnesses usually present a viral etiology, are self-limiting, and generally subside within a couple of weeks (Dicpinigaitis et al. 2009). However, frequent coughing usually causes a reduction in the patient's quality of life and can also lead to complications.

Ivy leaves formulations are a well established treatment of cough and several clinical trials are published (HMPC 2011; Holzinger and Chenot 2011). The dried leaves of ivy, *Hedera helix L.* (Araliaceae), contain different ingredients such as saponines, flavonoids, phenolic acids and essential oils. Among these, the group of saponines is primarily responsible for the therapeutic properties (Hegener et al. 2004; Runkel et al. 2005; Greunke et al. 2014; Wolf et al. 2011; Sieben et al. 2009; Trute et al. 1997; Schulte-Michels et al. 2016). Anti-inflammatory, mucolytic, bronchospasmolytic leading in turn to antitussive effects were shown for the ivy leaves dry extract EA 575® (Lang et al. 2015).

The liquid cough medication investigated in this clinical trial contained 35 mg EA 575® ivy leaves dry extract [5 - 7.5:1], in 5 ml (extraction solvent: ethanol 30 % (m/m), Prospan®, Engelhard Arzneimittel GmbH & Co. KG). The extract is well characterized (Landgrebe et al. 1999) and this medication is marketed to improve complaints of chronic-inflammatory bronchial diseases and acute inflammations of the respiratory tract accompanied by coughing. In a substantial number of clinical trials and observational studies, the mentioned therapeutic efficacy and very good tolerability of ivy leaves preparations containing the extract EA 575® have been shown (Lang et al. 2015). These data apply exclusively to this particular extract as herbal extracts that are obtained by using conditions different to the patented extraction procedure might result in different therapeutic efficacy, potency, and safety (Gaedcke and Steinhoff 2000; Blume et al. 2015).

This placebo controlled trial was conducted to assess the efficacy and safety of ivy leaves cough liquid in the treatment of acute cough in adults.

Abbreviations:
AE - adverse event; ANCOVA - analysis of covariance; AUC - area-under-the-curve; BSS - Bronchitis Severity Score; CA - competent authorities; CS - cough severity; EC - ethics committee; FAS - full analysis set; GEA - global efficacy assessment; ICH - International Conference on Harmonization; IMP - investigational medicinal product; LOCF - last-bservation-carried-forward; MID - minimal important difference; n - sample size or absolute frequency; p - p-value; RCT - randomized clinical trial; SAS - Statistical Analysis System; SD - standard deviation; t.i.d. - three times daily; URTI - upper respiratory tract infection; V - visit (1, 2, 3, 4, 5, 6); VAS - Visual Analogue Scale; VCD - Verbal Category Descriptive

2. Investigations and results

A total of 181 patients suffering from productive cough had been randomly assigned to one of the two treatment arms. The mean±SD time from onset of cough to visit 1 was 2.35±0.49 days. 178 patients completed the clinical trial. One subject was lost to follow-up after V5 and two subjects discontinued due to lack of efficacy (Fig. 1). The results of the per protocol population did not

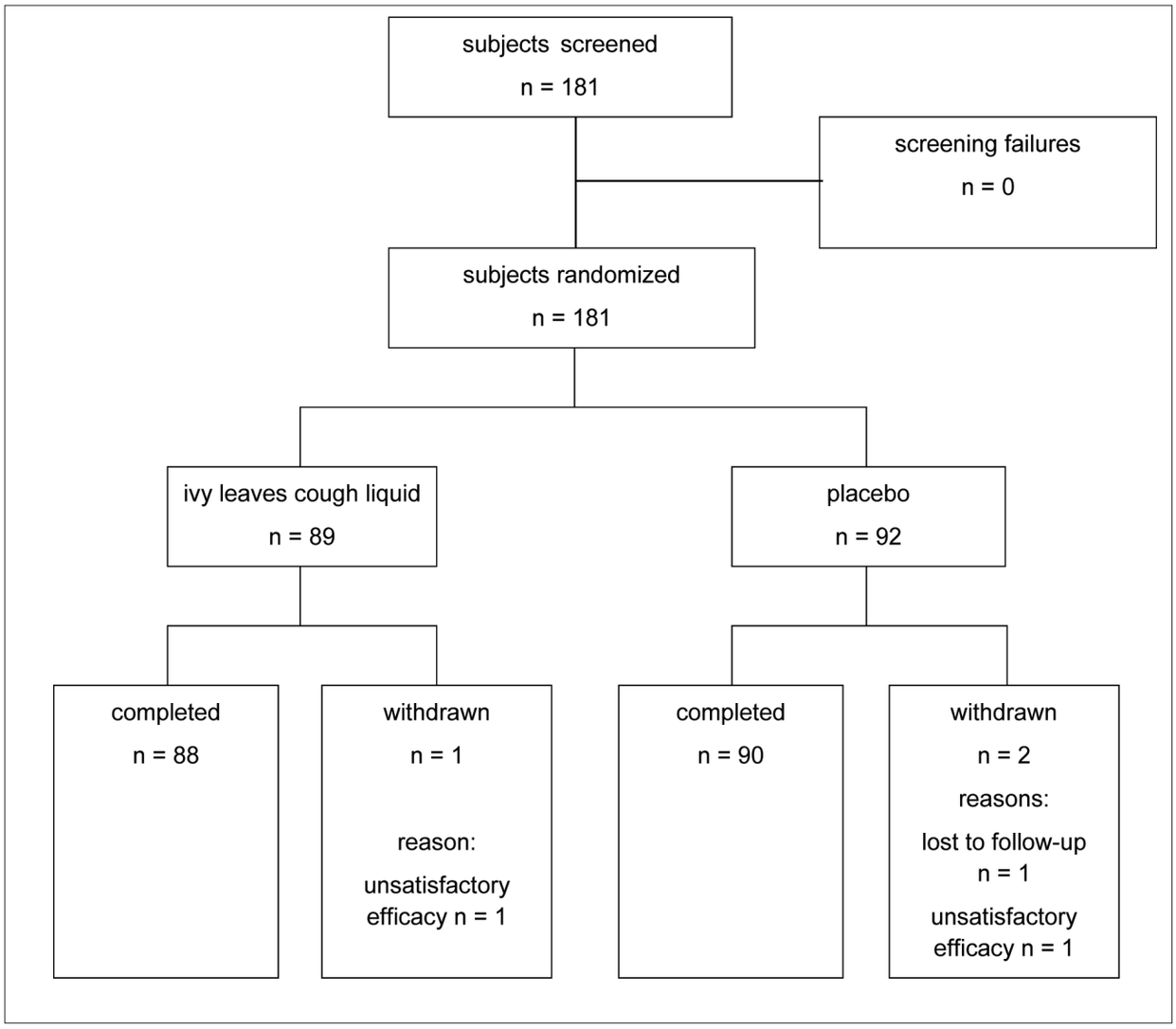

Fig. 1: Disposition of subjects

Table 1: Cough Severity assessments on VAS – $AUC_{0\text{-}168}$ h and VAS over time (FAS)

			Ivy leaves cough liquid (n=89)	Placebo (n= 92)	p
$AUC_{0\text{-}168\ h}$ (mm * h)	Mean		7902.6	9637.3	< 0.0001
	SD		2350.1	2270.3	
	Treatment effect (EA 575® - Placebo)		-1727.0		
	95 % confidence interval		-2405.7; -1047.6		
VAS (mm)	V1	Mean	72.8	72.3	-0.0125
		SD	8.9	10.0	
	V2	Mean	63.1	67.5	< 0.0001
		SD	12.2	11.3	
	V3	Mean	50.7	61.8	< 0.0001
		SD	15.6	14.6	
	V4	Mean	39.5	55.1	< 0.0001
		SD	21.2	17.9	
	V5	Mean	22.4	40.3	< 0.0001
		SD	20.5	21.7	
	V6	Mean	8.6	20.6	< 0.0001
		SD	16.8	19.9	

AUC – Area-under-the-ciurve, VAS – Visual Analogue Scale, n – Sample size, SD – Standard deviation, p – p-value, V – Visit, FAS – Full Analysis Set

Table 2: Cough Severity assessments on BSS – Total Score (FAS)

			Ivy leaves cough liquid (n=89)	Placebo (n= 92)	p
BSS (total score)	V1	Mean	11.2	11.3	-
		SD	1.5	1.3	
	V2	Mean	9.0	10.2	0.0003
		SD	2.5	2.3	
	V3	Mean	6.9	9.0	< 0.0001
		SD	2.9	3.0	
	V4	Mean	5.4	7.7	< 0.0001
		SD	3.2	3.4	
	V5	Mean	2.8	5.6	< 0.0001
		SD	3.0	3.4	

BSS – Bronchitis Severity Score, n = Sample size, SD – Standard deviation, p – p-value, V – Visit, FAS – Full Analysis Set

Table 3: Cough Severity assessments on VCD – Total Score (FAS)

			Ivy leaves cough liquid (n=89)	Placebo (n= 92)	p
VCD (total score)	V1	Mean	3.3	3.4	-
		SD	0.6	0.7	
	V2	Mean	3.0	3.2	0.0424
		SD	0.8	0.8	
	V3	Mean	2.6	3.0	0.002001
		SD	0.9	0.8	
	V4	Mean	2.2	2.8	< 0.0001
		SD	1.0	0.9	
	V5	Mean	1.4	2.1	< 0.0001
		SD	1.2	1.1	

VCD – Verbal Category Descriptive, V – Visit, n – Sample size, SD – Standard deviation, p – p-value, FAS – Full Analysis Set

Table 4: Demographics and baseline characteristics (FAS)

			Ivy leaves cough liquid (n=89)	Placebo (n= 92)
Age (yrs)	Mean		36.2	36.4
	SD		14.6	13.4
Sex	Male	n (%)	49 (55.1)	44 (47.8)
	Female	n (%)	40 (44.9)	48 (52.2)
Height (cm)	Mean		175.5	173.9
	SD		9.3	10.5
Weight (kg)	Mean		79.5	78.5
	SD		16.9	17.3
Ethnic origin	Caucasian	n (%)	89 (100.0 %)	89 (96.7)
	Afro-American		-	2 (2.2)
	Asian		-	1 (1.1)
Blood pressure systolic / diastolic (mmHg)	Mean		127.9 / 75.1	125.8 / 76.0
	SD		10.2 / 9.0	10.8 / 9.1
Pulse rate (b/min)	Mean		74.0	73.2
	SD		10.1	9.9
Body temperature (°C)	Mean		36.7	36.7
	SD		0.5	0.5

FAS – Full Analysis Set, SD – Standard deviation, n – Sample size or absolute frequency

differ from those of the Full Analysis Set (FAS) population (Tables 1-3, Figs. 2-3) and is therefore not presented in this paper. Subjects and investigators adhered tightly to the protocol as only 3 major protocol deviations occurred.

2.1. Efficacy

The primary efficacy outcome was the CS assessed by VAS over the whole treatment period (area-under-the-curve $AUC_{0\text{-}168\ h}$) of 7 days (V1, V2, V3, V4, and V5). Higher values of the $AUC_{0\text{-}168\ h}$ indicate a higher severity of cough. There was a significant ($p < 0.0001$) difference between the two study groups with regard to the primary variable: the mean $AUC_{0\text{-}168\ h}$ was 7902.6 mm*h in the verum group and 9637.3 mm*h in the placebo group (Table 1).
Concerning the secondary endpoints the cough severity assessed by VAS over the whole observation period (V1 – V6) and by BSS and VCD score was similar in the two treatment groups at baseline (Tables 1-3). At all follow-up visits a statistically significant reduction was detected in the ivy leaves cough liquid group compared to placebo in the FAS population for all three parameters (Fig. 2,

Tables 1-3). Until treatment end (V5) mean VCD had changed from 3.3 to 1.4 score points in the active treatment group and from 3.4 to 2.1 score points in the placebo group. For the same observation period mean BSS changed from 11.2 to 2.8 score points in the active treatment group and from 11.3 to 5.5 score points in the placebo group. For BSS a mean 20% improvement to the baseline value was achieved already after 48 h in the ivy leaves cough liquid group while the placebo group showed an improvement of 10% (Fig. 3). This statistically significant difference indicates an impressively rapid onset of action. Mean VAS improved from 72.8 mm to 22.4 mm (V5) in the active treatment group and from 72.3 mm to 40.3 mm in the placebo group. The effect continued after treatment end: at V6 VAS reached 8.6 mm (ivy leaves cough liquid) in comparison to 20.6 mm (placebo) at V6.

After a treatment period of 7 days (V5) and seven days later (V6), the treatment efficacy was assessed globally via 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 verum as more efficacious than placebo ($p<0.0001$). At V5 84.1% of the patients in the treatment group rated their conditions as "good" or "very good" (*vs.* 42.4% in the placebo group). At visit 6 the rating was 85.2% in the treatment group *vs.* 37.0% in the placebo group. Investigator's assessment did not differ significantly from the patient's assessment (Fig. 4).

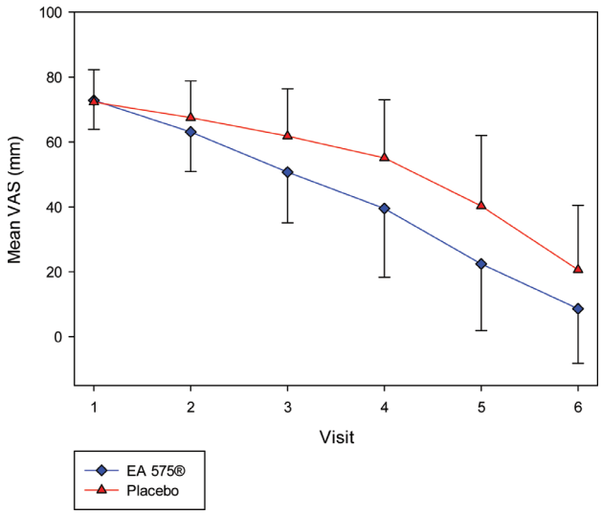

Fig. 2: CS assessed by VAS (Mean + SD) over time (FAS)

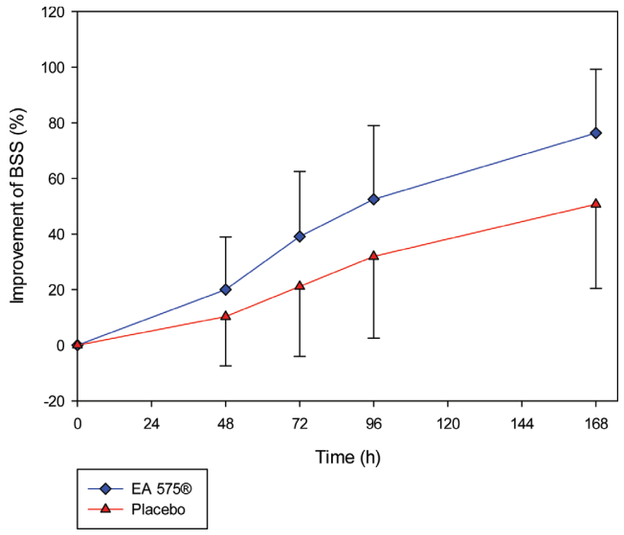

Fig. 3: Relative improvements from baseline on BSS (FAS)

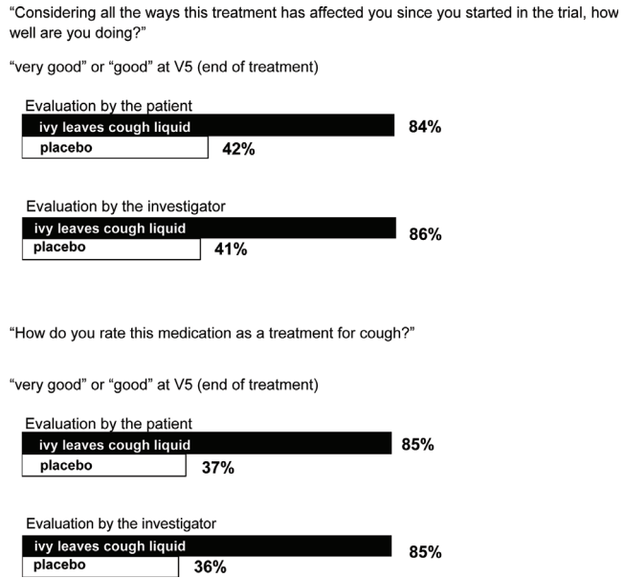

Fig. 4: Efficacy assessed by GEA at V5 (FAS)

2.2. *Tolerability and safety*

AEs occurred in 21 of 181 (11.6 %) subjects (active treatment: n=9, placebo: n=12). Of these, 18 subjects had one single AE, one subject in the active treatment group and one subject in the placebo group had two AEs each, another subject in the placebo group had four AEs. All reported AEs were relatively well-balanced between the treatment groups and are closely connected to the underlying disease as cough ("worsening of cough"), middle ear effusion, and sinusitis. It was mainly at one of the five sites where the investigator evaluated slight worsenings of 2 to 5 mm on VAS in the cough assessment as AEs. However, in most of these cases BSS and VCD remained at the same level.

For all PP subjects in both treatment groups the compliance was rated as "good" (> 80 % of the calculated theoretical intake had been applied).

A total of 8 subjects (active treatment: n=5, placebo: n=3) included in the clinical trial had an age of 65 – 75 years. The safety profile in this subgroup did not show any difference to the profile observed in the younger study population.

All AEs in this clinical trial were non-serious, of mild or moderate severity and not drug-related.

3. Discussion

The aim of this clinical trial was to evaluate the efficacy and safety of ivy leaves cough liquid (EA 575®) compared with placebo applied three times daily in adults with acute cough. Treatment of cough with ivy leaves extracts is a well-established phytotherapeutical approach in a number of countries. However, the number of recent clinical studies in compliance with present GCP guidelines is still limited. Therefore it appeared reasonable to document the efficacy of such a treatment based on standardized subjective parameters to assess patient-related aspects of cough. The impact of the treatment is one key indicator on the patients' clinical conditions. It was decided to use all of the above cited score systems to get a broad symptom-oriented impression of aspects of the effect of the treatment.

The primary efficacy outcome cough severity assessed by VAS over the treatment period of 7 days ($AUC_{0\text{-}168\ h}$) showed a significantly higher efficacy of ivy leaves cough liquid compared to placebo ($p < 0.0001$).

The known self-limiting nature of acute cough is clearly demonstrated in the reduction of symptoms observed in the placebo group, as highlighted in the approaching of the VAS curves in the attached graphs (Fig. 2). Therefore a faster reduction of symptoms in the treatment group is important for the efficacy assessment. The published MID for VAS (17 mm) in acute cough was achieved after 3 days of treatment for ivy leaves cough liquid and after 4 days for placebo (Table 1) (Lee et al. 2013). Also, the rate of cough severity assessed by VCD score and BSS differed significantly between verum and placebo at each visit in the treatment period. The mean VAS over the observation period of 14 days showed the same significance level. EA 575® showed a remarkably fast onset of action compared to placebo in all clinically relevant variables providing significant relief within the first 48 hours of treatment. Even 7 days after the end of treatment (V6) a significant treatment advance was detected in comparison to placebo. According to the global assessment of efficacy significantly more subjects in the active treatment group reached a higher level of satisfaction regarding efficacy and tolerability of the product.

A center effect at site 4 was detected. In this center no difference in terms of efficacy between treatment and placebo could be detected. However, this is not a generally surprising finding since the probability that in a multi-center trial with 5 sites at least one of the sites shows an 'effect reversal' is greater than 40 % (Senn 1997). Therefore, Senn recommends not to over-interpret results from single sites. No other center effect was detected. There was no pattern indicating any specific AE related to the study drug or specifically affecting any of the study subjects. None of the AEs in this clinical trial was drug-related. The very good tolerability of EA 575® was already shown in earlier clinical and non-interventional studies (Lang et al. 2015). However, the tolerability in this RCT was even better than in other studies (Kraft 2004; Fazio et al. 2009).

Only limited data in clinical trials are available for patients of the older generation. Although in this trial a small number of patients older than 65 years (n=8) have been included the ivy leaves cough liquid was safe also in these subjects. This seems worth mentioning considering the need for a well-tolerated medication in this population.

The results of this ICH-GCP clinical trial are clear-cut and consistent concerning all objectives of efficacy and safety variables. This supports the statement of Holzinger and Chenot (2011) who claimed that convincing evidence is dependent on methodology and the existence of placebo controls.

For the treatment of subjects with acute cough, the ivy leaves cough liquid containing EA 575® is an efficacious option with a very good tolerability and therefore represents an alternative to chemical cough medicine for adults. The clinical trial confirms again the data obtained from studies of more than 65.000 patients, showing that adults and children with cough profit from EA 575® preparations.

4. Experimental

4.1. Setting

This randomized, controlled, double-blind, multi-center trial was conducted in five ambulatory trial sites (4 general practitioners, 1 ear, nose and throat specialist) in Germany. The aim was to evaluate the efficacy and safety of liquid containing ivy leaves dry extract vs. placebo in the treatment of acute cough, in particular with regard to cough severity.

4.2. Subjects

Subjects aged 18 to 75 years of both genders suffering from acute cough with symptoms lasting 2 to 3 days prior to treatment were included in the clinical trial (Table 4). Subjects could be of any ethnicity and needed to be able to understand and to comply to trial instructions. Health needed to be satisfactory except for the cough as determined by the investigator based on medical history and physical examination. Other inclusion criteria were a cough severity score of at least 50 mm on a 100 mm VAS, an acute BSS of at least 10 points and a VCD score of at least 2 points. Exclusion criteria were allergic bronchial asthma, bronchial hyperreactivity, chronic bronchitis, other chronic or inherited lung disease, urticaria, severe allergic diathesis and known hypersensitivity against any excipient of the applied drugs. Patients with any gastrointestinal complaints within 7 days before inclusion, known chronic and significant diseases, pregnancy, lactation and treatment with drugs which are known to cause cough were excluded. The lack of such chronic conditions as highlighted above was confirmed by thorough evaluation of patient's anamnesis. During the clinical trial any medications or treatments that may influence acute bronchitis or mucociliary clearance were prohibited. All subjects were included in the clinical trial from January to June 2015.

4.3. Treatment

Eligible patients were randomized in a 1:1 ratio to receive active treatment (containing 35 mg EA 575® ivy leaves dry extract [5 - 7.5:1], in 5 ml, extraction solvent: ethanol 30 % (m/m), or an inactive, adequate placebo t.i.d. (three times daily). A randomization list and emergency envelopes were produced by an independent statistician with a block size of 4 using the software SAS (Statistical Analysis System). Each eligible patient received the lowest available randomization number which assigned the patient to one of the two treatment arms. All investigational medicinal products (IMP) were obtained from Engelhard Arzneimittel GmbH & Co. KG in 200 ml bottles. Approximate time of drug intake during the trial had to be recorded on the paper Case Report Form. Monitoring of drug intake compliance was performed by weighing the IMP at V1 and at V5. The use of IMP was calculated and compared with the calculated theoretical intake in order to evaluate patient's compliance.

4.4. Efficacy and safety assessment

The primary efficacy outcome was cough severity assessed by VAS over the whole treatment period (AUC over 7 days, V1, V2, V3, V4 and V5). Secondary end points included the cough severity on the BSS and on the VCD Score over the whole treatment period (V1 – V5), cough severity on VAS over the whole observation period (V1 – V6, 14 days in total) and a global efficacy assessment (GEA) at V5 and V6. The GEA consisted of two questions regarding efficacy and was completed by the subjects and the investigators using a 5-point rating scale. AEs were documented from inclusion until V6 and the tolerability was assessed by the patient and the investigator at V5 and V6.

4.5. Statistical methods

The sample size calculation was based on the assumption that the effect size for the difference in cough severity was 0.45, two-sided α was 5 %, power was 80 % and the dropout rate was 10 %. The data was un-blinded after database lock. The primary efficacy variable $AUC_{0\text{-}168\ h}$ of CS was compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment group and site as main effects and baseline value as a covariate. Secondary efficacy variables were analyzed by means of Mann-Whitney tests and Cochran-Mantel-Haenszel tests, respectively. Missing values for the dropouts were substituted by the last-observation-carried-forward principle (LOCF).

The incidence of all treatment-emergent AEs was tabulated after grouping by system organ class and preferred term. AEs were evaluated taking in consideration frequency, intensity and causality with regard to the IMP.

4.6. Ethical and legal aspects

The clinical trial was conducted according to ICH-GCP, the principles of the Declaration of Helsinki (1996) and Tokyo (1975), standard operating procedures and the clinical trial protocol. Favorable opinion from the responsible Ethics Committee (EC) of the Ärztekammer Nordrhein and approval from the competent authorities (CA) were both received before recruitment of the first subject (EC: 15Dec2014, trial registration number 2014403; BfArM (CA): 17Nov2014, approval number 4040217; EudraCT No. 2014-003590-41). For all patients provided written informed consent was obtained prior to trial inclusion.

Contributions: AS was principal investigator of this RCT and gave medical advice for this paper. MB was responsible statistician and gave statistical advice and BMG was CRO Chief Medical Officer and provided medical advice for this paper as well. MSK was project manager and wrote most of the article, CS was sponsor Medical Director and contributed to the manuscript.

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Conflicts of interest: MSK and CS are employees of the Engelhard Arzneimittel GmbH & Co. KG.

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