PAES information

Title	ASSESSMENT OF THE EFFICACY OF THE MEDICINAL PRODUCT HEDUSSIN® IN THE TREATMENT OF PRODUCTIVE (WET) COUGH
Version identifier of the final study report	EUP/HED/008/2016
Date of last version of the final study report	10.10.2017
EU PAS register number	EUPAS21094
Active substance	Hedera helix extract
Medicinal product	HEDUSSIN® syrup
Product reference	Phytopharm Klęka S.A., Klęka 1, 63-040 Nowe Miasto nad Wartą
Procedure number	Not applicable
Marketing authorisation holder	Phytopharm Klęka S.A., Klęka 1, 63-040 Nowe Miasto nad Wartą
Joint PAES	No
Research question and objectives	A PAES involving outpatients with productive cough in the course of respiratory tract infections treated with HEDUSSIN® by paediatricians, general practitioners, allergologists and pulmonologists from November 2016 to March 2017. This was non-randomized, non-interventional, multicentre. open-label, post authorisation efficacy study. The study protocol assumed a recruitment of children with productive cough in the course of infection. The inclusion criteria were prescription of medicinal product HEDUSSIN for therapy of productive (wet) cough study for children aged from 2 to 12 years. The study has been imposed as an obligation by EU competent authorities as a condition to the Marketing Authorisation in line with the requirements of Directive 2001/83/EC and ART 1(15) and ART 107m (1) and Regulation EC No 726/2004 (REG) Art 28b. According to Polish law, PAES studies are not interventional when patients will not undergo any additional medical procedures or monitoring, and are no medical experiments. Therefore, it did not require the approval a bioethical committee and it was not necessary to obtain informed consent from patients for inclusion in this study. This study collected real life data concerning subsidence of respiratory symptoms - especially cough (its strength) in the course of respiratory tract infection during the control visit (after 7-14 days) in a 5-step scale– Bronchitis Severity Score (BSS). Monitoring of ADRs was routine in patients managed by the physicians.
Country of study	POLAND
Author	prof. Zbigniew Doniec MD, PhD Institute of Tuberculosis and Lung Diseases, prof. Jana Rudnika 3B street, 34-700 Rabka Zdrój prof. Jerzy Chudek MD,PhD Department of Internal Diseases and Oncological Chemotherapy, School of Medicine in Katowice, Silesian Medical University in Katowice, Poland

Marketing authorisation holder

Marketing Authorisation Holder	Phytopharm Klęka S.A., Klęka 1, 63-040 Nowe Miasto nad Wartą

MAH contact person	Karina Schönknecht, Scientific Information Department Manager, QPPV

Table of contents

1. Abstract 5
2. List of abbreviations 8
3. Investigators 9
4. Other responsible parties 9
5. Milestones 9
6. Rationale and background 11
7. Research question and objectives 11
8. Amendments and updates 12
9. Research methods 12
9.2. Setting 12
9.3. Subjects 12
9.4. Variables 13
9.5. Data sources and measurement 13
9.6. Bias 14
9.7. Study size 14
9.8. Data transformation 14
9.9. Statistical methods 14
9.9.1. Main summary measures 15
9.9.2. Main statistical methods 15
9.9.3. Missing values 15
9.9.4. Sensitivity analyses 15
9.9.5. Amendments to the statistical analysis plan 15
9.10. Quality control 15
10. Results 15
10.1. Participants 15
10.2. Descriptive data 16
10.3. Outcome data 19
10.4. Main results 22
10.5. Other analyses 26
10.6. Adverse events/adverse reactions 26
11.1. Key results 26
11.2. Limitations 27
11.3. Interpretation 27
11.4. Generalisability 27
12. Other information 27
13. Conclusion 28
14. References 29
Appendices 29
Annex 1. List of stand-alone documents 30

1. Abstract

Title

Assessment of the efficacy of the medicinal product Hedussin® in the treatment of productive (wet) cough (EUP/HED/008/2016)

Final report ver. 2. (03-DEC-2017)

prof. Jerzy Chudek MD.PhD

Department of Internal Diseases and Oncological Chemotherapy, School of Medicine in Katowice, Silesian Medical University in Katowice, Poland

Keywords: respiratory tract infection; productive cough; Hedera helix extract;

Rationale and background: Study had been performed as a non-randomized, non-interventional open-label, post authorisation efficacy study (PAES) to evaluate the efficacy of a *Hedera helix* extract - HEDUSSIN® syrup (Phytopharm Klęka S.A., Poland).

The objectives of the study were to assess efficacy of HEDUSSIN® syrup in the therapy of productive cough in the course of respiratory tract infections in outpatients in daily clinical practice (real life).

Research question and objectives: Monitoring of the authorized medical product HEDUSSIN® efficacy in the therapy of productive (wet) couth in the course of respiratory tract infection in daily clinical practice (real life) in line with the requirements of Directive 2001/83/EC and ART 1(15) and ART 107m(1) and Regulation EC No 726/2004 (REG) ART 28b.

Primary objective was efficacy of treatment with authorized medical product HEDUSSIN® in the therapy of productive cough in the course of respiratory tract infection in daily clinical practice (real life).

Secondary objective was assessment of medical product HEDUSSIN® safety in the therapy of respiratory tract infection in daily clinical practice (real life).

Study design: The study was initiated voluntarily, managed, and financed by a MAH. The study was designed as non-randomized, non-interventional, multicentre. open-label, post authorisation efficacy study (PAES).

Setting: Efficacy of HEDUSSIN® (syrup) was assessed from November 2016 to March 2017 by 38 physicians in outpatients with productive cough in the course of respiratory tract infection during a control visit after 7–14 days from the prescription of the medicinal product.

Subjects and study size, including dropouts: The study involved 480 outpatients with productive cough in the course of respiratory tract infection prescribed with HEDUSSIN® syrup. Sixteen patients met the exclusion criteria and were excluded from the analysis. One-hundred-eleven patients (18.4% of the study population) referred to a control visit with a delay (after more than 14 days). There were no dropouts.

Variables and data sources: The study was supported by a Study Questionnaire (SQ) that included clinical diagnosis (type of respiratory tract infection), Bronchitis Severity Score (BSS), temperature, assessment of sleep and well-being deterioration, prescription of antibiotic therapy, concomitant diseases and their medication, ADRs reported by the patient.

Results: The study group consisted of 464 patients (mean age 5.8 ± 2.7 years), including 273 patients with viral and 62 with bacterial upper respiratory tract infections, and 109 with acute bronchitis. The intensity of productive cough (mean 2.3 ± 0.7 points) was usually moderate (52.4) or severe (36.4).

Hedussin® syrup was usually prescribed in the dose of 2 or 4 ml twice daily, in direct relation to patient's age (mean age was 3.7 ± 1.3 and 7.8 ± 1.9 years respectively).

Before the control visit, cough subsided in 25.4% of patients (N = 118), while an improvement was reported in 93.3% (90.1% with viral upper respiratory infection, 96.8% with bacterial upper respiratory tract infections and 99.1% with acute bronchitis, p = 0.003). Improvement in chest pain on coughing was reported in 84.7%, of wheezing in 90.0%, of dyspnoea in 88.7%, and of rales at auscultation in 94.8%. In addition, decline or normalization of body temperature was found in 96.0% of patients. An improvement in well-being was reported in 89.2% of children, and in feelings of weakness in 77.2%.

In the subgroup of patients referred to control visit between 7 and 14 days, coughing resolved (27.6%) or their strength decreased (67.3%) in total of 94.9%. An improvement in chest pain on coughing was reported in 83.5%, of wheezing in 91.2%, of dyspnoea in 88.0%, and of rales at auscultation in 96.3%. Body temperature lowed or normalized in 96.3%. In addition well-being and feelings of weakness improved in 87.8% and 76.5%, respectively.

The sub-analysis performed in the non-antibiotic-treated group showed similar proportions of patients who received improvement during the follow-up period.

No ADR or discontinuation of treatment due to lack of tolerance has been reported in the study population.

Discussion: The results of this PAES support the effectiveness of HEDUSSIN® prescribed for the treatment of productive cough in the course of respiratory tract infections irrespective of antibiotic therapy. In addition, this study points to the safety of medicinal product HEDUSSIN® in children with productive cough during respiratory tract infections.

In conclusion: The results of this PAES support the efficacy of HEDUSSIN® prescribed for the treatment of productive cough in the course of respiratory tract infections. HEDUSSIN® is well tolerated by sick children aged 2 to 12 years.

Marketing Authorisation Holder

Phytopharm Klęka S.A., str. Klęka 1, 63-040 Nowe Miasto nad Wartą

Names and affiliations of principal investigator

Principal Investigator	prof. Zbigniew Doniec MD, PhD Institute of Tuberculosis and Lung Diseases, prof. Jana Rudnika 3B street, 34-700 Rabka Zdrój

2. List of abbreviations

TERM	DEFINITION
AE	Adverse Event
ADR	Adverse Drug Reaction
BSS	Bronchitis Severity Score
CA	Competent Authority
CIOMS	Council for International Organizations of Medical Sciences (here: refers to CIOMS report form for adverse event reporting)
CRO	Contract Research Organisation
DM	Data Management
EMA	European Medicines Agency
GVP	Good Pharmacovigilance Practice
IMP	Investigational Medicinal Product
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PAES	Post-Authorisation Efficacy Study
PDS	Pharmacovigilance Drug Safety
PLRP	Person Locally Responsible for Pharmacovigilance
PM	Project Manager
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SQ	Study questioner
URPL	The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Polish: Urząd Rejestracji Produktów Leczniczych)

3. Investigators

Principal Investigator	prof. Zbigniew Doniec MD, PhD Institute of Tuberculosis and Lung Diseases, prof. Jana Rudnika 3B street, 34-700 Rabka Zdrój
Coordinating Investigators	**prof. Jerzy Chudek MD, PhD** Department of Internal Medicine nd Oncological Chemotherapy, School of Medicine in Katowice, Medical University of Silesia in Katowice, Poland **Agnieszka Almgren-Rachtan MD, PhD** Department of Pharmacovigilance Europharma Rachtan Co. Ltd. Katowice, Poland

4. Other responsible parties

Head of MAH Pharmacovigilance Department	Karina Schönknecht, Scientific Information Department Manager, QPPV
Product Manager	Karina Schönknecht, Scientific Information Department Manager, QPPV

5. Milestones

Milestone	Planned date	Actual date
Start of data collection	1.12.2016	1.12.2016
End of data collection	31.03.2017	31.03.2017

Registration in the EU PAS register	22.08.2017	28.09.2017
Study progress report	31.05.2017	31.05.2017
Final report of study results	15.10.2017	15.10.2017

6. Rationale and background

HEDUSSIN® (Phytopharm), containing a dry extract of ivy leaves in the form of syrup obtained a marketing authorization No. 22652 on 20th August 2015. No studies have been performed on the efficacy of this medicinal product in the Polish population.

Substances used in the treatment of productive cough exerts three main effects: secretolytic - increasing the volume of discharge, mucolytic - decreasing viscosity of the discharge, and mucokinetic - increasing the effectiveness of ciliary transport. One of the expectorants is a plant medicine derived from ivy leaves. The ivy extract contains triterpene saponins (hederacoside B and C), which give it its secretory and antioxidant properties.

Saponins stimulate the cough reflex and increase the secretion of secretions by the reflex nerve reflex, by irritating the nerve endings in the gastric mucosa. In addition, ivy leaf extract exhibits spasmolytic activity against smooth bronchial muscles, which further facilitates the evacuation of the discharge [Szumny D et al.; 2007]. The secretolytic, mucolytic and spasmolytic mechanism of ivy leaves has been demonstrated by the microscopic method with spectroscopic fluorescence. α-hederin derivatives from hetacoside C, that indirectly reduces the G-protein-coupled receptor kinase 2 (GRK2) activity, leading to inhibition of β2-adrenergic receptor internalization, and enhancing β2-adrenergic activation [Schulte-Michels J et al.; 2016]. Stimulation of β2-adrenergic receptors increases the production of surfactant by type II alveocytes in pulmonary vesicles [Sieben A et al.; 2009]. Activation of β2-adrenergic receptors also results in smooth muscle relaxation, reducing their elastic resistance, and further enhances bronchial-mucosal clearance [Runkei F et al.; 2005, Wolf A et al.; 2011, Greunke C et al.; 2015]. Clinical studies have also shown potential anti-inflammatory and antifungal effects of ivy leaf extract.

The efficacy of ivy leaf extract in children 2-10 years of age with acute bronchitis is comparable to acetylcysteine from which it was better tolerated [4]. Clinical trials on the efficacy of ivy leaf extracts have also been conducted in adult populations with both acute and chronic respiratory diseases (obstructive pulmonary disease, chronic bronchitis) [EMA report, Blumenthal M, et al. 2000, Zeil S et al.; 2014, Hofmann D et al.; 2003].

The treatment with ivy leaves extract should last for approximately 7 days [Podlewski J. & Chwalibogowska-Podlewska A. 2017]. Preparations should not be used in the evening. Caution is advised in their administration in patients with gastritis and peptic ulcers.

7. Research question and objectives

Monitoring of the authorized medical product HEDUSSIN® (syrup) efficacy in the therapy of productive cough in daily clinical practice (real life) in line with the requirements of Directive 2001/83/EC and ART 1(15) and ART 107m(1) and Regulation EC No 726/2004 (REG) Art 28b.

Primary objective was efficacy of treatment with authorized medical product HEDUSSIN® in the therapy of productive cough in the course of respiratory tract infection in daily clinical practice (real life).

Secondary objective was assessment of medical product HEDUSSIN® safety in the therapy of respiratory tract infection in daily clinical practice (real life).

The study was initiated voluntarily, managed, and financed by a MAH.

8. Amendments and updates

None

9. Research methods

Non-randomized, non-interventional open-label, post authorisation efficacy study (PAES).

9.1. Study design

The study was designed as non-randomized, non-interventional, multicentre, open-label, post authorisation efficacy study (PAES) obtaining the recruitment of 500 outpatients with productive cough in the course of acute respiratory tract infection by 50 paediatricians, general practitioners, allergologists and pulmonologists, prescribed with HEDUSSIN® syrup. Efficacy of the therapy with HEDUSSIN® was assessed during the control visit after 7–14 days based on improvement in Bronchitis Severity Score (BSS), temperature, quality of sleep and well-being.

9.2. Setting

Thirty-eight (38) paediatricians, general practitioners, aerologists and pulmonologists (of 50 planed) working in outpatient clinics were recruited via the Internet and by medical representatives in all territorial areas (voivodeships) in Poland.

The study was performed and data collected from November 2016 to March 2017.

9.3. Subjects

The inclusion criteria was the prescription of HEDUSSIN® syrup in therapy of productive cough in a child aged from 2 to 12 years in doses recommended by Summary of Product Characteristics.

The exclusion criteria were (in line with Summary of Product Characteristics): known hypersensitivity to the active substance - ivy leaf extract, other Araliaceae plants or excipients (noncrystalline liquid sorbitol, potassium sorbate, xanthan gum, anhydrous citric acid), concomitant corticosteroid, β_2-mimetics, theophylline or other drugs that can inhibit cough reflexes for the last 7 days prior to inclusion into the study, respiratory tract cancer.

9.4. Variables

The study was supported by a Study Questionnaire (SQ) that included questions concerning clinical diagnosis (type of respiratory tract infection), Bronchitis Severity Score (BSS), temperature, assessment of sleep deterioration (scored as: interrupted sleep, shallow sleep, insomnia) and well-being deterioration (in 10 pts. VAS), feelings of weakness (in 5 pts. scale: any, mild, moderate, severe, very severe), prescription of antibiotic therapy, concomitant diseases and their medication. AEs reported by the patient and whether AEs were related to or probably related to, the use of HEDUSSIN® syrup (listed for the original product characteristics with the possibility of adding new ones).

Outcomes:

1. Efficacy data for HEDUSSIN® was assessed based on changes in the intensity of cough, chest pain on coughing, wheezing, dyspnoea, and of rales at auscultation, the components of BSS, between initial and control visit.
2. Safety data: the occurrence of ADRs (AEs related to HEDUSSIN®), reported by outpatients, during control visits (check-ups), after the initiation therapy with HEDUSSIN®.

The data was entered into a Study Questionnaire completed within the initial and subsequent control visits.

Exposures: The exposure to HEDUSSIN® was calculated from the all patient, that were prescribed with the syrup during initial visit. The prescribed doses were recorded in the study questionnaire. Pharmacokinetic was not assessed.

9.5. Data sources and measurement

A Study Questionnaire, completed by the physicians, during two visits (initial and control) was the primary data sources.

Description of Study Questionnaire

The first part of the questionnaire included demographic data (gender, age, place of residence), clinical diagnosis of respiratory tract infection, chronic comorbidities and their medication, BSS, body temperature, assessment of sleep deterioration, assessment of well-being and feelings of weakness, recommended dose of HEDUSSIN® syrup and frequency of application, prescription of an antibiotic, other symptomatic medication and dietary supplements.

The second part of the questionnaire concerned the continuation / discontinuation of therapy with HEDUSSIN® and eventually cause of discontinuation (ADR, the lack of availability in the local pharmacy, the lack of clinical response, resolution of the cough), currently used dose of HEDUSSIN® and frequency of application, new comorbidities and their medication, BSS, body temperature, assessment of sleep deterioration, assessment of well-being and feelings of weakness, AEs as reported by the patient, and whether AEs were related to or probably related to the use of HEDUSSIN® (listed in the Summary of Product Characteristic)-.

The data was manually entered into a database with the use of a data entry mask. All records were verified for correctness and completeness.

All AEs, their severity, and potential relation to the use of HEDUSSIN® reported by physicians, were analysed, and if necessary, reclassified by the safety team in the Pharmacovigilance Department. Cases of doubt were resolved after telephone conference with the reporting physician.

9.6. Bias

Not applicable

9.7. Study size

The study size of 500 patients was determined as an appropriate sample size, taking into account some practical limitations, and was not supported by statistical power analysis.

9.8. Data transformation

Not applicable

9.9. Statistical methods

Intention-to-treat analysis was performed after exclusion of patients not meeting inclusion criteria (the lack productive cough; N=4) or meeting exclusion criteria (coexisting bronchial asthma; N=12). In addition, a sub-analysis of patients that referred to a control visit without a delay (in a period of 7 - 14 days from initial visit). There was no patient that stop the treatment for any reason or were lost to follow-up. However, 111 patients (18.4% of the study population) referred to a control visit with a delay (after more than 14 days).

The final analysis included total of 464 patients, and 369 in the sub-analysis of referred to a control visit in a period of 7 to 14 days.

Analyses were performed using the STATISTICA 11.0 PL (StatSoft Polska, Kraków, Poland). A “p” value of less than 0.05 was considered statistically significant.

9.9.1. Main summary measures

All data are expressed as percentages or means with standard deviations.

9.9.2. Main statistical methods

The χ^2 and t-student tests were used to compare variables between time points within the group and between subgroups.

9.9.3. Missing values

No records were excluded from the analysis of drug safety.

Some data sets were incomplete (mostly medication of comorbidities), however no systematic irregularities were found.

No data imputation and interpolation was performed.

9.9.4. Sensitivity analyses

Not applicable

9.9.5. Amendments to the statistical analysis plan

Not applicable

9.10. Quality control

Before statistical analysis consistency of data was checked. The database was secured against unauthorised changes.

10. Results

10.1. Participants

A total of 464 patients diagnosed with productive cough in the course of respiratory tract infection were recruited and observed by 38 physicians. Data concerning eligible patients not included in the study was not collected. Therefore, the data concerning non-participants are not available.

10.2. Descriptive data

Characteristics of study group are given in Table 1. The mean age of study patients was 5.8 ± 2.7 years. Concomitant chronic diseases were reported in 44 patients (9.4% of study cohort) and are listed in the Table 1.

During the initial visit, productive cough was reported in all 464 patients - Table 2. In most patients (88.8%) it was moderate or severe. Chest pain on coughing was reported by 25.4% of children, wheezing in 36.6%, dyspnea (usually mild or moderate) in 34.3%, and rales at auscultation in 58%.

Among included 47.4% had fever. Sleep deprivation, mainly intermittent sleep, was reported by 61.3% of patients. In addition, all patients reported well-being deterioration and 84.9% experienced filling of weakness - Table 3.

Antibiotic therapy was prescribed in 36.4% of patients.

Table 1: Characteristics of the study group of patients with productive cough (N=464).

Age [years]	5.8±2.7
Sex [n; %]	
Boy	200; 43.0
Girl	264; 57.0
Place of residence [n; %]	
City	370; 79.7
Village	94; 20.3
Clinical diagnosis of the illness [n; %]	
Viral upper respiratory tract infection	273; 58.9
Bacterial upper respiratory tract infection	62; 13.4
Acute bronchitis	109; 23.5
Otitis externa	1; 0.2
Otitis media	3; 0.6
Rhinopharyngitis	1; 0.2
Acute respiratory tract infection multiple or undefined	7; 1.5
Bacterial pneumonia	1; 0.2
Pneumonia	6; 1.3
Chronic rhinopharyngitis	1; 0.2
Concomitant diseases [n; %]	44; 9.4
Allergic rhinitis	33; 75.0
Chronic sinusitis	2; 4.5
Gastro-oesophageal reflux	1; 2.3
Allergy	2; 4.5
Other	6; 13.7

Table 2: Clinical assessment of sign and symptoms (BSS) during initial visit [N=464].

	BSS	

	0	1	2	3	4	Mean±SD
Cough [%]	0	8.6	52.4	36.4	2.6	2.3±0.7
Dyspnoea [%]	65.7	23.5	8.0	2.8	0	0.5±0.4
Rales at auscultation [%]	42.0	22.0	24.6	11.0	0.4	1.1±0.9
Chest pain on coughing [%]	74.6	19.4	3.7	2.4	0	0.3±0.2
Wheezing [%]	63.4	23.9	9.1	3.7	0	0.5±0.3
Total [pts]						5.0±4.0

0 – No symptom; 1 – mild; 2 – moderate; 3 – severe; 4 – very severe

Table 3: Additional clinical data during initial visit [N=464].

Body temperature [ºC]	**37.5±0.9**
Normal 36.6 ± 0.3 ºC [n; %]	61; 13.1
Increased 37.0-37.9 ºC [n; %]	183; 39.4
Mild fever 38.0-38.4 ºC [n; %]	161; 34.7
Moderate fever 38.5-39.4 ºC [n; %]	51; 11.0
Severe fever ≥ 39.5 ºC [n; %]	8; 1.7
Sleep deterioration [n; %]	**284; 61.3**
Interrupted sleep [n; %]	249; 87.8
Shallow sleep [n; %]	31; 11.0
Insomnia [n; %]	3; 1.1
Well-being [pts]	**5.9±2.1**
0 – very bed [%]	0
1-3 [%]	70; 15.1
4-5 [%]	145; 31.1
6-7 [%]	121; 26.1
8-9 [%]	113; 24.4
10 - fine [%]	15; 3.2
Feelings of weakness [x]	**1.4±0.9**
0 - Any	70; 15.1
1 – Mild	185; 39.9
2 – Moderate	167; 36.0
3 – Severe	41; 8.8
4 – Very severe	1; 0.2
Antibiotic prescription [n; %]	**169; 36.4**

HEDUSSIN® syrup was usually prescribed in a dose of 2 or 4 ml twice daily (Table 4). The dose was related to the patient's age. Mean age in subgroups prescribed with lower and higher doses was 3.7 ± 1.3 and 7.8 ± 1.9 years, respectively (p <0.001). In 15 subjects the prescribed doses of the medicinal product were different from those recommended in the leaflet (i.e.: 1.5 ml, 2.5 ml and 5 ml).

Table 4: Prescribed HEDUSSIN® doses [N=464].

	[n; %]
1.5 ml twice a day	2; 0.4
2 ml twice a day	221; 47.6
2.5 ml twice a day	6; 1.3
3 ml twice a day	3; 0.6
4 ml twice a day	226; 46.3
5 ml twice a day	7; 1.5
6 ml twice a day	10; 2.2

10.3. Outcome data

All four-hundred-sixty-four patients were referred to the control visit after a median period of 8 days (range 5 – 60 days). Among them there was 369 children that were referred in the period from 7 to 14 days. As the consequence of this fact we performed the main analysis of the efficacy data for the whole group (N=464) of patients and a sub-analysis for this smaller subgroup (N=369) of children.

In the subgroup referred within the period from 7 to 14 days, 301 patients (81.6%) continued the use of Hedussin®.

In the whole group of patients [N = 464] before the control visit, cough subsided in 118 patients (25.4%) - Table 5. The percentage of patients with chest pain on coughing decreased significantly ($p < 0.001$) to 7.5%, of those with dyspnoea to 8.6%, with wheezing to 9.1% and with rales at auscultation to 16.8%.

Significant decrease ($p <0.001$) was observed in the proportion of patients with increased temperature and fever (10.8 and 1.5%, respectively). There was a significant decrease ($p <0.001$) in the proportion of patients still reporting sleep deterioration (to 3.6%), worsening of well-being (to 53.9%) and feeling of weakness (up to 47%) - Table 6. There was even greater decrease in the occurrence of patients feeling unwell (0-5 pts) – from 46.3% to 3.7% ($p < 0.001$); and feeling of moderate to very severe weakness (2-4 pts) from 45.0% to 6.4% ($p < 0.001$). Further antibiotic therapy was recommended in 19 3% of patients.

Similar observations were made in a subgroup not treated with antibiotics (Tab. 5 and 6).

Table 5: Clinical assessment of sign and symptoms (BSS) during a control visit [N=464].

	BSS					
	0	1	2	3	4	Mean±SD
Whole group [N=464]						
Cough [%]	25.4	63.6	10.1	0.9	0	0.9±0.6
Dyspnoea [%]	91.4	8.0	0.4	0.2	0	0.1±0.3
Rales at auscultation [%]	83.2	13.8	2.8	0.2	0	0.2±0.5
Chest pain on coughing [%]	92.5	7.1	0.4	0	0	0.1±0.3
Wheezing [%]	90.9	7.8	1.3	0	0	0.1±0.4
Total [pts]						1.4±1.1
Without antibiotic prescription [N=295]						
Cough [%]	28.8	60.3	9.2	0.7	0	0.8±0.6
Dyspnoea [%]	92.2	6.1	0.7	0	0	0.1±0.3
Rales at auscultation [%]	89.5	7.5	1.7	0.3	0	0.1±0.4
Chest pain on coughing [%]	93.2	5.4	0.3	0	0	0.1±0.3
Wheezing [%]	91.9	6.4	0.7	0	0	0.1±0.3
Total [pts]						1.2±0.9

0 – No symptom; 1 – mild; 2 – moderate; 3 – severe; 4 – very severe

Table 6: Additional clinical data during a control visit [N=464].

	Total [N=464]	**Non treated with antibiotic [N=295]**	**Treated with antibiotic [N=169]**	p
Body temperature [ºC]	**36.4±0.4**	**36.3±0.4**	**36.5±0.4**	Ns
Normal 36.6 ± 0.3 ºC [n; %]	407; 87.7	267; 90.4	141; 83.2	0.07
Increased 37.0-37.9 ºC [n; %]	50; 10.8	24; 8.2	25; 15.0	
Mild fever 38.0-38.4 ºC [n; %]	4; 0.9	2; 0.7	2; 1.2	
Moderate fever 38.5-39.4 ºC [n; %]	3; 0.6	2; 0.7	1; 0.6	
Severe fever ≥ 39.5 ºC [n; %]	0	0	0	
Sleep deterioration [n; %]	**17; 3.6**	**12; 4.0**	**5; 3.0**	Ns
Interrupted sleep [n; %]	11; 2.4	8; 2.8	3; 1.5	Ns
Shallow sleep [n; %]	5; 1.0	3; 1.2	2; 1.2	Ns
Insomnia [n; %]	1; 0.3	1; 0.4	0	Ns
Well-being [pts]	**9.0±1.4**	**9.0±1.5**	**9.0±1.1**	Ns
0 – very bed [%]	0	0	0	Ns
1-3 [%]	5; 1.1	5; 1.7	0	
4-5 [%]	12; 2.6	8; 2.7	4; 2.4	
6-7 [%]	26; 5.6	19; 6.5	7; 4.2	
8-9 [%]	207; 44.6	111; 37.7	94; 55.7	
10 - fine [%]	214; 46.1	152; 51.4	64; 37.7	
Feelings of weakness [x]	**0.6±0.5**	**0.5±0.4**	**0.7±0.6**	Ns
0 - Any	246; 53.0	170; 57.5	74; 43.7	Ns
1 – Mild	188; 40.5	106; 36.0	84; 49.7	
2 – Moderate	15; 3.2	7; 2.4	8; 4.8	
3 – Severe	12; 2.6	10; 3.4	2; 1.2	
4 – Very severe	3; 0.6	2; 0.7	1; 0.6	

In the subgroup referred to a control visit within the period from 7 to 14 days cough subsided before the control visit in 102 patients (27.6%). The percentage of patients with chest pain on coughing decreased to 7.6%, dyspnoea to 8.7%, wheezing to 8.9%, and rales at auscultation to 16.5% $p < 0.001$ (Table 7).

The proportion of patients with increased body temperature and fever decreased significantly ($p < 0.001$) in 9.8 and 1.3% of the patients, respectively. In addition, there was a significant ($p < 0.001$) decrease ($p < 0.001$) in the proportion of patients reporting sleep disorders (to 3.4%), impaired well-being (to 49.9%) and feeling of weakness (to 48%) - Table 8. The percentage of patients feeling unwell (0-5 pts) decreased from 43.1% to 3.3% ($p < 0.001$); and those with feeling of moderate to very severe weakness (2-4 pts) from 46.1% to 5.9% ($p < 0.001$). Similar observations were made in patients not prescribed with antibiotics (Table 8).

Table 7: Clinical assessment of sign and symptoms (BSS) during a control visit in a subgroup referred to a control visit within the period from 7 to 14 days [N=369].

	BSS					
	0	1	2	3	4	Mean±SD
Whole group [N=369]						
Cough [%]	27.6	64.5	7.3	0.5	0	0.8±0.6
Dyspnoea [%]	91.3	7.9	0.5	0.3	0	0.1±0.3
Rales at auscultation [%]	83.5	14.9	1.4	0.3	0	0.2±0.4
Chest pain on coughing [%]	92.4	7.0	0.5	0	0	0.1±0.3
Wheezing [%]	91.1	7.9	1.1	0	0	0.1±0.3
Total [pts]						1.3±1.1
Without antibiotic prescription [N=233]						
Cough [%]	24.8	70.3	4.5	0.3	0	0.8±0.5
Dyspnoea [%]	92.3	7.3	0	0.3	0	0.1±0.3
Rales at auscultation [%]	87.8	11.9	0.3	0	0	0.1±0.3
Chest pain on coughing [%]	93.0	6.6	0.3	0	0	0.1±0.3
Wheezing [%]	91.6	8.0	0.3	0	0	0.1±0.3
Total [pts]						1.0±0.7

0 – No symptom; 1 – mild; 2 – moderate; 3 – severe; 4 – very severe

Table 8: Additional clinical data during a control visit in a subgroup referred to a control visit within the period from 7 to 14 days [N=369].

	Total [N=369]	**Non treated with antibiotic [N=233]**	**Treated with antibiotic [N=136]**	p
Body temperature [ºC]	36.4±0.4	36.3±0.4	36.5±0.4	<0.01
Normal 36.6 ± 0.3 ºC [n; %]	328; 88.9	214; 91.7	115; 84.3	0.07
Increased 37.0-37.9 ºC [n; %]	36; 9.8	16; 7.0	19; 14.2	
Mild fever 38.0-38.4 ºC [n; %]	3; 0.8	2; 0.9	1; 0.7	
Moderate fever 38.5-39.4 ºC [n; %]	2; 0.5	1; 0.4	1; 0.7	
Severe fever ≥ 39.5 ºC [n; %]	0	0	0	
Sleep deterioration [n; %]	13; 3.4	9; 3.7	4; 3.0	<0.001
Interrupted sleep [n; %]	9; 2.5	8; 3.3	1; 1.0	<0.001
Shallow sleep [n; %]	3; 0.7	0	3; 2.0	<0.01
Insomnia [n; %]	1; 0.4	1; 0.6	0	Ns
Well-being [pts]	9.1±1.3	9.1±1.5	9.1±1.1	<0.05
0 – very bed [%]	0	0	0	<0.01
1-3 [%]	4; 1.1	4; 1.7	0	
4-5 [%]	8; 2.2	5; 2.2	3; 2.2	
6-7 [%]	12; 3.3	9; 3.2	3; 2.2	
8-9 [%]	160; 43.4	82; 35.8	76; 56.0	
10 - fine [%]	185; 50.1	133; 57.0	54; 39.6	
Feelings of weakness [x]	0.6±0.5	0.5±0.4	0.8±0.6	Ns
0 - Any	192; 52.0	135; 57.8	55; 40.3	<0.01
1 – Mild	155; 42.0	85; 36.5	72; 53.0	
2 – Moderate	10; 2.7	4; 1.7	6; 4.5	
3 – Severe	9; 2.4	7; 3.0	2; 1.5	
4 – Very severe	3; 0.8	2; 0.9	1; 0.7	

10.4. Main results

Efficacy data for HEDUSSIN® in the whole group [N=464]

In the whole study group, cough subsided in 25.4%, or in severity decreased in 67.9% (in total Improved in 93.3%), followed by decrease in chest pain on coughing reported in 84.7%, wheezing in 90.0%, dyspnoea in 88.7%, and rales at auscultation in 94.8%.

Reduction or normalization of body temperature was reported in 96.0%. The improvement in well-being and feelings of weakness was achieved in 89.2% and 77.2%, respectively.

Some variation in the improvement was observed in relation to the clinical diagnosis (Table 9). Improvement in cough was found in 90.1% of children with viral upper respiratory tract infections, 96.8% of patients with bacterial upper respiratory tract infection and 99.1% of those with acute bronchitis (p = 0.003). The other data are summarized in Table 9.

Table 9: HEDUSSIN® efficacy in the whole analysed group.

	Improvement [N; %]	No improvement [N; %]	Deterioration [N; %]
The whole group [N=464]			
Cough [N=464]	433; 93.3	29; 6.3	2; 0.4
Dyspnoea [N=159]	141; 88.7	16; 10.1	2; 1.3
Rales at auscultation [N=269]	255; 94.8	11; 4.1	3; 1.1
Chest pain on coughing [N=118]	100; 84.7	18; 15.3	0
Wheezing [N=170]	153; 90.0	16; 9.4	1; 0.6
Increased temperature /fever [N=405]	389; 96.0	13; 3.2	3; 0.7
Impaired well-being [N=464]	414; 89.2	27; 5.8	23; 5.0
Feeling of weakness [N=394]	304; 77.2	74; 18.8	16; 4.1
Diagnosed with viral upper respiratory tract infection [N=273]			
Cough [N=273]	246; 90.1	25; 9.2	2; 0.7
Dyspnoea [N=67]	59; 88.1	8; 11.9	0
Rales at auscultation [N=123]	116; 94.3	6; 4.9	1; 0.8
Chest pain on coughing [N=48]	42; 87.5	6; 12.5	0
Wheezing [N=69]	61; 88.4	8; 11.6	0
Increased temperature /fever [N=225]	216; 96.0	8; 3.6	1; 0.4
Impaired well-being [N=273]	229; 83.9	23; 8.4	21; 7.7
Feeling of weakness [N=214]	154; 72.0	50; 23.4	10; 4.7
Diagnosed with bacterial upper respiratory tract infection [N=62]			
Cough [N=62]	60; 96.8	2; 3.2	0
Dyspnoea [N=24]	21; 87.5	2; 8.3	1; 4.2
Rales at auscultation [N=34]	31; 91.2	2; 5.9	1; 2.9
Chest pain on coughing [N=20]	18; 90.0	2; 10.0	0
Wheezing [N=29]	25; 86.2	3; 10.3	1; 3.4
Increased temperature /fever [N=59]	55; 93.2	3; 5.1	1; 1.7
Impaired well-being [N=62]	60; 96.8	1; 1.6	1; 1.6
Feeling of weakness [N=60]	49; 81.7	9; 15.0	2; 3.3
Diagnosed with acute bronchitis [N=109]			
Cough [N=109]	108; 99.1	1; 0.9	0
Dyspnoea [N=54]	49; 90.7	5; 9.3	0
Rales at auscultation [N=94]	91; 96.8	3; 3.2	0
Chest pain on coughing [N=37]	29; 78.4	8; 21.6	0
Wheezing [N=58]	54; 93.1	4; 6.9	0
Increased temperature /fever [N=101]	99; 98.0	2; 2.0	0
Impaired well-being [N=109]	106; 97.2	3; 2.8	0
Feeling of weakness [N=101]	85; 84.2	13; 12.9	3; 3.0

In a subgroup not treated with antibiotics [N = 295], improvement in cough was found in 91.2%. Chest pain on coughing improved in 78.0%, wheezing in 86.4%, dyspnoea in 84.0% %, rales at auscultation in 94.4%. Reduction or normalization of body temperature was shown in 95.8%. The improvement in well-being and feelings of weakness was achieved in 85.8% and 71.6%, respectively. The results obtained in this subgroup were similar to those observed in the whole study group.

There were no differences in improvement in patients with main clinical diagnoses (Table 10). Improvement in cough was reported in 90.1% of viral upper respiratory tract infections, 100% of patients with bacterial upper respiratory tract infection and 100% with acute bronchitis (p = 0.20). The other data are summarized in Table 10.

Table 10: HEDUSSIN® efficacy in the subgroups without antibiotic prescription [N=295].

	Improvement [N; %]	No improvement [N; %]	Deterioration [N; %]
All without antibiotic prescription [N=295]			
Cough [N=295]	269; 91.2	24; 8.1	2; 0.7
Dyspnoea [N=81]	68; 84.0	12; 14.8	1; 1.2
Rales at auscultation [N=142]	134; 94.4	6; 4.2	2; 1.4
Chest pain on coughing [N=59]	46; 78.0	13; 22.0	0
Wheezing [N=88]	76; 86.4	12; 13.6	0
Increased temperature /fever [N=240]	230; 95.8	8; 3.3	2; 0.8
Impaired well-being [N=295]	253; 85.8	22; 7.5	20; 6.8
Feeling of weakness [N=236]	169; 71.6	55; 23.3	12; 5.1
Diagnosed with viral upper respiratory tract infection [N=262]			
Cough [N=262]	236; 90.1	24; 9.2	2; 0.8
Dyspnoea [N=61]	52; 85.2	8; 13.1	1; 1.6
Rales at auscultation [N=117]	109; 93.2	6; 5.1	2; 1.7
Chest pain on coughing [N=45]	38; 84.4	7; 15.6	0
Wheezing [N=66]	57; 86.4	9; 13.6	0
Increased temperature /fever [N=213]	203; 95.3	8; 3.8	2; 0.9
Impaired well-being [N=262]	222; 84.7	21; 8.0	19; 7.3
Feeling of weakness [N=206]	146; 70.9	49; 23.8	11; 5.3
Diagnosed with bacterial upper respiratory tract infection [N=8]			
Cough [N=8]	8; 100	0	0
Dyspnoea [N=3]	2; 66.7	1; 33.3	0
Rales at auscultation [N=2]	2; 100	0	0
Chest pain on coughing [N=3]	2; 66.7	1; 33.3	0
Wheezing [N=4]	4; 100	0	0
Increased temperature /fever [N=6]	6; 100	0	0
Impaired well-being [N=8]	7; 87.5	1; 12.5	0
Feeling of weakness [N=7]	5; 71.4	2; 28.6	0
Diagnosed with acute bronchitis [N=25]			
Cough [N=25]	25; 100	0	0
Dyspnoea [N=17]	14; 82.4	3; 17.6	0
Rales at auscultation [N=23]	23; 100	0	0
Chest pain on coughing [N=11]	6; 54.5	5; 45.5	0
Wheezing [N=18]	15; 83.3	3; 16.7	0
Increased temperature /fever [N=21]	21; 100	0	0
Impaired well-being [N=25]	24; 96.0	0	1; 4.0
Feeling of weakness [N=23]	18; 78.3	4; 17.4	1; 4.3

Efficacy data for HEDUSSIN® in the subgroup referred after 7 to 14 days

In this subgroup improvement – cough resolution (27.6%) or reduction (67.3%) was revealed in 94.9% of patients. Chest pain on coughing subsided in 83.5% initially presenting this sign, wheezing in 91.2%, dyspnoea in 88.0%, rales at auscultation in 96.3%.

Decrease or normalization of body temperature was reported in 96.3% of children. The improvement in well-being was achieved in 87.8% and the reduction in feelings of weakness in 76.5% (Table 11).

Table 11: HEDUSSIN® efficacy in the subgroup referred to a control visit after 7 to 14 days [N=369].

	Improvement [N; %]	No improvement [N; %]	Deterioration [N; %]
Cough [N=369]	350; 94.9	18; 4.9	1; 0.2
Dyspnoea [N=125]	110; 88.0	13; 10.4	2; 1.6
Rales at auscultation [N=219]	211; 96.3	7; 3.2	1; 0.5
Chest pain on coughing [N=91]	76; 83.5	15; 16.5	0
Wheezing [N=137]	125; 91.2	11; 8.0	1; 0.7
Increased temperature /fever [N=324]	312; 96.3	10; 3.1	2; 0.6
Impaired well-being [N=369]	324; 87.8	25; 6.8	20; 5.4
Feeling of weakness [N=319]	244; 76.5	63; 19.7	12; 3.8

10.5. Other analyses

Not applicable

10.6. Adverse events/adverse drug reactions

No adverse drug reactions have been reported by the physicians in the study population prescribed with HEDUSSIN® syrup. There was also any case of HEDUSSIN® syrup discontinuation due to lack of tolerance of the evaluated medicinal product. Severe cough observed in two patients on the control visit, was rather related to a severe course of infection than administration of HEDUSSIN®.

In addition, no ADRs and discontinuations of treatment due to the lack of tolerance of the evaluated medicinal product were reported in 14 patients with asthma excluded from the analysis.

11. Discussion

11.1. Key results

The results of this study confirm the efficacy of HEDUSSIN® in the treatment of productive (wet) cough. Improvement or resolution of cough after 17 ± 13 days of treatment was observed in 90.1% of patients with viral upper respiratory tract infection, less frequently than in patients with bacterial upper respiratory tract infection (96.8%) and bronchitis (99.1%). This may indicate a persistence of bronchial hyperreactivity following a viral infection. Similar results were obtained after exclusion of patients that received antibiotic therapy in addition to symptomatic treatment.

Results presented in this report are similar to those obtained in other post-registration studies using syrups containing ivy extract. In a study of 9,657 patients, including 5181 children with acute or chronic bronchitis, 95% of patients had an improvement or decrease in cough intensity after 7 days lasting therapy [Fazio S eta al. 2009]. Similarly, in 268 children up to 12 years of age with cough in the course of acute bronchitis, after 14 days of ivy extract medication, cough improved of was absent in 94.2%, and viscous mucus improved in 97.7% of patients [Schmidt M et al; 2012]. In another study, different ivy extracts were used in 590 patients with acute bronchitis. Irrespective of the product used, significant improvement was obtained - a reduction in BSS symptoms from 6.2-6.3 to 1.4-1.6 pts. [Cwientzek U et al; 2011]. The improvement obtained with HEDUSSIN@ (from 5.0 to 1.5 points) was similar to that observed in the cited study. In addition, similar efficacy of ivy leaf extract and acetylcysteine as the comparator was show in children 2-10 years of age with acute bronchitis [Balbot Y et al; 2004].

In 2015, a summary of clinical trials conducted using ivy extract in acute and chronic respiratory diseases was published. The summary covered more than 65,000 patients [Lang C et al; 2015]. However, the lack of hard endpoints prevented meta-analysis.

The second objective of the study was to evaluate the tolerability of HEDUSSIN® syrup. There were no reported adverse events associated with the use of HEDUSSIN® in the study population. Furthermore, no single case of discontinuation of therapy related to the lack of tolerance of the evaluated medicinal product has been reported. On this basis, it is reasonable to formulate a thesis on good tolerance of HEDUSSIN® syrup. Evaluation of the tolerance of ivy extract (Prospan® Cough Tablets) in the conducted studies was based on a subjective assessment by the patient or by patient and managing physician [Stauss-Grabo M et al; 2011]. In these studies, Prospan® was accepted by 98.8% of patients. In large studies AEs were reported rarely (2.1%), mainly gastrointestinal complaints [Fazio S et al; 2009]. It is difficult to assess how often these events were related to infections and were the effects of other concomitant medications.

Beneficial effects were also observed in a small group of asthmatic patients (N=12) excluded from the analysis (due to the use of corticosteroid therapy and/or β_2-mimetics, in line with to GINA recommendations). Also in this small group HEDUSSIN® was well tolerated.

11.2. Limitations

Limitations of the study are related to its methodology - the study was open and the effectiveness of the therapy was not controlled against placebo.

11.3. Interpretation

The study population of 464 patients had a high probability of detecting AEs that might have occurred with a frequency over 1 per 150 cases.

11.4. Generalisability

The data is representative to the whole Caucasian population of children aged 2-12 years with acute respiratory tract infections treated in outpatient settings. However, may not be representative for non-Caucasians, which probably were seldom enrolled, due to the intrinsic nature of the Polish population. Race was not recorded in the study.

12. Other information

Not applicable

13. Conclusion

The results of this PAES support the efficacy of HEDUSSIN® prescribed for the treatment of productive cough in the course of respiratory tract infections. HEDUSSIN® is well tolerated by sick children aged 2 to 12 years.

14. References

1. Zasowska-Nowak A, Nowak D, Leki mukoaktywne. Alergoprofil 2010, vol. 6 (1), pp. 7-13.

2. Szumny D, Szypuła E, Szydłowski M, et al. Leki roślinne stosowane w chorobach układu oddechowego. Dent. Med. Probl. 2007, 44 (4), pp. 507-515.

3. Podlewski J, Chwalibogowska-Podlewska A. Leki współczesnej terapii. Ed XXI. Medical Tribune; 2017.

4. Balbot Yu, Prokhorov E, Mokia S, Yurtseva A. Comparing the efficacy and safety of high-concentrate (5-7,5;1) ivy leaves extract and acetylcysteine for treatment of children with acute bronchitis. Drugs of Ukraine 2004; 11: pp. 1-4.

5. Assessment report on Hedera helix L, folium; Committee on Herbal Medicinal Products (HMPC); EMA/HMPC/586887/2014; 24 November 2015.

6. Blumenthal M, Goldberg A, Brinckann J. Herbal Medicine. Expanded Commission E Monographs. Ivy Leaf. 1st ed. American Botanical Council. Newton 2000: pp 215-17.

7. Zeil S, Schwanebeck U, Vogelberg C. Tolerance and effect of an add-on treatment with a cough medicine containing ivy leaves dry extract on lung function in children with bronchial asthma Phytomedicine, 2014 vol. 21(10) pp. 1216-20.

8. Hofmann D, Hecker M, Völp A. Efficacy of dry extract of ivy leaves in children with bronchial asthma - a review of randomized controlled trials. Phytomedicine, 2003 vol. 10 (2-3) pp. 213-20.

9. Sieben A, Prenner L, Sorkalla T, Wolf A, Jakobs D, et al. Alpha-hederin, but not hederacoside C and hederagenin from Hedera helix, affects the Winding behavior, Dynamics and regulation of beta2-adrenergic receptors. Biochemistry 2009; vol. 48: pp. 3477-82.

10. Runkei F, Prenner L, Haberlein H. In-vitro-Studien. Ein Beitrag zum Wirkmechanismus von Efeu. (in Eng.) Pharm Ztg 2005; vol. 4: pp. 27-32.

11. Fazio S, Pouso J, Dolinsky D, Fernandez A, Hernandez M, Clavier G, Hecker M. Tolerance, safety and efficacy of Hedera helix extract in inflammatory bronchial diseases under clinical practice conditions: a prospective, open, multicentre postmarketing study in 9657 patients. Phytomedicine. 2009; vol. 16(1): pp. 17-24.

12. Schmidt M, Thomsen M, Schmidt U. Suitability of ivy extract for the treatment of paediatric cough. Phytother Res. 2012; vol. 26(12): pp. 1942-7.

13. Cwientzek U, Ottillinger B, Arenberger P. Acute bronchitis therapy with ivy leaves extracts in a two-arm study. A double-blind, randomised study vs. another ivy leaves extract. Phytomedicine. 2011; vol. 18(13): pp. 1105-9.
14. Lang C, Röttger-Lüer P, Staiger C. A Valuable Option for the Treatment of Respiratory Diseases: Review on the Clinical Evidence of the Ivy Leaves Dry Extract EA 575®. Planta Med. 2015; vol. 81(12-13): pp. 968-74.
15. Stauss-Grabo M, Atiye S, Warnke A, Wedemeyer RS, Donath F, Blume HH. Observational study on the tolerability and safety of film-coated tablets containing ivy extract (Prospan® Cough Tablets) in the treatment of colds accompanied by coughing. Phytomedicine. 2011; vol. 18(6): pp. 433-6.
16. Fazio S, Pouso J, Dolinsky D, Fernandez A, Hernandez M, Clavier G, Hecker M.
Tolerance, safety and efficacy of Hedera helix extract in inflammatory bronchial diseases under clinical practice conditions: a prospective, open, multicentre postmarketing study in 9657 patients. Phytomedicine. 2009; vol. 16(1): pp. 17-24.
17. Schulte-Michels J, Wolf A, Aatz S, Engelhard K, Sieben A, Martinez-Osuna M, Häberlein F, Häberlein H. α-Hederin inhibits G protein-coupled receptor kinase 2-mediated phosphorylation of β2-adrenergic receptors. Phytomedicine. 2016; vol. 23(1): pp. 52-7.
18. Wolf A, Gosens R, Meurs H, Häberlein H. Pre-treatment with α-hederin increases β-adrenoceptor mediated relaxation of airway smooth muscle. Phytomedicine. 2011; vol. 18(2-3): pp. 214-8.
19. Greunke C, Hage-Hülsmann A, Sorkalla T, Keksel N, Häberlein F, Häberlein H. A systematic study on the influence of the main ingredients of an ivy leaves dry extract on the β2-adrenergic responsiveness of human airway smooth muscle cells. Pulm Pharmacol Ther. 2015; vol. 31: pp. 92-8.

Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	EUP/HED/008/2016/PB	21.11.2016	Protocol of the PAES study
2	EUP/HED/008/2016/KO	16.11.2016	Observational Questionaire
3	EUP/HED/008/2016/LO	22.11.2017	Legal Opinion
4	EUP/HED/008/2016/EUPASREG	28.09.2017	EU PAS REGISTER NUMBER