ASSESSMENT OF THE EFFICACY OF THE HEDUSSIN® MEDICINAL PRODUCT USE IN THE TREATMENT OF PRODUCTIVE (WET) COUGH

PROTOCOL FOR A NON-INTERVENTIONAL STUDY

STUDY NUMBER: **EUP/HED/008/2016**

MEDICINAL PRODUCT NAME: **HEDUSSIN®**

Name of the Marketing Authorisation Holder:
Phytopharm Klęka S.A.
ul. Klęka 1
63-040 Nowe Miasto nad Wartą

Contact in case of adverse effects:
info@europlant-group.pl

Person responsible for the pharmacotherapy safety on behalf of the Sponsor:
Karina Schönknecht, tel. 601-863-704
Danuta Stanisławska-Frąckowiak: 697-741-808

Office of the Study Organizer:
Europharma M. Rachtan Sp. z o.o.
ul. Krzywa 6
40-061 Katowice
Tel.: 32 771 14 60
Fax: 32 731 50 32

Name of the Coordinator:
prof. Zbigniew Doniec MD, PhD, associate professor

LEGAL NOTICE

This Protocol does not in any way constitute a basis for a decision on any diagnostic or therapeutic methods with respect to any participant of the Study.

Europharma M. Rachtan Sp. z o.o. acts as the organizer of the study (CRO - Contract Research Organizer) as requested by the Marketing Authorization Holder: **Phytopharm Klęka S.A**.

SIGNATURES UNDER THE PROTOCOL

Investigator Signature:
I confirm that I have read the Protocol for the non-interventional observational study entitled:

ASSESSMENT OF THE EFFICACY OF THE MEDICINAL PRODUCT HEDUSSIN® IN THE TREATMENT OF PRODUCTIVE (WET) COUGH

I am aware of the investigator's responsibilities imposed on me resulting from binding regulations and the Study Protocol. I agree to conduct this study in accordance with these guidelines.

Name and last name	Signature
……..……	……
……	
Position: *Investigator*	
Address of the Medical Centre:	Date:
……	……..……
……	
……	

PROTOCOL SUMMARY

PROJECT TITLE	**ASSESSMENT OF THE EFFICACY OF THE HEDUSSIN® MEDICINAL PRODUCT USE IN THE TREATMENT OF PRODUCTIVE (WET) COUGH**
THE AIMS:	**Main aim of the Study:** The assessment of the efficacy of the **HEDUSSIN®** medicinal product use in the treatment of productive (wet) cough evaluated on the basis of the severity and the treatment time of the infection occurring with a productive (wet) cough of various aetiologies in children aged 2-12. **Additional aim of the Study:** The assessment of the treatment tolerance.
PHASE OF THE STUDY:	Non-interventional, multicentre, open-label, post-authorization study. Observational Study of the efficacy of the treatment (PAES – Post Authorization Efficiency Study)
DESIGN OF THE STUDY:	The staff that will take part in the study consists of paediatricians, general practitioners, internists, allergists, pulmonologists or doctors currently in the process of obtaining these specializations who lead the treatment of patients (in the form of outpatient healthcare) suffering from productive cough of various aetiologies in which, due to clinical indications, the **HEDUSSIN®** medicinal product has been introduced. Data on the efficacy of the treatment with the **HEDUSSIN®** medicinal product will be gathered in the Study Questionnaires (SQ) during two subsequent routine visits: first (1), where the Patient will be included in the Study, and second (2) approximately 7-10 days after the first one. The visits will be scheduled in accordance with the needs resulting from the Patient's clinical state. The inclusion of the Patient into the group where the given treatment method is used should not result from the Study Protocol. It should be dependent solely on the current medical practice and remain in accordance with the current medical knowledge. The medical history collection period, conducted by 50 investigators, is scheduled for 3 months.
STUDY POPULATION	Patients (N=500) aged 2-12 of both sexes, diagnosed with productive (wet) cough of various aetiologies.
MEDICINAL PRODUCT TO BE USED IN THE STUDY	In 100ml of the syrup, **HEDUSSIN®** contains 825g of dry extract of ivy leaves. It is a medicine in the form of a brown, opalescent liquid of sweet flavour, possibly with a light sediment. **HEDUSSIN®** is recommended productive (wet) cough of various aetiologies as an expectorant.
ENDPOINTS:	**Endpoints and methods of their assessment:** The gathering of information on the therapeutic effects of the treatment with the **HEDUSSIN®** medicinal product based on the evaluation of the severity of the symptoms associated with the respiratory system, the Patient's overall wellbeing and the duration of the infection. All adverse effects caused by the drug must be reported to Phytopharm Klęka S.A. and to the URPL. Additionally, they can be reported to the Study Organizer via the website: **www.dzialanianiepozadane.com**
STATISTICAL METHODS:	The sample size of 500 Patients was based on the feasibility study. The analysis of the data obtained in the Study will be descriptive: the compiled data will consist of summarizing statistics such as quantities, average values, standard deviations, medians, minimal and maximal values of the observed frequencies/proportions. The effectiveness analysis will be conducted on the basis of the population of Patients who will partake in all of the visits described in the Study Protocol.

Table of contents

1. INTRODUCTION

1.1. Basic information on the subject affliction of this Study

Cough is a reflex defence reaction in response to factors irritating the nerve endings present in the mucous membrane of the upper respiratory passages. The coughing reflex results in a sudden contraction of both the chest muscles and the diaphragm initially occurring with the closure of the glottis which, in turn, results in a rapid expulsion of air from the respiratory passages at the moment of its opening.

The coughing reflex can be triggered by damaging the mucous membrane of the upper respiratory passages in course of viral and bacterial infections, by a foreign matter in the respiratory passages themselves or through the irritation of the nerves responsible for the conduction of this reflex's impulses, e.g. through the irritation of the auricular branch of the vagus nerve.

Cough is characterised as a wet (productive) one if it is accompanied by secretion expectoration (either mucous or purulent). In the children population, it is often swallowed. Cough is described as a dry one if it is not accompanied by the abovementioned expectoration of secretion. Dry cough often appears in the initial phases of (often viral) infections and later evolves into a productive cough.

An etiological factor which is definitively more rare in the population of children are primary infections of the respiratory passages. However, bacteria can be a cause of viral respiratory tract superinfections. In the population of children, productive cough is often caused by the inflammation of the upper sections of the said tract but also by (most commonly) chronic rhinitis or by sinusitis (ethmoidal sinus inflammation in younger children; the other sinuses develop fully after the age of 6). This type of cough is defined as one related to upper airways.

The cough which is characteristic for viral infections of the upper respiratory passages, due to the damage made to the mucous membrane of the upper airways and the irritation of the nerve endings present there, may last up to 4 weeks and it is then characterised as acute.

Common causes of chronic cough in the children population include bronchial asthma. The symptom of which may be bronchitis occurring with an obturation. Allergic rhinitis can also be a common cause. Less common causes of chronic cough in children include inherited diseases, cystic fibrosis or syndromes associated with the disturbance of the activity of the airways' mucous membrane cilia. They are characterised by an early symptom onset, a more severe clinical course and disorders of many internal organs. In case of chronic cough in children, it is advised to always undergo an appropriate diagnostic which takes into account the possibility of the aspiration of a foreign body into the bronchial tree as well as causes of cough which are not associated with the respiratory system, e.g. gastroesophageal reflux or psychogenic causes.

Productive cough is a form of the bronchial tree's cleansing procedure as it allows the evacuation of the secretion retained in it. Therefore, it should not be inhibited pharmacologically. Instead, medicine that dilutes the secretion and facilitates its expectoration should be used.

Substances used in the treatment of wet cough demonstrates the following activity:

- Expectorant; secretolytic activity which increases the volume of the secretion and enhances improves its parameters,
- Mucolytic which reduce the secretion viscosity,
- Mucokinetic, which increase the effectiveness of the ciliary transport

One of the expectorants which increase the volume of the secretion is an herbal medicine obtained from common ivy leaves. The ivy extract contains triterpenoid saponins (hederacoside B & C) which grant it

the secretolytic and antioxidant properties. They stimulate the coughing reflex and increase the secretion production on the basis of a reflex from the vagus nerve, through the irritation of the nerve endings in the mucous membrane of the stomach. Moreover, the ivy leaves extract demonstrates spasmolytic activity in relation to the smooth muscles of the bronchial walls which additionally facilitates the evacuation of the secretion [2].

The secretolytic, mucolytic and spasmolytic activity mechanism of the ivy leaves was proved on the basis of the fluorescence correlation spectroscopy microscopic method.

α-hederin, formed from the hederacoside C contained in the extract, increases the production of the surfactant in the lung alveoli [9] through the stimulation of the β_2-adrenergic receptors. The stimulation of the β_2-adrenergic receptors also results in the relaxation of the airways' smooth muscles by decreasing their elastic resistance. Moreover, it improves the mucociliary clearance of the bronchi [10].

The conducted clinical research also indicated the potential anti-inflammatory and antifungal activity of the common ivy leave extract.

It is recommended that the treatment with the preparations including the ivy leave extract lasts approximately 7 days [3]. The preparation should not be used in the evening. Caution is recommended when administering the preparation in Patients suffering from gastritis and peptic ulcer disease.

The effectiveness of the ivy leave extract use in the children population (aged 2-10) with symptoms of acute bronchitis was comparable to acetylcysteine. Furthermore, it depicted demonstrated better tolerance [4].

The clinical research on the efficacy of the common ivy leave extract was conducted also in the adult population suffering from both acute and chronic diseases of the respiratory system (lung obstructive diseases, chronic bronchitis) [5, 6, 7, 8].

1.2. Information on the study drug

HEDUSSIN® (active substance: dry ivy leave extract).

HEDUSSIN® is recommended for use in treatment of wet cough of various aetiology as an agent facilitating expectoration – expectorant – in both adults and children. The medicine is administered orally and should be shaken before use.

In children aged 2-5, it is recommended to administer 2 ml of the syrup twice daily (which corresponds to 33 mg of dry ivy leave extract daily).

In children aged 6-12, it is recommended to administer 4 ml of the syrup twice daily (which corresponds to 66 mg of dry ivy leave extract daily).

In adults and children above the age of 12, it is recommended to administer 6 ml of the syrup twice daily (which corresponds to 99 mg of dry ivy leave extract daily).

Contraindications for the use of the dry extract of ivy leaves include:

- Hypersensitivity to the active substance, other plants from the Araliaceae family or any of the excipients (non-crystallizing liquid sorbitol, potassium sorbate, xanthan gum, anhydrous citric acid)
- Age below 2 years.

Special warnings and precautions for use

Persistent or recurring cough in children aged 2 to 4 requires a thorough diagnostic before the commencement of the treatment.

In case of the occurrence of dyspnoea, fever or purulent sputum, one should seek advice from a doctor or pharmacist.

It is not recommended to administer the **HEDUSSIN®** syrup concomitantly with antitussive medicine such as codeine or dextromethorphan. Caution is recommended when administering the syrup in Patients suffering from gastritis or the peptic ulcer disease.

The **HEDUSSIN®** syrup contains sorbitol, therefore it should not be used by Patients with rare inherited fructose intolerance disorders.

There is no data on the influence of the medicinal product on fertility. The usage safety during pregnancy and breastfeeding has not been established. Therefore, it is not recommended to use the product during that time.

The research on the influence of the preparation on the ability to operate machines has not been conducted.

Interactions with other medicinal products and other forms of interactions

No research conducted.

Adverse effects resulting from the use of the HEDUSSIN® medicinal product include:

- Very common (≥ 1/10): none
- Common (≥1/100 to <1/10): nausea, vomiting, diarrhoea
- Uncommon (≥1/1000 to <1/100): allergic reactions (hives, skin rash, angioedema, dyspnoea)
- Rare (≥1/10 000 to <1/1000): none
- Very rare (<1/10000): none
- Frequency not known: none

Overdosage

Administering a dose exceeding the recommended one may cause nausea, vomiting, diarrhoea and agitation. The treatment is symptomatic. Individual cases of overdosage were reported in children aged 4. Accidental administration of a large dose of the ivy extract (correspondent to 1,8 g of ivy leaves approximately equal to 36 ml of the **HEDUSSIN®** syrup) resulted in agitation and diarrhoea.

1.3. The clinical reason for conducting this Observational Study

HEDUSSIN® is a preparation containing dry extract of common ivy leaves as the active substance (825mg in 100 ml of the syrup) which is recommended in the treatment of wet cough of various aetiologies.

HEDUSSIN®, a medicinal product containing dry extract of common ivy leaves in the form of syrup, obtained the marketing authorisation (no. 22652) for medicinal products in Poland on 20.08.2015. Therefore the Study focusing on the assessment of the efficacy of the treatment in patients diagnosed with productive cough of various aetiologies is especially important to obtain data from the Polish population (the hitherto effectiveness findings were not obtained from the research on the Polish population). The data will be used for the purposes of planned marketing campaigns as well as staff, doctor and pharmacist trainings. The planned study of the **HEDUSSIN®** medicinal product can be carried

out only on the trade name, as the subject of research interest is the specific medicinal product, administered in the form of syrup.

2. THE AIM OF THE STUDY

2.1. The main aim of the Study

The assessment of the efficacy of the **HEDUSSIN®** medicinal product use in the treatment of productive (wet) cough evaluated on the basis of the severity and the treatment time of the infection occurring with a productive (wet) cough of various aetiologies in children aged 2-12.

The assessment of the efficacy of the **HEDUSSIN®** medicinal product will be based on:

1. **Observation of the below symptoms and changes in their intensity during the treatment*:**
    - The severity of the cough (from 0 to 4)
    - Dyspnoea (from 0 to 4)
    - Auscultatory changes (wheezing, dry rale, crackles) (from 0 to 4)
    - Chest pain during cough (from 0 to 4)
    - Hoarse breathing (from 0 to 4)

*The assessment will be carried out on the basis of the BSS (Bronchitis Severity Score) scale where:

0- absent; 1- mild; 2- moderate; 3- severe; 4- very severe

2. **Determination of the infection duration (measured in days)**
3. **Evaluation of the body temperature**
4. **The use of concomitant treatment:**
    - **The inclusion of an antibiotic**
    - **The inclusion of other medications and dietary supplements**

2.2. The additional aim of the Study

The assessment of the tolerance of the recommended therapy in the course of the infection with wet cough.

The assessment of the tolerance of the **HEDUSSIN®** syrup has been conducted on the basis of:

1. **Sleep quality disturbances (intermittent sleep, shallow sleep, insomnia)**
2. **The feeling of weakness***
   *The evaluation will be conducted on the basis of a 5-level estimation scale where:

   0- absent; 1- mild; 2- moderate; 3- severe; 4- very severe

3. **The VAS scale focused on the overall wellbeing (from 0 to 10)**

3. STUDY DESIGN

3.1. Basic information

This is a post-authorization study. Data on the efficacy of the **HEDUSSIN®** medicinal product in the treatment of Patients diagnosed with productive (wet) cough of varying aetiology.

The medicinal product will be used in the usual manner strictly in accordance with the terms of the marketing authorization and in the manner specified in the Summary of Product Characteristics.

Patient inclusion into the study is independent from the previous decision regarding the treatment with **HEDUSSIN®**.

3.1.1. Characteristics of the study population

The study population will consist of patients aged 2 to 12 of both genders, diagnosed with wet cough of various aetiologies.

3.1.2. Study design

This project is an open-label, non-randomized, multicentre, non-interventional, post-authorization efficacy study (PAES).

3.2. Endpoints

The gathering of information on the therapeutic effects of the treatment with the **HEDUSSIN®** medicinal product includes the assessment of: the number of days until full recovery of the Patient measured from the day of the 1st visit until the closure of the observation – the day of the 2nd visit.

- Exclusion from the Study – the number of days measured from the day of the 1st visit until the occurrence of complications, intensification of the state, occurrence of additional infections, etc. – visit 2: closure of the observation and the conducting of a medical interview on the health status/Patient wellbeing.
- The change in the intensity of the symptoms, associated with the respiratory system, resulting from the treatment will be assessed on the basis of the BSS scale (Bronchitis Severity Scale) (evaluation of the measurements taken during visit 1 and 2)
- The evaluation of the changes in the overall wellbeing resulting from the treatment will be based on the VAS scale (Visual Analog Scale) (evaluation of the measurements taken during visit 1 and 2)
- The evaluation of the treatment tolerance based on the occurrence of sleep quality disturbances and weakness feeling will take place on the basis of a 5-level estimation scale (evaluation of the measurements taken during visit 1 and 2)

All adverse effects caused by the drug must be reported to **Phytopharm Klęka S.A.** or the URPL or to the Study Organizer via the **www.dzialanianiepozadane.com** website.

3.3. Substantiation of the study construction

This is a non-interventional Observational Study focusing on the assessment of the efficacy of the treatment with the **HEDUSSIN®** medicinal product. No additional diagnostic or monitoring procedures will be applied and the analysis of the gathered data will be performed using epidemiological methods only.

The Study aims to gather data on the efficacy of the treatment with the **HEDUSSIN®** medicinal product [the duration of the infection, the symptoms associated with the respiratory system] and the evaluation of the overall wellbeing of the Patient as well as the tolerance of the treatment in the Patient population where the **HEDUSSIN®** medicinal product will be used as part of the routine therapy and in accordance with the terms of the marketing authorization and in the manner specified in the Summary of Product Characteristics. Collection of such data in the population of Polish patients is very important from the scientific and practical point of view as **HEDUSSIN®**, a medicinal product containing dry extract of common ivy leaves in the form of syrup, obtained the marketing authorisation for medicinal products in 2015. The data will be used for the purposes of planned marketing campaigns as well as staff and doctor training.

The study is scheduled for 3 months and will be conducted in 500 patients diagnosed with productive (wet) cough of various aetiologies who started the treatment with the **HEDUSSIN®** medicinal product as part of the routine therapy. The observation of the efficacy in a single patient will continue up to 10 days. During this time, centres will collect data on the efficacy of the treatment which will be recorded in the Study Questionnaire. The Study Questionnaires will also be recording data on the tolerability of the treatment. The Study Questionnaires will then be returned to the ordering party in order to develop the report.

3.4. Duration of the Study

The Observation of the Patients during the Study will continue up to 10 days from the date of the first visit. The number of assessments will not influence neither the number of visits nor the amendment of the therapy application as specified in the SPCh criteria. The duration of the study is 3 months.

4. COMPLIANCE WITH TERMS OF GOOD CLINICAL PRACTICE, ETHICAL ISSUES

This is a non-interventional study and thus is not subject to the provisions of the 2001/20/WE Clinical Trial Directive of the European Parliament and of the Council of Europe of 4 April 2001.

The study will be conducted in accordance with all applicable provisions of the local law.

5. STUDY POPULATION

5.1. Records of the Study participants

Each Investigator will be required to keep a list of patients included in the study. The list should include the Patient number, their name and surname, initials and date of birth, and must be kept confidentially at the study centre.

The study is planned to include 500 patients treated in Poland by 50 paediatricians, general practitioners, internists, allergists and pulmonologists or doctors currently in the process of obtaining these specializations. Each physician should include into the Study and observe 10 Patients. Finally, the size of the study group will amount to 3000 patients.

The selection of doctors:

- Paediatricians, general practitioners, internists, allergists and pulmonologists or doctors currently in the process of obtaining these specializations who lead the treatment of an appropriate number of Patients - who meet the Study inclusion criteria - under conditions of ambulatory health care
- current license to practice

Recruitment to participate in the Study realisation is done by filling in and submitting the Study Application Form on the basis of which is the qualification is conducted. Due to the limited number of investigators **Europharma M. Rachtan Sp. z.o.o.** (CRO – Study Organizer) stipulates that the inclusion in the study will be conducted on the first come, first served basis. After the Contract Research Organizer (CRO) has been provided with the original Study Questionnaires, in special cases justified with a research need and where the Investigator is willing to continue the Study (the Investigator shall have a group of Patients meeting the Study inclusion criteria), the Study may be continued by the given Investigator from the moment of the reception of the original questionnaires from the Study Organizer.

5.2. Inclusion criteria

Each study participant must meet the following criteria:

- Patient of either sex, aged 2 to 12
- Diagnosis of a productive (wet) cough of various aetiology

The inclusion into the Study will take place during the 1st visit. Only Patients in which the earlier recommendation to use **HEDUSSIN®** in the therapy of productive cough of various aetiology was made due to solely medical reasons and independently from this Study, and who did not take the first dose of the syrup at the moment of the inclusion, are eligible. The inclusion of the patient into the group where the given treatment method is used should not result from the study protocol. It should be dependent solely on the current medical practice and remain in accordance with the current medical knowledge.

5.3. Exclusion criteria

Patients meeting the following criteria will not be included in the study:

1. Patients under the age of 2 and above the age of 12 years.
2. Hypersensitivity to the active substance – ivy leave extract; to other plants from the Araliaceae family or to the excipients (non-crystallizing liquid sorbitol, potassium sorbate, xanthan gum, anhydrous citric acid).
3. Concomitant treatment with corticosteroids, beta-2 mimetics, theophylline or other medicine that may inhibit the coughing reflex during the 7 day period prior to the inclusion into the Study.
4. Neoplastic diseases of the respiratory system.

5.4. Procedures for treatment discontinuation or if the patient withdraws from the study

If the patient is excluded from the Study (i.e. they discontinue the participation in the Study before the evaluations schedule in the Assessment Protocol), the main reason for discontinuation will be recorded in the Study Questionnaire (SQ). Discontinuation from the study due to adverse effects must be adequately described in the patient records.

The investigator provides patients excluded from the study with adequate further treatment - personally or by another doctor with the existing documentation of the disease course.

6. METHODOLOGY

6.1. Schedule of the Study

A summary of observations and assessments that will be conducted during the study is presented in the following table.

Table1. Schedule of the assessments during the Study realisation

Procedures for particular assessments	Visit 1*	Visit 2*
Demographic data	X	
Qualification of the Patient into the PAES Study (inclusion criteria)	X	
History concerning comorbidities and their treatments	X	X
Basic diagnosis and its duration	X	
The dose of the medicinal product used		X
The assessment of : • The symptoms associated with the respiratory system (BSS scale) • Assessment of the body temperature • Assessment of the overall wellbeing (VAS scale) • Assessment of the sleep quality disturbances • The use of concomitant treatment	X	X
Duration of the infection (number of days)		X
Reporting adverse effects related to the **HEDUSSIN®** medicinal product use		X

*The assessments will take place as part of the routine Patient observation

6.2. Assessments in a specialist and primary care clinics under the study

6.2.1. Initial visit (Visit 1) - (day 0)

The Study Questionnaire of Patients using the **HEDUSSIN®** medicinal product, in accordance with the leading physician as well as in accordance with the marketing authorization criteria, shall contain the following information:

- patient number;
- patient initials;
- demographic data;
- interview data on comorbidities;
- initial diagnosis;
- data on the long-term medicine administration in the treatment of comorbidities;
- decision on the Patient's compliance with the inclusion criteria and noncompliance with the exclusion criteria;
- data on the recommended dose of the **HEDUSSIN®** medicinal product;
- the assessment of the following symptoms:
  1. cough severity (from 0 to 4)
  2. dyspnoea (from 0 to 4)
  3. auscultatory changes during the cough (from 0 to 4)
  4. chest pain during the cough (from 0 to 4)
  5. hoarse breathing (from 0 to 4)

  *in accordance with the 5-level BSS scale (Bronchitis Severity Scale) where:
  0- absent; 1- mild; 2- moderate; 3- severe; 4- very severe

- assessment of the body temperature;
- evaluation of the weakness feeling*
  *on a 5-level estimation scale where:
  0- absent; 1- mild; 2- moderate; 3- severe; 4- very severe
- assessment of the overall wellbeing using the VAS scale;
- assessment of the sleep quality disturbances;
- the used concomitant treatment.

6.2.2. Visit 2 (approximately 7-10 days after the previous visit) in accordance to the schedule resulting from the clinical needs of the Patient

The Patients will be present on the control visits in the study centre at the scheduled time. During these visits, the Investigator will collect and record in the Study Questionnaire (SQ) the following information:

- Duration of the infection (number of days until the symptoms receded)

A secondary conducting of:

- The assessment of the symptoms associated with the respiratory system on the basis of the BSS scale
- The evaluation of the body temperature
- The assessment of the weakness feeling on the basis of a 5-level estimation scale
- The assessment of the wellbeing based on the VAS scale
- The assessment of the sleep quality disturbances
- The used concomitant treatment

The Patient Observation last approximately 10 days.

7. ASSESSMENTS PERFORMED IN THE STUDY

The Study assumes the assessment of the efficacy of the treatment with the **HEDUSSIN®** medicinal product.

7.1. Endpoints and the methods of their evaluation

7.1.1. Assessment of the efficacy of the treatment

Data on the current clinical status of the Patient will be collected during the 2 visits scheduled in the Study Protocol. The efficacy will be assessed on the basis of the assessment of the intensity of the symptoms associated with the respiratory system, the overall wellbeing of the Patient, the duration of the infection and the duration of the WET cough on the day of the first and second assessment.

8. STUDY DRUG

8.1. Administration of the drug

The **HEDUSSIN®** medicinal product will be used based on a recommendation from the doctor leading the treatment, after the product is purchased at a public pharmacy. The inclusion of the patient into the group where the given treatment method is used should not result from the study protocol. It should be dependent solely on the current medical practice and remain in accordance with the current medical knowledge.

Study drug

It is a preparation containing the dry extract of common ivy leaves as the active substance.

Excipients: non-crystallizing liquid sorbitol, potassium sorbate, xanthan gum, anhydrous citric acid, purified water

Pharmaceutical form: syrup

Potency: 100 ml of the syrup contains 825 mg of the dry extract of ivy leaves

Name and address of the manufacturer responsible for batch release: Phytopharm Klęka S.A.

8.2. Patient identification

Throughout the duration of the Study all of the included patients must be identifiable. The investigator will maintain the list of the numbers of patients as well as their names and surnames, so that the records can be reached in the future, if necessary. The list of Patients participating in the Study should be kept confidentially at the study centre.

Patient number will be assigned during the first assessment in accordance with the chronological order of inclusion in the study in the resort. Patients in the course of this study will be identified using a unique identification number. Patient number and centre number will be recorded in the Study Questionnaire.

Patients qualified for the study are not covered by randomization.

8.3. Drug delivery

Not applicable.

8.4. Concomitant medication

Data on other drugs used concomitantly with the **HEDUSSIN®** medicinal product will be recorded in the Study Questionnaire (SQ) during each control assessment.

9. REPORTING RELATED ADVERSE EFFECTS

If a related adverse event occurs, the Investigator is obliged to report each observed event by completing the DRUG RELATED ADVERSE EVENT REPORT and sending it in accordance with the Law on Medicinal Products to:

- Phytopharm Klęka S.A.
  And

- URPL

Should any severe adverse drug reaction occur, these should be reported within 24h.

The Investigator may additionally report the drug related adverse event to the Study Organizer through the **www.dzialanianiepozadane.com** website. The events reported to the Study Organizer via the abovementioned platform are forwarded to the URPL.

The addresses of all parties are available below:

Phytopharm Klęka SA, Klęka 1, 63-040 Nowe Miasto nad Wartą

Karina Schönknecht and Danuta Stanisławska-Frąckowiak (deputy) — Persons responsible for the pharmacotherapy safety on behalf of the Sponsor.

e-mail: info@europlant-group.pl

fax: 61 28-68-529

Department for Monitoring of Adverse Action Medicines, Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL)

Al. Jerozolimskie 181C

02-222 Warszawa

tel.: + 48 22 49 21 301

fax: + 48 22 49 21 309

e-mail: ndl@urpl.gov.pl

Study Organizer Office: Europharma M.Rachtan Sp.z o.o.

ul. Krzywa 6

40-061 Katowice

Reporting via the platform: **www.dzialanianiepozadane.com**

The procedure for reporting ADR will be carried out in accordance with the standards of GVP

Reporting of adverse reactions associated with the use of the **HEDUSSIN®** medicinal product will be carried out in accordance with the provisions of the Pharmaceutical Law, in particular with art. 45 of the Act on professions of physicians and dentists.

10. STATISTICAL CONSIDERATIONS

10.1. Patient classification and definition

Treated Patient: Patient who received at least one dose of study drug.

10.2. Analyses, populations, definitions

The analysis of the data on the efficacy will be conducted on the basis of the results of the changes in the intensity of symptoms associated with the respiratory system, the overall wellbeing and the duration of the infection in Patients who participated in all of the assessments outlined in the Study Protocol.

10.3. Method of determining the sample size

This is a post-authorization study. The size of the research group (n=500) was determined taking into account some practical limitations associated with the Study realisation and without the use of statistical sample selection tools. This should be taken into account when interpreting the study results.

10.4. Statistical analysis

Statistical analysis of the collected data will be carried out in accordance with the standards of the EU-GCP / ICH.

In general, all data will be summarized and presented using descriptive statistical methods. Appropriate statistical tests will be used for the analysis of the changes in assessed parameters, depending on the distribution of the variables and their type (continuous, categorized).

10.4.1. Demographic data and other basic characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency for demographic and basic characteristics data (medical history, co-morbidities, the primary disease diagnosis, previous treatment) will be presented.

10.4.2. Distribution of patients and cases of exclusion from the study

The number of patients treated, the number of patients who discontinued treatment with the study drug, and the number of patients who participated in the study visits will be presented in the form of tables. The main reasons for patients' discontinuation from participation in the study will be presented in the form of tables.

10.4.3. Adverse effects analysis

This Study is an efficacy assessment study (PAES) and its main aim is not focused on the research of the medicinal product safety – especially, the analysis of the reported adverse events will be conducted in a general manner as an auxiliary analysis in relation to the main aim of the Study, i.a. the efficacy assessment. The details on the safety of the used treatment contained within the Study Questionnaires will be included in the summaries of data on individual patients. Analysis and summary tables will be based on data from the study population taking into account the duration of exposure to the medicinal product under investigation.

All adverse effects will be coded in accordance with Medical Dictionary for Regulatory Activities (**MedDRA**).

The prevalence of all reported adverse effects and severe adverse effects occurring during the study will be presented in the form of tables.

In addition, summary tables will be presented, that will include data the maximum intensity of the adverse effect, the relationship to the study drug administration and related data on adverse effects as well as patients who discontinued treatment with the study drug due to the occurrence of adverse effects.

It is considered that related adverse effects occurring during the use of the study drug are any adverse effects that occur during an active study phase if:

- They were not present prior to the first dose of study medication

or

- They were present prior to receiving the first dose of study drug, but its severity has been increasing during the observation.

All adverse effects occurring during the use of the study drug will be noted in the tables of adverse effects. Other medications used to treat concomitant diseases will be coded in accordance with the WHO Medication Coding Dictionary and will be summarized with the number and percentage of patients receiving concomitant medications and these patients will be grouped according to the pharmacological class of the medicine and International Non-proprietary Name (INN) of the drug.

10.5. Factors which may affect the statistical analysis and modify the results of the Study

- The Patients failure to report on the scheduled control visit
- The discontinuation of the study drug use for reasons other than adverse effects,
- Use other drugs during observation,
- Omission by the investigator to answer some of the questions included in the survey,
- The lack of information about the fate of the patient in the event of failure to report on the control visit

10.6. Factors limiting the Study

The limitations result from the duration of the observation (the length of the exposure) on the study drug.

The safety analysis will allow the assessment of the frequency of the adverse effects of the drug occurring in more than 1/1000 (very common, common and uncommon).

The obtained data will not permit a reliable assessment of the occurrence of rare and very rare adverse effects of the study drug which does not exclude the observation of drug adverse effects occurring with unknown frequency.

11. MONITORING PROCEDURES

The Investigator is responsible for the validation of all data collected in the centre.

In this study, the patients should not be subjected to any additional diagnostic procedures and monitoring. The completeness of the Study Questionnaire (SQ) will be checked at the Office of the Study Organizer and any missing or inconsistent data will be clarified with the Investigator by the people involved in data management.

12. MANAGEMENT OF THE STUDY

12.1. Inspections and audits

Not applicable.

12.2. The scope of the data collected

The Investigator is required to record all the data relating to the procedures detailed in the Study Protocol, including use of the study drug in the Study Questionnaires provided for the purpose of this study.

The Investigator is required to sign the page of the SQ relating to the completion of study and a certificate of study completion to prove that all entered data is accurate and complete.

Any corrections in the SQ and source documents must be placed in such a way that the original entries were still legible (strikethrough single thin line). If the reason for the change is not obvious, this should be clearly stated.

12.3. Verification of the source data

Not applicable.

12.4. Verification of data quality

The Study Questionnaires (SQ), transferred from the Study centre to the Office of the Study Organizer will be analysed in terms of completeness, consistency, clarity and compliance with the Protocol.

If data elements are missing from the Study Questionnaires, the Investigator should state the reason for the missing data or other deviations from the Protocol. The Office of the Study Organizer will communicate to the Investigator any questions regarding the processing of data and the points that have not been sufficiently explained, for the purpose of clarification or improvement. The Investigator must ensure that all requests for clarification of data are immediately addressed. The Investigator is obliged to keep copies of all data, including a record of all changes and clarifications in the Study Questionnaire.

12.5. Data management

Data management will be conducted by the Office of the Study Organizer (CRO).

All the procedures of data processing will be carried out in accordance with standard operating procedures of the Office of the Study Organizer.

The Office of Study Organizer has an obligation to ensure that appropriate input methods (e.g. double data entry) are applied, and that all inquiries on missing or inconsistent data are addressed.

In addition, during the formation of the database, rules for creating a database allowing to avoid mistakes during the statistical analysis will be included, such as:

1. Entering data as numerical variables in all cases where this is possible.
2. Variable names are clearly described, so as not to raise questions during their use in statistical analysis.
3. One variable will be assigned to one column.
4. The data of each study subjects are entered in the same order and the method of recording missing data will be consistent.
5. Each respondent will be given their own, unique identification number.
6. The data of all respondents will be entered into a single database.
7. Source qualitative variables will be introduced.
8. The project database will be consulted with a biostatistics specialist prior to their introduction.
9. The data will be entered by one person, and then verified by a second.

12.6. Committee for Study management

Not applicable.

12.7. Archiving and storage of databases

The data will be stored by the Study Organizer for the whole period of 5 years.

13. ADMINISTRATIVE PROCEDURES

13.1. Consent of the relevant authorities to carry out this study

In accordance with paragraph 36u of the Act No. 2 of 6 September 2001 r. on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals), published in Journal of Laws 2001 No. 126, item 1381, The Study Protocol does not require the approval from President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products and consent for conducting the study as it is a drug efficacy study (PAES) and not a drug safety study (PASS).

The Ethics Committee approval is not needed for this study because it is a non-interventional study. Due to the same reason formal patient consent is not needed. Moreover, the Patient's consent is not needed as the gathered data will contain the Patient's initials only, which does not permit their identification.

13.2. Rules of publication

Determined separately.

13.3. Report on the Study

The report on the study will be prepared by the Office of the Study Organizer.

13.4. Details concerning contracts and financing

Contracts with the Investigators will be concluded by the Office of the Study Organizer.

13.5. The insurance, taking responsibility and compensation

The Study Participants are not covered by any additional insurances.

14. AMENDMENTS TO THE PROTOCOL

Amendments can be made by the Office of the Study Organizer and need to be approved by the sponsor.

15. BIBLIOGRAPHY

1. Zasowska-Nowak A., Nowak D., Leki mukoaktywne. Alergoprofil 2010, Vol. 6, Nr 1, 7-13.
2. Szumny D., Szypuła E., Szydłowski M., i inni. Leki roślinne stosowane w chorobach układu oddechowego. Dent. Med. Probl. 2007, 44, 4, 507-515 ISSN 1644−387X.
3. Podlewski J., Chwalibogowska-Podlewska A. Leki współczesnej terapii. Wydanie XX.
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; 11:1-4.
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 2000:215-17
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; 48:3477-82.
10. Runkei F, Prenner L, Haberlein H. In-vitro-Studien. Ein Beitrag zum Wirkmechanismus von Efeu. (in Eng.) Pharm Ztg 2005; 4:27-32.