Sponsor:

Pediatrica SRL
Via Nicolodi 28/A, 57121
Livorno (LI), Italy

Title of the Clinical Investigation Plan:

A randomized, open, controlled study to evaluate the efficacy and safety of PediaFlù® (dietary supplement) along with standard of care in children with acute tonsillopharyngitis / rhinopharyngitis versus standard of care only

Code of Protocol: **OPPED/0120/FS**

Version: **3.0 (final) – 16/03/2021**

Register No: **www.clinicaltrials.gov**

Clinical investigation type: **Interventional**

Contract Research Organization:
Opera Contract Research Organization S.r.l.
10, Cozia Street, 300209, Timisoara (Romania)

Scientific Supervisor:
Prof Fabio Cardinale

The information contained in this protocol is confidential and will not be disclosed to anyone without written authorization from Pediatrica SRL, except for eventual discussions with regulatory authorities, Ethical Committees or persons participating in the conduct of the study.

CLINICAL INVESTIGATION PLAN APPROVAL

Sponsor

I declare that the clinical investigation protocol OPPED/0120/FS (Version: 3.0 final – 16/03/2021) contains all necessary information required for the conduct of the study.

Dr. Centi Alessandro – CEO

Signature: _____ Date : _____/_____/_____

Clinical Site 01 – Principal Investigator

I have carefully read this clinical investigation protocol OPPED/0120/FS (Version: 3.0 final– 16/03/2021) and agree to conduct study in accordance with Good Clinical Practice, Declaration of Helsinki, local laws and regulations relevant to the use of new and approved therapeutic agents in human subjects.
I agree that Pediatrica SRL, its delegates and Regulatory Authorities have direct access to all study documentation.
I agree to obtain the written Informed Consent from all participating subjects.
I agree to maintain the confidentiality of all information received or developed in connection with this clinical investigation plan.

Dr. _____

Signature: _____ Date: _____/_____/_____

Institution:_____

Clinical Site 02 – Principal Investigator

I have carefully read this clinical investigation protocol OPPED/0120/FS (Version: 3.0 final– 16/03/2021) and agree to conduct study in accordance with Good Clinical Practice, Declaration of Helsinki, local laws and regulations relevant to the use of new and approved therapeutic agents in human subjects.
I agree that Pediatrica SRL, its delegates and Regulatory Authorities have direct access to all study documentation.
I agree to obtain the written Informed Consent from all participating subjects.
I agree to maintain the confidentiality of all information received or developed in connection with this clinical investigation plan.

Dr. _____

Signature: _____ Date: _____/_____/_____

Institution:_____

Clinical Site 03 – Principal Investigator

I have carefully read this clinical investigation protocol OPPED/0120/FS (Version: 3.0 final – 16/03/2021) and agree to conduct study in accordance with Good Clinical Practice, Declaration of Helsinki, local laws and regulations relevant to the use of new and approved therapeutic agents in human subjects.
I agree that Pediatrica SRL, its delegates and Regulatory Authorities have direct access to all study documentation.
I agree to obtain the written Informed Consent from all participating subjects.
I agree to maintain the confidentiality of all information received or developed in connection with this clinical investigation plan.

Dr. _____

Signature: _____ Date: _____/_____/_____

Institution:_____

Clinical Site 04 – Principal Investigator

I have carefully read this clinical investigation protocol OPPED/0120/FS (Version: 3.0 final – 16/03/2021) and agree to conduct study in accordance with Good Clinical Practice, Declaration of Helsinki, local laws and regulations relevant to the use of new and approved therapeutic agents in human subjects.
I agree that Pediatrica SRL, its delegates and Regulatory Authorities have direct access to all study documentation.
I agree to obtain the written Informed Consent from all participating subjects.
I agree to maintain the confidentiality of all information received or developed in connection with this clinical investigation plan.

Dr. _____

Signature: _____ Date: _____/_____/_____

Institution:_____

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	-	Adverse Event
CIP	-	Clinical Investigation Plan
CRF	-	Case Report Form
CRO	-	Contract Research Organization
CSR	-	Clinical Study Report
DB	-	Data Base
DMP	-	Data Management Plan
EC	-	Ethical Committee
EU	-	European Union
FPI	-	First patient In
GCP	-	Good Clinical Practice
GDPR	-	General Data Protection Regulation
ICF	-	Informed Consent Form
ICH	-	International Conference on Harmonization
IGAE		Investigator Global Assessment of Efficacy
IP	-	Investigational Product
LPO	-	Last Patient Out
SIL	-	Subject Information Leaflet
RCI	-	Randomized Clinical Investigation
SAE	-	Serious Adverse Event
SD	-	Standard Deviation
SOPs	-	Standard Operating Procedures
TCF	-	Trial Centre File
TMF	-	Trial Master File
TSS		Tonsillopharyngitis Severity Score
WHO	-	World Health Organization

SYNOPSIS

Title	A randomized, open, controlled study to evaluate the efficacy and safety of PediaFlù® (dietary supplement) along with standard of care in children with acute tonsillopharyngitis / rhinopharyngitis versus standard of care only.
Protocol code	OPPED/0120/FS
Version	3.0 (final) – 16/03/2021
Registry	www.clinicaltrials.gov
Type	Interventional study
Sponsor	Pediatrica SRL Via Nicolodi 28/A, 57121 Livorno (LI), Italy Phone: +39 0586 426473 e-mail: info@pediatrica.it
CRO	Opera CRO Str Cozia 10, 300209 Timisoara (Romania) The Sponsor has authorized and delegated the CRO to perform: • Support to define the rationale and research hypothesis • Clinical investigation protocol writing; • CRF preparation; • SIL, ICF and other study documents preparation; • Romanian local version of study documents; • TMF and TCF preparation and maintenance; • Local Ethics Committees issues and submissions in Romania; • Financial Agreements with investigational Service Providers in Romania; • Clinical Monitoring; • Data Management; • Safety Management; • Statistical Analysis; • Final Report preparation
Introduction and Rationale	Sore throat or acute tonsillopharyngitis, often referred to as angina catarrhalis in Central and Eastern Europe, affects mainly children, adolescents and young adults and represents one of the most common reasons to consult a family physician. While most patients complaining of sore throats have an infection, it has been estimated [1] that fewer than 20% present with a clear indication for antibiotic therapy, i.e., are positive for hemolytic streptococcus. Acute tonsillopharyngitis (ATP) is a highly prevalent, seasonal infective disorder characterized by an inflammation of the pharynx and the palatine tonsils, which occurs in all age groups and accounts for about 5% of all visits in pediatric care [2]. Common symptoms of ATP include sore throat, dysphagia, red pharynx, enlarged tonsils sometimes covered with exudate, fever with sudden onset, malaise, gastrointestinal complaints, halitosis, rhinorrhea and cough [3]. Children with non-streptococcal tonsillopharyngitis are often over-treated with antibiotics [4]. The scientific literature currently available shows that the extract of Pelargonium sidoides may be effective in the treatment of disorders affecting the respiratory tract [5–7]. A 6-day study with administration of an extract of Pelargonium sidoides in pediatric patients with acute non-streptococcal tonsillopharyngitis showed a clinically relevant decrease of disease symptoms significantly superior to placebo [5]. Furthermore, a herbal drug made from roots of Pelargonium sidoides extract, has been shown to exhibit antiviral [8], antibacterial as well as modulating and stimulating effects on the non-specific immune system, which are based on inhibition of bacterial adhesion to host cells, improved phagocytosis and intracellular killing of microbes, increased mucociliary clearance,

	interferon-like action and enhancing effects on the production of cytokines [8]. The latter two are especially essential for activation of innate defense mechanisms against infections. Evidence shows that zinc is beneficial for the common cold in healthy children and adults living in high-income countries and it may inhibits replication of the virus [9]. In addition, zinc (lozenges or syrup) reduces the average duration of the common cold in healthy people assuming zinc within 24 hours of onset of symptoms. In people taking zinc, their cold symptoms are also less likely to persist beyond seven days of treatment [9]. Moreover, it has been observed that hair zinc levels were lower in children with recurrent wheezing in comparison to healthy children [10] . Propolis is a well-known natural resinous mixture produced by honeybees from exudates from buds, plants, poplars, conifers, birch, pine, alder, willow, palm etc. Being the main constituents, flavonoids contribute greatly to the pharmacological activities of propolis [11]. Flavonoids from propolis, almost exclusively aglycones, despite their antibacterial, antiviral, antifungal, and anti-inflammatory properties, are characterized by low solubility and poor bioavailability. Propolis has been widely investigated for its antibacterial, antiviral, and anti-inflammatory properties [12] and is administered as an add-on therapy during watchful waiting for better control of symptoms in non-streptococcal pharyngitis [13]. The above-mentioned considerations, have suggested Pediatrica Srl to develop a food supplement specific for pediatric age for the well-being of the airways (PediaFlù). This product is actually on the market as adjuvant in seasonal diseases and its effectiveness has been evidenced on a bibliographic basis, in line with the category to which it belongs. Notably, in a study with the University of Trieste using the diffusion disk method, it was shown that, with the same concentration, PropolNext® PLUS (the Propolis contained in PediaFlù) inhibits bacterial growth to a much greater extent than other extracts, in particular compared to simple propolis (data on file, Pediatrica Srl). The present clinical investigation is planned to verify and confirm these encouraging results in a setting of standard clinical practice. Therefore, the Research Question is the following: in a group of subjects suffering from acute tonsillopharyngitis, will the 6-day administration of the dietary supplement PediaFlù along with standard of care improve the acute tonsillopharyngitis symptomatology in comparison with subjects receiving only standard of care?
Objectives	The **primary objective** is to evaluate the efficacy and safety of the tested dietary supplement administered along with standard care vs standard care alone in children affected by ATP. The **secondary objectives** of the study are the assessment of the use of rescue medicine (Ibuprofen or high dose of Paracetamol) and the evaluation of the overall improvement symptoms.
Outcomes	**Primary efficacy outcome:** • Tonsillitis severity score (TSS). The results will be compared in terms of absolute change of tonsillitis severity score from baseline to final visit, between groups and intra-groups. • Number of treatment failure. The result of using rescue medicine (Ibuprofen or dosage of over 30 mg/Kg/dose daily of paracetamol) will be compared in the two groups; • AE/SAE incidence **Secondary efficacy outcomes:** • IP compliance • Overall symptoms improvement through IGAE (Investigator Global Assessment of Efficacy)
Design	Randomized, open-label, multicenter clinical investigation, with two parallel groups of subjects.
Disease	Acute tonsillopharyngitis / rhinopharyngitis (ATP)

Inclusion criteria	• male and female (children 3 - 10 years old); • acute tonsillopharyngitis / rhinopharyngitis (sore throat, catarrhal angina), duration of complaints ≤ 48 hours, • negative rapid test for β-hemolytic streptococcus or nasal and/or pharyngeal exudate culture and identification, and SARS-COV-2 infection • tonsillitis symptoms score (TSS) ≥ 8 points, • both parents capable of and freely willing to provide written informed consent prior to participating in the clinical investigation. • for children above 6 years old capable willing to provide written informed consent prior to participating in the clinical investigation.
Exclusion criteria	• evidence of lacunar or follicular angina. • more than two episodes of tonsillitis within the last 12 months, • mandatory indication for therapy with antibiotics (e.g., abscess, septic tonsillitis, status post rheumatic fever, post-streptococcus glomerulonephritis, and chorea minor Sydenham), • treatment with antibiotics within 4 months prior to study inclusion, • increased hemorrhagic diathesis, chronic diseases (e.g. severe heart, kidney or liver diseases, primary or secondary immunodeficiencies • history of close contact with SARS-COV-2 infected individuals in the last 10 days before symptoms onset, • known or suspected hypersensitivity to study medication, • concomitant treatment potentially influencing study outcome or known interactions with study medication (e.g., coumarin derivatives), • participation in another clinical study within the last 3 months prior to clinical investigation inclusion.
Number of patients	150 screened subjects (130 enrolled subjects + 20 screening failure) 130 enrolled subjects (120 evaluable subjects + 10 drop outs): - 65 subjects: standard care - 65 subjects: standard care + PediaFlù®
Sample size calculation	The sample size was calculated based on the primary outcome Tonsillitis severity score (TSS) and based on the results of similar investigation [14]. We have considered the minimally clinically difference between the tested group (dietary supplement PediaFlù® along with standard of care) and control group (standard of care only), after 6 days of treatment, to be 2 points decrease in mean TSS. Therefore, based on the sample size formula for comparison of two means (2-sample) at a significance level of 5%, a power of 80% and a minimally clinically important difference of 2 ±3.85 points, 120 subjects are required to be enrolled for this study. To obtain this number of evaluable subjects it will be needed to screen about 150 subjects (including potential screening failure and estimated drop-out subjects).
Number of Centers	4-5 Centers (located in Romania)
Not allowed concomitant treatment	During the study period, antibiotics and other concomitant treatment potentially influencing study outcome or known interactions with study medication (e.g., coumarin derivatives),
Active Administration	Group A: Standard of care Group B: Standard of Care + PediaFlù® (food supplement based on Pelagon P-70 ™ (equal to Pelargonium sidoides d.e. 133,3mg /100ml), PropolNext® PLUS (equal to propolis d.e. 7.7mg / 100ml), zinc (13.3 mg / 100ml), honey (5.5gr / 100ml) 5ml x 3/day for children below 6 years old for 6 days (oral administration) 10ml x 3/day for children above 6 years old for 6 days (oral administration).
Administration duration	6 days

Chronogram of visits	**The study foresees 4 visits per subject:** • Visit 1 (day -2 to day -1): Screening • Visit 2 (day 0): Baseline - Start of administration • Visit 3 (day 4): Interim visit • Visit 4 (day 6): End of the study visit
Procedures	**a) Visit 1: Screening assessments (day -1 to day -2)** • Informed consents • Inclusion/ Exclusion Criteria • Demographics and Medical History • Physical examination • Concomitant treatments • Disease assessment • Rapid test for detection of beta-hemolytic streptococci or nasal and/or pharyngeal exudate culture • Rapid test for detection of SARS-COV-2 • TSS questionnaire • AE/SAE collection **b) Visit 2: Baseline (Day 0)** • Exclusion criteria; • Physical examination • Disease assessment; • Concomitant treatments; • TSS • AE/SAE collection; • Products delivery to subject • Patient's diary delivery with instructions on how to fill it; **c) Visit 3: Interim visit (Day 4)** • Exclusion criteria; • Physical examination • Disease assessment; • Concomitant treatments; • TSS • AE/SAE collection; • Patient's diary verification **d) Visit 4: Final visit (Day 6)** • Exclusion criteria; • Physical examination; • Disease assessment; • Concomitant treatments; • TSS • IGAE; • PGAE (Patient global assessment of efficacy); • Return of the patient's diary • Return of the unused study products and accountability; • Safety assessment through IGAS and AE/SAE collection.
Statistical analysis	All statistical analyses will be performed using the R statistical software v 3.5. The final analysis will be completed after all subjects have been exited from the study, all queries have been resolved, and the database has been locked. The overall type I error rate will be preserved at 5%. All tests will be two-sided. Data from unscheduled visits will not be included in the analysis. Statistical analyses will be conducted on all subjects who have successfully completed the study without a CIP deviation that is regarded as impacting the assessment of the

	key variables (as per CIP). The quality and completeness of the collected data will be evaluated preliminarily compared to data analysis. If a subject is missing information for one or more variables, even after the resolution of its query, the missing data will not be replaced. If a subject has been involved in violation of inclusion/exclusion criteria, the respective data will be excluded from the analysis. Quantitative variables (i.e. demographic) if normally distributed will be described through media, standard deviation (SD); non-normally distributed variables will be described using median and range of interquartile. The Student's t-test and the Mann-Whitney U will be employed to perform comparative analysis in accordance to the distribution of these variables. Factorial variance analysis can also be used to evaluate any interactions between quantitative variables and linear progression models to relate possible confounding bias with independent variables. Categorical variables will be finally described using frequencies and percentages and comparative analysis will use the chi^2 test.	
GCP Statement, Guidelines and legislation	The clinical investigation plan of the present study will be developed in accordance with the following: • Directive 2002/46/EC • ICH Harmonized Tripartite guidelines for Good Clinical Practice (ICH GCP) requirements • Local Romanian legislation	
Timing	Start of the Project	(Time 0)
	Protocol submission to EC	19.03.2021
	EC positive vote	26.03.2021
	Start of enrolment (FPI)	09.04.2021
	End of administration (LPO)	10.06.2021
	Final Analysis (first draft)	20.07.2021

OBSERVATION AND ASSESMENTS' SCHEDULE

Procedures	***Visit 1***	***Visit 2***	***Visit 3***	***Visit 4***
Days	***-2 to-1***	***0***	***4***	***6***
Informed consent	X			
Inclusion Criteria	X			
Exclusion Criteria	X	X	X	X
Demographics and Medical history	X			
Physical examination	X	X	X	X
Disease assessment	X	X	X	X
Rapid test for detection of beta-hemolytic streptococci or nasal and/or pharyngeal exudate culture (if Mc Isaac score is 0-1) and SARS-COV-2	X			
Concomitant treatments	X	X	X	X
TSS	X	X	X	X
Product delivery (food supplement + standard of care/ standard of care)		X		
Product return (food supplement + standard of care/ standard of care)				X
Subject diary delivery		X		
Patient's diary verification			X	
Subject diary return				X
Products accountability				X
IGAE				X
PGAE				X
Adverse Events	X	X	X	X

1. GENERAL INFORMATION

1.1 Title

A randomized open, two arms, controlled study to evaluate the efficacy and safety of PediaFlù® (dietary supplement) along with standard of care in children with acute tonsillopharyngitis / rhinopharyngitis versus standard of care only.

1.2 Trial Registration

Following the WHO statement on public disclosure of clinical trial results (world health organization, 2015), before a clinical trial is initiated its details must be registered in a publicly available, free to access, searchable clinical trial registry complying with WHO's international agreed standards. The final version of this protocol will be recorded in www.clinicaltrials.gov before submitting to the Local Ethics Committees (EC).

1.3 Protocol Version

ISSUE DATE: 3.0 (FINAL) – 16/03/2021

1.4 Funding

1.4.1 Sources and types of financial, material and other support

Pediatrica SRL is the Sponsor of this trial. As requested by the current legislation, the Sponsor is funding all the costs related to the study and it will provide PediaFlù®, the nutraceutical product to the Clinical Sites.

1.5 Roles and Responsibilities

1.5.1 Contributor ship

Pediatrica SRL originally conceived the project and assigned Opera CRO to elaborate the study protocol. The personnel of Opera CRO (Dionisio Franco Barattini, Simone Guadagna, Nicola Gavrila) defined the study rationale, design, and protocol content; statistical and data management expertise was given by Georgeta Burov (Opera CRO). The final manuscript, previously approved by all authors and by the Sponsor, will be presented to the potential Investigators.

1.5.2 Sponsor

Sponsor	Pediatrica SRL
Contact Name	Alessandro Centi
Address	Via Nicolodi 28/A, 57121 Livorno (LI), Italy
Phone	+39 0586 426473
e-mail:	info@pediatrica.it

The role of Pediatrica SRL as Sponsor is defined by the current legislation in clinical trial. In this study, Pediatrica SRL will have no role in the collection, management, analysis, and

interpretation of study data. The Sponsor will have no role in scientific conclusion of the final report.
In addition, the Sponsor reserves the right to use the results obtained as documentary and scientific backing in proceedings regarding the regulatory authorities and/or for updating their own staff.

1.5.3 Investigational Centers

Four or five private clinical centers located in Romania, with all necessary tools required by the present CIP for the investigations, will be selected for this trial. The centers list will be included in TCF and TMF.

1.5.4 Principal Investigators Roles:

- Indications and suggestions for potential protocol revisions and amendments.
- General coordination of the trial.
- Indications and general coordination for article publication and dissemination of study results.

1.5.5 CRO

Pediatrica SRL, as Sponsor of the trial, designated Opera Contract Research Organization (Opera CRO) to perform the following activities:

- Supporting to protocol development.
- Supporting the Investigator to perform the ethical and administrative procedure.
- Monitoring and source data verification of the trial.
- Quality control.
- Data Management with maintenance of the information technology (IT) system and data entry.
- Statistical Analysis.
- Supporting the Principal Investigator to the final report and article writing.

The extent of the delegation had been specified in a contract between the involved parties. During the study period, the CRO should implement quality assurance and quality control procedures, but the Sponsor will have the right to supervise the implementation of the methods to ensure the quality.

1.6. Current legislation and guidelines

This trial is in accordance with the Guidelines for Good Clinical Practices and complies with the current Romanian legislation concerning the food supplements:

- "Ordinul pentru aprobarea procedurii privind modul de realizare a notificării produselor finite pe bază de plante medicinale, aromatice şi produse ale stupului care se notifică de către operatorii din domeniu şi se încadrează ca suplimente alimentare, produse de uz intern sau extern, exclusiv produsele cosmetice emis de Ministerul Agriculturii si Dezvoltarii Rurale"
- "Ordinul pentru aprobarea Normelor privind suplimentele alimentare emis de Ministerul Sănătății Publice"
- "Ordinul privind modificarea și completarea Ordinului ministrului agriculturii, pădurilor și dezvoltării rurale și al ministrului sănătății nr 244/401 din 22 aprilie 2005

privind prelucrarea, procesarea și comercializarea plantelor medicinale și aromatice utilizate ca atare, partial procesate sau procesate sub formă de suplimente alimentare predozate emis de Ministerul Agriculturii și Dezvoltării Rurale”

1.7 Timing

Activity/Step	Time (Milestones dates)
Start of the Project	(Time 0)
Protocol submission to EC	19.03.2021
Approval by Competent Authority	26.03.2021
Start of enrolment (FPI)	09.04.2021
End of treatment (LPO)	10.06.2021
Final Analysis (first draft)	20.07.2021

2. INTRODUCTION

2.1 Background and Rationale

2.1.1 Acute tonsillitis or acute pharyngitis (acute tonsillopharyngitis -ATP).

The tonsils are part of the systemic immune system. Additionally, the tonsils represent a local defense that involves B- and T-cell activity.
Tonsillopharyngitis is an acute infection of the pharynx, palatine tonsils, or both. Symptoms may include sore throat, dysphagia, cervical lymphadenopathy, and fever. Diagnosis is clinical, supplemented by culture or rapid antigen test.
Acute tonsillitis is mainly caused by viruses, such as double-stranded DNA viruses (human adenoviruses, Epstein Barr Virus), single-stranded DNA viruses (Human Boca Virus), single-stranded RNA viruses (influenza and para-influenza viruses; rhinoviruses; entero-viruses including Coxsackie viruses; corona viruses; respiratory syncytial virus (RSV); human meta-pneumo-virus), retroviruses [human immunodeficiency viruses (HIV)] [15].
The term sore throat is used to define all kinds of acute inflammatory symptoms in the throat. Sore throat is more common in children than in adults. Children may experience six to eight upper respiratory tract infections [16]. Half of these infections are associated with pharyngitis. A viral pharyngitis is frequently accompanied by a runny nose and cough. In normal children both viral (15–40%) and bacterial infections (30–40%) are common. In adults' infections are generally viral. Group A beta-hemolytic streptococcal (GABHS) is generally the primary causative organism rather than a secondary invader. GABHS infections are rarely seen in and in adults and children below the age of two [17,18].
In about 30% of patients, the cause is bacterial. Group A beta-hemolytic streptococcus (GABHS) is most common, but Staphylococcus aureus, Streptococcus pneumoniae, Mycoplasma pneumoniae, and Chlamydia pneumoniae are sometimes involved. Rare causes include pertussis, Fusobacterium, diphtheria, syphilis, and gonorrhea. GABHS occurs most commonly between ages 5 and 15 and is uncommon before age 3 [19].
Pain with swallowing is the hallmark and is often referred to the ears. Very young children who are not able to complain of sore throat often refuse to eat. High fever, malaise, headache, and GI upset are common, as are halitosis and a muffled voice. A rash may also be present. The tonsils are swollen and red and often have purulent exudates. Tender cervical lymphadenopathy may be present. Fever, adenopathy, palatal petechiae, abdominal pain and exudates are somewhat more common with GABHS than with viral tonsillopharyngitis, but there is much overlap. However, the use of simple clinical scores (Mc Isaac score) may be useful in the screening of children with suspected GABHS tonsillopharyngitis who should have undergone GABHS rapid test detection [20].

2.1.2 Rationale and Research Hypothesis

Sore throat or acute tonsillopharyngitis, often referred to as angina catarrhalis in Central and Eastern Europe, affects mainly children, adolescents and young adults and is one of the most common reasons to consult a family physician. While most patients complaining of sore throats have an infection, it has been estimated that fewer than 20% present a clear indication for antibiotic therapy [1], i.e., are positive for hemolytic streptococcus.
Since only a small subset of patients suffers from streptococcal infections and even these cases only rarely develop late complications such as rheumatic fever, widespread prescription of

antibiotics for sore throat has come under increased criticism. These opinions have been supported by the American Academy of Pediatrics [21], which recommends antibiotic therapy only for children with pharyngitis, evidently caused by group A streptococcus. Thus, there is certainly a therapeutic need for new treatment strategies, at least for those without streptococcal infection [5]. The use of antibiotics for viral pharyngitis is incorrect, expensive, and encourages antibiotic resistance, in addition to causing adverse reactions (ie, rash, abdominal pain, diarrhea, and vomiting), with no medical benefit. Non-streptococcal pharyngitis normally follows a benign course but:

- can have an unusually long and severe symptomatology, which is disabling and prevents the normal daily activities of the child such as eating, and is treated with repeated administration of drugs like paracetamol or ibuprofen; and
- can evolve to tracheitis, bronchitis, or rhinosinusitis [13].

Acute tonsillopharyngitis (ATP) is a highly prevalent, seasonal infective disorder characterized by an inflammation of the pharynx and the palatine tonsils, which occurs in all age groups and accounts for about 5% of all visits in pediatric care [2]. Common symptoms of ATP include sore throat, dysphagia, red pharynx, enlarged tonsils covered with a yellow, blood-tinged exudate, fever with sudden onset, malaise, gastrointestinal complaints, halitosis, rhinorrhea and cough [3]. Children with non-streptococcal tonsillopharyngitis are often over-treated with antibiotics [4]. In an acute viral disease like ATP, only minimal treatment emergent risk and side effects can be justified, notably in children. Unless there is evidence of bacterial infection (in which antibiotic treatment could be indicated), the focus of treatment is therefore on symptom control and accelerated recovery. In ATP, current disease management guidelines from Europe and North America agree that antibiotic treatment should only be administered in cases of confirmed bacterial infection, even in which some guidelines advocate the use of antibiotics only for patients who are at an increased risk of severe complications [20]. Supportive treatment, which is recommended in all other cases, is aimed at relieving the symptoms caused by ATP, and includes analgesia, hydration, and rest. In some cases, antitussive medication (e. g., dextromethorphan, codeine, hydrocodone) is suggested. Still, the American Academy of Pediatrics and the Food and Drug Administration (FDA) does not recommend the use of antitussive drugs in children under 6 years of age [22,23].The scientific literature currently available shows that the extract of Pelargonium sidoides may be effective in the treatment of disorders affecting the respiratory tract [5,12,13].

A 6-day study with administration of an extract of Pelargonium sidoides in pediatric patients with acute non-streptococcal tonsillopharyngitis showed a clinically relevant decrease of disease symptoms significantly superior to placebo [5]. The Pelargonium sidoides extracts are also mentioned in list of Botanicals (European Food Safety Authority, Compendium of Botanicals) as able to support the physiological and correct functionality of the upper airways and the well-being of the body. Furthermore, a herbal drug made from roots of Pelargonium sidoides extract, has been shown to exhibit antiviral [8], antibacterial as well as modulating and stimulating effects on the non-specific immune system, which are based on inhibition of bacterial adhesion to host cells, improved phagocytosis and intracellular killing of microbes, increased mucociliary clearance, interferon-like action and enhancing effects on the production of cytokines [9]. The latter two are especially essential for activation of innate defense mechanisms against infections. Pelargonium sidoides is a traditional medicinal plant native to South Africa, shares the same genus (Pelargonium) with the common ornamental geraniums. The roots of P. sidoides have centuries-long been used as herbal remedies for respiratory and gastrointestinal infections by the local populations. It was described over 120 years ago by the Englishman Charles Henry Stevens, who praised the root as a new remedy for tuberculosis. Identification of numerous compounds of P. sidoides roots, such as prodelphinidins,

methoxycoumarin, and proanthocyanidins, led to the production of different extracts [24]. An extract known as Pelagon P 70™ is the active ingredient of the product PediaFlù®. This extract is obtained with ethanol at 11% m / m starting from a dose / extract ratio of 8-10: 1, subsequently dried by spray drying. In the package of PediaFlù® it is called dry extract, which contains 70% of dried liquid extract and 30% of maltodextrin (the powder product has, at the end of the process, a D / E ratio of 4-25: 1). EPS 7630® extract, registered by the Schwabe company as API, is a liquid extract obtained with 11% m / m ethanol and dose / extract ratio 8-10: 1. The quantities shown in the nutritional table below referring to the recommended daily dose are in line with the data reported in the scientific literature in terms of efficacy of the herbal extract of Pelargonium sidoides [25]. The scientific literature currently published shows that the extract of Pelargonium sidoides has been shown to be effective in the treatment of diseases affecting the respiratory tract [6,7,14].
In addition, the investigational product also includes Propolis and Zinc, two substances with a long tradition of use and literature to support their use in seasonal prevention and / or in the acute phase of colds [9,26].

Evidence shows that zinc is beneficial for the common cold in healthy children and adults living in high-income countries and it may inhibit replication of the virus [9]. Pooled results from the trials showed that zinc reduced the duration of common cold symptoms when used therapeutically [9]. Moreover, it has been observed that hair zinc levels were lower in children with recurrent wheezing in comparison to healthy children [10].

Propolis is a well-known natural resinous mixture produced by honeybees from exudates from buds, plants, poplars, conifers, birch, pine, alder, willow, palm etc. Raw propolis consists of about 50% resins, 30% waxes, 10% essential oils, 5% pollen, and 5% various organic compounds, including flavonoids, phenylpropanoids, terpenes, stilbenes, lignans, coumarins, and their prenylated derivatives, with >300 different substances identified [27]. The precise chemical composition of propolis depends on geographical location, botanical origin, and bee species involved. The main chemical components in propolis, studied mostly in terms of pharmacological activity, are pinocembrin, pinobanksin, caffeic acid phenethyl ester, artepillin C, cinnamic acid, p-coumaric acid, caffeic acid, ferulic acid, isoferulic acid, chrysin, galangin, kaempferol, and quercetin. Being the main constituents, flavonoids contribute greatly to the pharmacological activities of propolis [11]. Flavonoids from propolis, almost exclusively aglycones, despite their antibacterial, antiviral, antifungal, and anti-inflammatory properties, are characterized by low solubility and poor bioavailability [28]. The solubility and oral bioavailability of flavonoids have been reported to be increased by utilizing the phytosome forms and cogrinding technology. Propolis has been widely investigated for its antibacterial, antiviral, and anti-inflammatory properties [12], and could be administered as an add-on therapy during watchful waiting for better control of symptoms in non-streptococcal pharyngitis. It was shown that the use of propolis lessens the severity of viral pharyngitis, reduces the use of antipyretics and anti-inflammatory drugs, and decreases the rate of evolution to tracheitis, bronchitis, and rhinosinusitis. Studies shows that propolis could be used as a safe add-on therapy in case of viral pharyngitis and/or early acute otitis media [19]. Moreover, it was observed that PropolNext® PLUS (the Propolis contained in PediaFlù) inhibits bacterial growth to a much greater extent than other extracts, in particular compared to simple propolis [29].

The above-mentioned considerations, have suggested Pediatrica Srl to develop a food supplement specific for pediatric age for the well-being of the airways (PediaFlù). This product

is currently on the market as adjuvant in seasonal diseases and its effectiveness has been evidenced on a bibliographic basis, as it is requested for food supplements.
The present clinical investigation is planned to verify and confirm these encouraging results in a setting of standard clinical practice. Therefore, the research question is the following: in a group of subjects suffering from acute tonsillopharyngitis, will the 6-day administration of the dietary supplement PediaFlù® along with standard of care improve the acute tonsillopharyngitis symptomatology in comparison with subjects receiving only standard of care?

2.2 Study Objective

The primary objective is to evaluate the efficacy and safety of the tested dietary supplement administered along with standard care vs standard care alone in children affected by ATP.

The secondary objectives of the study are the assessment of the use of medicines in SOC and rescue and the evaluation of the overall improvement symptoms.

2.3 Study Design

This is a randomized, open label, controlled, multicenter study, with two parallel groups of subjects with a superiority hypothesis. This clinical investigation will be performed in Romania.

2.4 Potential risks and benefits

2.4.1 Risks

The potential risks for the involved subjects are those relative to the oral *P. sidoides* extracts administration. Commonly cited side effects include stomach upset, nausea, heartburn, or worsening respiratory symptoms [30].

Pelargonium contains a substance known as coumarin that acts as an anticoagulant (blood thinner). Because of this, the subjects should avoid taking pelargonium with prescription anticoagulants like warfarin as this could lead to excessive bleeding. For the same reason, the administration of pelargonium should be stopped at least two weeks before a surgery or a dental procedure even if the European Medicines Agency (EMA) reports that it is unlikely that an increased bleeding tendency can arise in patients treated with *P. sidoides* extracts [31].
Pelargonium should also be used with caution in people with autoimmune diseases like psoriasis, rheumatoid arthritis, lupus, and autoimmune hepatitis, according to EMA [31]. Doing so may activate the antibodies that trigger autoimmune symptoms.

2.4.2 Benefits

Participation in this investigation should not cause to the enrolled subjects any discomfort or harm. In fact, this clinical investigation has been planned (i.e. the study design is open, the Investigators have specific experience in clinical trial in pediatrics and they will be trained before the study starts), to minimize discomfort and any predictable risk for the enrolled population of children. The potential anticipated clinical benefits for the subjects should be similar or better than those of the population treated with the single ingredients of PediaFlù® (Pelargonium, Propolis, Zinc and Honey) in clinical investigations observed in the literature.

3. METHODS

3.1 Study setting

We chose the 4-5 participating clinical sites so that they could be representative for this clinical investigation.

3.2 Selection of population

The study population will include the subjects fulfilling the inclusion and exclusion criteria and submitted in the involved centers for acute tonsillopharyngitis or acute pharyngitis (ATP).

3.3 Enrolment of subjects

The randomization procedure will be performed centrally by Opera CRO. The randomization list will be generated by the CRO statistician using the package *blockrand* (General Public License. ≥ 3) from R statistical software v 3.5 [32,33]. The randomization list was split in blocks to avoid major kits displacements between and within clinical sites. Copy of the randomization list will be kept at the CRO's office in Timisoara.

The investigational product will be delivered to clinical sites according to a randomization scheme 1:1 and to the randomization list. Each clinical site will be re-supplied when the study investigational product will be almost totally allocated to enrolled subjects.

Once the eligibility was established according to Inclusion/Exclusion Criteria, subjects will be allocated in a 1:1 group assignment ratio to standard of care + PediaFlu® (tested food supplement) or standard of care (control group) using an online web service (https://edc.operacro.com:4xx), available 24 hours a day. The Investigator should login using the credential received at SIV or before the enrolment start, to create a new subject using the specific function, to confirm that the eligibility criteria are met and after to access the button for randomization. The web service will indicate to the Investigator the assigned group, specific for each subject in each site. In the eventuality of a non-functional electronic randomization method, the investigator should report immediately to the CRA the situation and will receive the assigned group by phone call and/or fax.

3.4 Subject identification

Each subject enrolled will be identified by a five digits code (i.e. 01.001), which will be the only identification element and will be used only for the purposes of this study. This code will be the Clinical Centre number (i.e. 01-004 corresponding to the Investigational Centers) and the sequence number of the subject (i.e. .001 that means the 1st subject patient in this Centre).

3.5 Number of subjects

It is estimated that the data will be collected from about 150 screened subjects and 130 enrolled subjects in multiple clinical sites.

3.6 Inclusion and exclusion criteria

3.6.1 General information about inclusion and exclusion criteria

The following criteria must be evaluated before doing any procedure planned by the protocol.

3.6.2 Inclusion criteria

- Patients will be eligible for inclusion if all the following criteria are respected:
- male and female (children 3 - 10 years old);
- acute tonsillitis / rhinopharyngitis (sore throat, catarrhal angina), duration of complaints ≤ 48 hours,
- Absence of pharyngeal exudate and/or Mc Isaac score 0-1 + negative rapid test for β-hemolytic streptococcus and SARS-CoV-2 identification
- tonsillitis symptoms score (TSS) ≥ 8 points,
- both parents capable of and freely willing to provide written informed consent prior to participating in the clinical investigation.
- for children above 6 years old capable willing to provide written informed consent prior to participating in the clinical investigation.

3.6.3 Exclusion criteria

Patients fulfilling ***ANY*** of the following exclusion criteria will not be included in the study:

- evidence of lacunar or follicular angina.
- more than two episodes of tonsillitis within the last 12 months,
- mandatory indication for therapy with antibiotics (e.g., abscess, septic tonsillitis, history of rheumatic fever, post-streptococcus glomerulonephritis, and chorea minor Sydenham),
- history of close contact with SARS-COV-2 infected individuals in the last 10 days before symptoms onset
- treatment with antibiotics within 4 months prior to study inclusion,
- increased hemorrhagic diathesis, chronic diseases (e.g. severe heart, kidney or liver diseases), immunosuppression,
- known or suspected hypersensitivity to study medication,
- concomitant treatment potentially influencing study outcome or known interactions with study medication (e.g., coumarin derivatives),
- participation in another clinical study within the last 3 months prior to clinical investigation inclusion.

3.7 Withdrawal criteria

Patients may withdraw from the study at any time at their own request without giving any reason for. In these cases, if the patient gives a reason, the Investigator will explain on the CRF the reasons for the withdrawal from the study and the subject will be considered as drop out.

3.8 Premature termination/suspension of the trial

The Sponsor may stop this clinical investigation in a clinical center for any of the following reasons:

- the centers cannot include an adequate number of subjects;

- serious and/or persistent non-compliance with the protocol;
- careless or premeditated false documentation in the CRFs;
- inadequate co-operation with the CRO and/or Clinical Center;
- non-compliance with GCP, Standard Operating Procedures (SOPs) or regulatory requirements;
- any of the Investigator asks to discontinue the trial;
- lack of confidentiality.

If the trial is prematurely terminated or suspended for any reason, patients will be informed promptly, and the EC will be notified.

3.9 Investigational Product

3.9.1 Investigational food supplement active ingredients

PediaFlù® oral solution is a food supplement based on pelargonium sidoides, propolis and zinc. The qualitative and quantitative composition inherent to the active ingredients is reported in Annex 1.

3.9.2 Investigational food supplement preparation and delivery

The Investigational nutraceutical products will be provided by Pediatrica SRL, as Sponsor of the trial. The boxes will be labelled according to *EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use- Annex 13 Investigational Medicinal Products (paragraph 26 – labelling)* that complies with the requirements of *Directive 2003/94/EC.*

3.9.3 The investigational food supplement administration and duration

During the 6 days of the clinical investigation, the subject will administer 5ml x3 times per day for children below 6 years and 10mlx3 times per day for children above 6 years of PediaFlù®. Its composition is listed at point 3.9.1

3.9.4 Packaging and labelling of the investigational food supplement

Each PediaFlù® box will be labelled with the following information:

- Route of administration, quantity of dosage units;
- Investigational Centre number;
- Subject number;
- Study code;
- Directions of use;
- Storage conditions;
- Statement “For clinical investigation purpose only. Do not sell”;
- Statement “Keep away from children”
- Batch number and expiry date;
- Sponsor and CRO names and addresses.

The text of labels will be made according to the legislation in force.

3.9.5 Investigational product storage and accountability

It will be the Investigators responsibility to ensure the following:

- The deliveries of the investigational product will be supplied by the Sponsor to the Centre (CRO personnel will collect the receipt forms);
- The investigational food supplement must be handled and stored safely (at an ambient temperature of up to 25 ° C, away from light and heat) in a secured area;

The investigational product will be delivered to the subject only by authorized personnel (Principal Investigator or Co-Investigators under his/her direct supervision) in accordance with the protocol.
The investigational food supplement inventory and accountability records will be kept by the Investigator, by the Pharmacist, or by other authorized persons.
To ensure adequate records, all investigational product administration will be recorded in the accountability forms. Patients must be reminded to return all unused investigational product to the Investigator, unless otherwise stated by the Sponsor, at the end of the clinical investigation the investigational product not allocated, unused or partially used by the patients will be collected by the CRO personnel and sent to the Sponsor or destroyed as indicated by the Sponsor.

3.9.6 Investigational product discontinuation or dose change

During the study period no dose change is planned.
In any case, the Investigator can always decide to stop the administration of the investigational food supplement for AE/SAE or to administer different therapies if he considers it necessary for the health of the patient.
The cause for discontinuation of administration, if applicable during the study, must be recorded in the source documents and also in the Case Report Form.
The Investigator will advise the patient to resume the administration after a discontinuation of administration, if indicated.

3.9.7 Concomitant care and interventions

During the study period, the following concomitant treatments will not be allowed: coumarin based products, antibiotics.

There is no restriction on treatments taken previously by subjects for clinical conditions not related to the study condition.

Any change in the treatment dose taken by the patient, for clinical conditions not related to the study pathology, will be recorded by the Investigator in the CRF.

3.9.8 Standard of care

Standard of care for acute tonsillitis / rhinopharyngitis is focused on symptomatic treatment:

- Nasopharyngeal liberation through hydration with drinking fluids to support body fluid excretion, aspiration of secretions, NaCl solution for nasal irrigation, Nasal sprays with sea water, nasal spray with active compound (to be used only at special indication of the medical doctor)

- Throat spray with Benzydamine hydrochloride (Tantum Verde®), Pediatric use: children over 6 and below 12: 4 sprays 2 - 6 times a day. Children (under 6 years): 1 spray per 4 kg of body weight, a maximum of 4 sprays at once, 2-6 times a day according to the leaflet. Each spray equals 0.17 ml of solution.
- Acetaminophen (Paracetamol) per os: at need, as antipyretic (>38,5C), 10 mg/kg/dose, per need every 6-8 hours or according to the leaflet, maximum dosage 80 mg / kg / day. A dosage of over 30 mg/Kg/dose will result in an IP failure;

3.9.9 Rescue medicine

If standard of care treatment does not succeed in the amelioration of symptoms for a subject, the Investigator will decide to use additional AINS as anti-inflammatory medicine; Ibuprofen will be administered per os with a dose of 10 mg/Kg/dose (dosage maximum 30-40 mg/Kg/die). In these cases, all the administrations of the rescue medicine will be documented and the subject will be considered in the group treatment failure.

3.10 Study procedures and collected variables

Data will be collected and evaluated as follows:

a) Visit 1: Screening assessment (day -1 to day -2)
- Informed consents
- Inclusion/ Exclusion Criteria
- Demographics and Medical History
- Physical examination
- Concomitant treatments
- Disease assessment
- Rapid test for detection of beta-hemolytic streptococci or nasal and/or pharyngeal
- Rapid test for detection of SARS-COV-2
- TSS questionnaire
- AE/SAE collection

b) Visit 2: Baseline (day 0)
- Exclusion criteria;
- Disease assessment;
- Concomitant treatments;
- TSS
- AE/SAE collection;
- Products delivery to subject
- Patient’s diary delivery with instructions on how to fill it;

c) Visit 3: Interim visit (day 4)
- Exclusion criteria;
- Disease assessment;
- Concomitant treatments;
- TSS
- AE/SAE collection;
- Patient’s diary verification

d) Visit 4: Final visit (day 6)

- Exclusion criteria;
- Physical examination;
- Disease assessment;
- Concomitant treatments;
- TSS
- IGAE;
- Return of the patient's diary
- Return of the unused study products and accountability;
- Safety assessment through IGAS and AE/SAE collection

d) Unscheduled visits

The Investigator can perform at any time an unscheduled visit for a physical examination and/ or other tests if he/she deems it necessary in order to check the patient's wellbeing and collect any examinations or relevant data. Relevant data collected will be noted in the CRF.

3.11 Definitions

Adverse Event

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational product (IP). This definition includes events related to the IP. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to IP.

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

- Results in death. This includes any death that occurs during the conduct of a clinical trial, including deaths that appear to be completely unrelated to the IPs (e.g., car accident).
- Is life-threatening. This includes any AE during which the subject is, in the view of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include events that may have caused death if they had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Other medical events that based upon appropriate medical judgment are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Note:

Planned hospitalization due to a pre-existing condition (corrective procedure, etc.) will not be registered as a SAE.

Signs/symptoms related to lack of efficacy should not be considered as AEs.

3.12 Safety

Any AE/SAE will be reported by the Investigators according to the current legislation. In any case, all adverse events will be collected by Investigators and evaluated for safety (secondary outcomes of the study).

Adverse Event Relatedness

The investigator will be responsible for deciding on the causal relationship of the AE. Specifically, the investigator will report whether the AE was related to the procedures or IP administration.

The causal relationship for each adverse event will be rated as follows:

- Unrelated: The event is not related to the procedures, IP, or progression of disease.
- Unlikely Related: The temporal sequence is such that the relationship is unlikely. It is unlikely there is any relation between the event and the procedure, IP, or progression of disease.
- Possibly Related: The temporal sequence is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the patient's condition. There is a possibility of any relation between the event and the procedure, IP, or progression of disease.
- Related: The temporal sequence is relevant, or the event abates upon completion of the procedure, IP, or the event cannot be reasonably explained by the patient's condition or comorbidities. The event is related or most likely associated with the procedure, IP, or progression of disease.

Adverse Event Severity

Each AE should be assessed for its severity, or the intensity of an event, experienced by the subject.

- Mild: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient and is resolved without treatment or sequelae.
- Moderate: May interfere with the subject's activity and require additional intervention and/or treatment and may have additional sequelae.
- Severe: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and/or treatment are necessary. Additional sequelae occur. Severe is used to describe the intensity of an event experienced by the subject.

Adverse Event Reporting

All adverse events will be reported by the investigator and reviewed by the Sponsor in compliance with applicable regulations. Adverse events may be volunteered by patients, elicited by the investigator or designee, or collected via observation by the investigator.

All AEs will be assessed by the investigator who will determine whether or not the event is related to the procedure, related to the tested product, and whether or not the event meets serious criteria. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE form on the CRF. Documents must be submitted to the sponsor within a timely manner to ensure timely assessment of the event as appropriate.

In addition, patients will be instructed to contact the investigator or a member of their care team if any significant adverse events occur between study visits.

An adverse event assessment will be performed at each visit. Adverse events are reported starting from the day of study procedure until patient participation has ended (i.e., completion of study or withdrawal of consent). All adverse events must be followed until resolution, AE has stabilized, or the study has been completed.

Pre-existing medical conditions or symptoms observed prior to the study procedure date will not be recorded as an AE and should be collected in the patient's medical history. In the event there is a change (i.e., worsening) in the pre-existing medical condition or symptoms after the study procedure then an AE must be reported.

Serious Adverse Event Reporting

A completed SAE form must be entered in the clinical study database of the Sponsor within 24 hours of knowledge of the event according to national requirements.

Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator. All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the patient to be stable.

The Sponsor will notify the regulatory agency of any unexpected, fatal, or life-threatening experience (expedited report) associated with the study as soon as possible but no later than ten working days after becoming aware of the event.

Copies of any reports to regulatory bodies regarding serious and unexpected AEs will be provided to the investigators for review and submission to the EC. The communication of any SAEs to the EC and Competent Authority if needed, will be done according to national requirements in Romania by the Investigator). Copies of SAEs correspondence with the investigators, regulatory bodies, and Sponsor must be retained with study records.

3.13 Schedule of observation points and assessments

Procedures	***Visit 1***	***Visit 2***	***Visit 3***	***Visit 4***
Days	***-2 to-1***	***0***	***4***	***6***
Informed consent	X			
Inclusion Criteria	X			
Exclusion Criteria	X	X	X	X
Demographics and Medical history	X			
Physical examination	X	X	X	X
Disease assessment	X	X	X	X
Rapid test for detection of beta-hemolytic streptococci or nasal and/or pharyngeal exudate culture (if Mc Isaac score is 0-1) and SARS-COV-2	X			
Concomitant treatments	X	X	X	X
TSS	X	X	X	X
Product delivery (food supplement + standard of care/ standard of care)		X		
Product return (food supplement + standard of care/ standard of care)				X
Subject diary delivery		X		
Patient's diary verification			X	
Subject diary return				X
Products accountability				X
IGAE				X
PGAE				X
Adverse Events	X	X	X	X

3.14 Timing of assessments

Timing of assessments to be documented is specified as follows:

3.14.1 Visit 1: Screening assessments (day -2 to -1)

Before any specific procedures are conducted and following an explanation of the purpose and risks of the study, subject's parents will sign an informed consent form (ICF). The subject will have a special ICF made according to their comprehension.

At each Centre, subjects must be enrolled consecutively following the eligibility criteria reported in paragraph *3.6.2.* and *3.6.3.* For each subject a screening form must be filled out to documented whether or not he is eligible for inclusion. If not eligible, the reason must be documented. If the subject's parents agree to give their consent along with the subject, they will sign the informed consent forms and will be enrolled into the study, but prior any study procedure or IP administration. The Investigator will start to report data on the subject's CRF from -2 to -1 days before the administration of the IP. Data to be collected include date of the ICFs sign, medical history, physical signs, disease assessments, diagnostic procedures including tonsillopharyngitis severity score (TSS).

Recording of adverse events/concomitant medication will start following consent and will continue until completion of the clinical investigation.

During screening following assessments/procedures will be performed:

- TSS
- Rapid test for detection of beta-hemolytic streptococcus or nasal and/or pharyngeal
- Rapid test for detection of SARS-Cov-2

The subjects fulfilling the inclusion criteria will receive the nutraceutical product to be administered together with the instruction to use. They will also receive the subject's diary along with the instructions to fill it.

3.14.2 Visit 2 (day 0)

For this visit, the subject will come to the site in the required timeframe, where the Investigator will undergo a general (physical) and a disease assessment.
The Investigator will undergo the following:

- Randomization of the subject to the two groups (SOC/SOC + PediaFlù)
- Verify the administration of any concomitant medication
- Product delivery
- Subject's diary delivery
- Make safety assessment through AE/SAE collection

3.14.3 Visit 3: Interim assessment (day 4)

For this visit, the subject will come to the site in the required timeframe, where the Investigator will undergo a general (physical) and a disease assessment.
The Investigator will undergo the following:

- Verify the administration of administration of IP
- Verify the administration of any concomitant medication
- Verify the completion of Subject's diary
- Make safety assessment through AE/SAE collection

3.14.4 Visit 4: Final visit assessment (day 6)

Data to be collected include disease assessments made in routine check-up and a general assessment (physical signs).

The Investigator will undergo the following:

- Verify the administration of administration of IP
- Verify the administration of any concomitant medication;
- IGAE;
- Make an accountability of the IP to evaluate if the subject followed the administration recommendation; also collect the remained products and empty boxes.
- Make safety assessment through AE/SAE collection;
- Collect the subject's diary and verify the completion.

3.14.4 End of the Trial

For each subject, the final data collection (last study observation point) is Visit 4: Final Assessment Day 6, the end of IP administration, or at the end of the study, whichever is first. The date of termination of the study will be the final visit of the last patient.

4. MODE OF COLLECTION, MANAGEMENT AND ANALYSIS OF DATA

4.1 Data collection

The documents concerning the trial [with the informed consent forms (ICF) and subject information leaflets (PIL)] will be submitted before the beginning of the study to the local EC for obtaining positive vote. After obtaining such an approval, the investigator will verify if the subjects are eligible for inclusion and will inform them about the study. The parent's subjects and subjects that agree to participate will sign the ICFs, giving the consent to be enrolled in the study.

4.2 Data storage and monitoring

Investigators will be required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual entered into the study. Data reported on the CRF must be consistent with the source documents.
All clinical data will be collected and maintained by experienced personnel who are trained in the use of clinical and research assessments. All data will be used for research purposes only, and access to data will be available only to Investigators involved in the study, to the Sponsor or Sponsor's representatives and to competent and regulatory authorities.
This trial will be conducted in accordance to the principles of GCP.
Before clinical trial initiation, the CRO personnel will visit the clinical Centers to determine the adequacy of the facilities, discuss with the Investigators and other personnel involved in the study their responsibilities with regard to protocol adherence, and the responsibilities of Sponsor or its representatives.
During the study, the CRO personnel will have regular contacts with clinical sites, including visits to:

- provides information and support to the Investigator(s);
- confirms that facilities remain acceptable;
- confirms that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRF
- performs source data verification with direct access to all original data for each subject (e.g. clinical records).

4.3 Data management

Data verification will be performed by the CRO personnel. All requested information must be entered on the CRF in the provided spaces. If an item is not available or is not applicable, it must be documented as such.
The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
The Investigator will maintain a Signature Sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. A data correction will be made only by the authorized persons.
The CRFs for this protocol will be formatted in a sequence of modules, which will correspond to the various study periods through which study subjects will progress.
The data of completed CRF will be entered in a data base by the CRO personnel for rapid data processing.

4.4. Electronic Case Report Form

Principal Investigators will collect all data on CRO's Electronic Data System (EDC). The EDC platform is an Openclinica clinical management system (www.openclinica.com). It is the CROs responsibility to keep all above-mentioned software tools to their latest and most secure versions. The web address where the EDC will reside will be provided to the investigators at the initiation visit. The access to this system is secured by a HTTPS protocol and will be kept live for an additional 6 months after the study's end.

The collected data will be subjected to multiple checks for correctness (entry errors). Every information will be verified by an SDV (Source Data Verification) process, performed by the study monitors. Data Clarification Forms (called Discrepancy Notes in Openclinica) will be implemented to obtain clean data. In addition, EDC system will be automatically checked for completeness and extreme vales (outliers) presence. Any anomalies will be forwarded by the statistician/data manager to the Investigator and/or Clinical Research Associates.

Because of legal considerations (GDPR directive effective from 21.05.2018 in all European Union countries), patients or their legal surrogates may have an absolute right to request that their data be removed from the study database. As a result, there are potentially two datasets: the full list of enrolled patients, and the patients who have kept their data available. The latter is obtained after deleting the data for patients who withheld or withdrew their consent and did not allow their data to be submitted or maintained in the database. Only the latter dataset can be used in the analysis.

The database lock will be performed as soon as the study's statistician will approve all the data for correctness and completeness, no later than 90 days after the Last Patient's Out date.

Data will be stored according to ISO 14155:2012-01. The printed hard copies (paper) of CRF will be stored in the Trial Centre File.

5. STATISTICAL CONSIDERATIONS

5.1 Sample size

The sample size was calculated based on the primary outcome Tonsillitis severity score (TSS) and based on the results of similar investigation [14].
We have considered the minimally clinically difference between the tested group (dietary supplement PediaFlù® along with standard of care) and control group (standard of care only), after 6 days of treatment, to be 2 points decrease in mean TSS.
Therefore, based on the sample size formula for comparison of two means (2-sample) at a significance level of 5% , a power of 80% and a minimally clinically important difference of 2 ±3.85 points, 130 subjects are required to be enrolled for this study. To obtain this number of evaluable subjects it will be needed to screen about 150 subjects (including potential screening failure and estimated drop-out subjects).

5.2 Statistical analysis

All statistical analyses will be performed using the R statistical software v 3.5. The final analysis will be completed after all subjects have finalized the study, all queries have been resolved, and the database has been locked.
The overall type I error rate will be preserved at 5%. All tests will be two-sided. Data from unscheduled visits will not be included in the analysis.
Statistical analyses will be conducted on all subjects who have successfully completed the study without any PMCF study deviation that is regarded as impacting the assessment of the key variables (as per protocol). The quality and completeness of the collected data will be evaluated preliminarily compared to data analysis. If a subject is missing information for one or more variables, even after the resolution of its query, the missing data will not be replaced. If a subject has been involved in violation of inclusion/exclusion criteria, the respective data will be excluded from the analysis.
Quantitative variables (i.e. demographic) if normally distributed will be described through media, standard deviation (SD); variables non-normally distributed will be described using median and range of interquartile. The Student's t-test and the Mann-Whitney U will be employed to perform comparative analysis in accordance to the distribution of these variables. Factorial variance analysis can also be used to evaluate any interactions between quantitative variables and linear progression models to relate possible confounding bias with independent variables.
Categorical variables will be finally described using frequencies and percentages and comparative analysis will use the chi^2 test.

Additional details about statistical analysis will be documented in the Statistical Analysis Plan (SAP), enclosed to the Trial Master File.

5.3 Study outcomes

Primary **outcomes**:

- Tonsillitis severity score (TSS, Intensity score 0-3, see Annex 2). The results will be compared in terms of absolute change of tonsillitis severity score from baseline to final visit, between groups and intra-groups;

- Number of treatment failure. The result of using rescue medicine (Ibuprofen or dosage of over 30 mg/Kg/dose daily of paracetamol) will be compared in the two groups;
- AE/SAE incidence.

Secondary **outcomes**:

- IP compliance (the amount of IP ingested divided by the value the subject should have ingested and multiplied by 100);
- Overall symptoms improvement through IGAE (Investigator Global Assessment of Efficacy), a 4-point scale: 1= very good efficacy, 2 = good efficacy, 3 = moderate efficacy and 4 = poor efficacy.

6. ETHICAL ASPECTS

6.1 Informed Consent

After approval of the study by the local EC, the Investigator is responsible for and will obtain the informed consent from each subject in the study, in accordance with the ICH-GCP Guidelines and the current version of the Declaration of Helsinki.
All subject's parents invited to participate in the clinical study are entitled to make their decision based on all current available information provided to them by the Investigator/designee. They will be given a document in native language written in clear concise lay language for review and consideration. According to the Romanian legislation for the subjects (children> 6 years) will be made a specific document in a language that can be understood by them. Depending on the EC a third document will be made for children under 6 years. The documents will previously have been approved by relevant EC and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the trial.
These documents will tell potentially eligible subjects / parents of the subjects about the nature of the food supplement, its efficacy and safety profile, and the human experience available. It will also outline the steps of the protocol as they will apply to the individual, including the number of visits and types of procedures/assessments to be performed so that the individual has a clear picture of the risks, inconveniences and benefits that may occur from the trial. The subject/parents subject must be made aware that he/she/they may refuse to join the trial or may withdraw his/her/their consent at any time without prejudicing further medical care. Contact details (telephone no, etc.) to report and discuss suspected study-related adverse events will be provided. Subjects parents must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by Regulatory Authorities and EC and that personal information will be collected and retained in a confidential database. Conditions for ensuring the pseudo anonymity of data and the security and confidentiality of the database should be explained.
Consent will always be given in writing after the subject/parent's subject has had adequate time to review the information and ask questions. The subject/parent's subject and the Investigator conducting the informed consent discussion will both personally write the name, sign and date the consent form. Two copies of the informed consent forms shall be signed. The Investigator shall provide one signed copy of the signed informed consent and one copy of the subject information sheet to the subject/parent's subject and will keep the second copy of the original signed forms in the onsite study file. The signed form will be reviewed by CRO personnel.

6.2 Subject's data protection

The right, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
Study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective tasks.
This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).
Systems with procedures will be implemented to assure the quality of every aspect of the study.
The Sponsor, its delegates and regulatory authorities have direct access to subject records and for the protection of the enrolled subjects, this study will be conducted respecting the actual general data protection regulations (GDPR).

According to local Legislation regarding the protection of personal data, the responsible of the data treatment/intervention of the subject in each clinical Centre is the medical doctor responsible of the Centre.

6.3 Ethical Principles

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Seventh revision, 2013), the Convention of Oviedo, April 4th, 1997 and additional Protocol January, 12th 1998 and will be consistent with GCP. In addition, the study will be in compliance with international laws and regulations and national laws of the countries in which the trial is performed, as well as any applicable guidelines. If there are conflicts between local laws and regulations, the more stringent requirements will be adopted.
The study will be conducted in compliance to the protocol: all its revisions must be discussed with and prepared by the Sponsor. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the Ethical Committee of an Amendment. Any significant deviation must be documented in the CRF.

6.4 Protocol Amendments

Any modification of the protocol which may have an impact over the study, or the safety of the patients will require a formal amendment to the protocol. This revision must be prepared by the Principal Investigator and discussed with all the authors and the Sponsor. Finally, the amendment will be submitted for approval to the Local Ethical Committees of the involved Centre.
In any case a single Investigator cannot implement any deviation or change to the protocol.

7. ADMINISTRATIVE ASPECTS

7.1 Audits and inspections

Authorized representatives of the Sponsor or a regulatory authority may visit the center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were properly conducted and data was recorded, analyzed and accurately reported according to the protocol, GCP, the guidelines of the International Conference on Harmonization (ICH) and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at his/her center.

7.3 Records retention

The Investigator must retain copies of CRFs, source documents, ICF and other documents pertaining to the study conduction for 15 years. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

7.4 CRO

The CRO, Opera Contract Research Organization Srl will be employed by Sponsor to perform the following:

- Supporting the Investigator to perform the ethical and administrative procedure;
- Monitoring of the trials and quality control;
- Data Management;
- Statistical Analysis.
- Supporting the Final Report preparation

The extent of the delegation must be specified in a contract between the involved parties. The CRO should implement quality assurance and quality control but Sponsor will have the right to supervise the implementation of the methods for quality assurance and quality control.

8. REPORTING POLICY AND PUBLICATION OF RESULTS

All information regarding this trial, obtained as a result of the study, will be regarded as confidential.
The Investigators agree that scientific results from this study are to be considered the property of the Sponsor.
Information regarding the operations and procedures of the Sponsor, obtained as a result of or in association with the conduct of this study, must be kept confidential.
Unpublished information contained herein, as well as any information received from the Sponsor for the purposes of this study, may not be disclosed to any third party without the prior written approval of the Sponsor.
No data will be used for scientific meetings and/or publication in scientific journals without prior written authorization from the Sponsor.
Any publication of data from the center in this trial will be allowed only after the study is concluded and data are published, and upon written the Sponsor approval.
The Sponsor reserves the right to use the results obtained as documentary and scientific backing in proceedings regarding the regulatory authorities and/or for updating their own staff.
The Investigators and Sponsor agree that it needs to ensure the widest publication and dissemination of data in a coherent and responsible manner. The Principal Investigator will send the clinical trial results to the Sponsor following the request of both Sponsor and CRO.
The Sponsor is committed to publication of results after study conclusion through scientific journals, ministerial bulletins, direct communications to the IEC, etc., also in the case of negative results; in addition, the Sponsor agree to notice all the Investigators (Italian Law DM 12/5/06, art.5) and to comply with the prescriptions of the Italian Ministry of Health (n. 6 dated 2/9/2002) regarding the rules for the transparency of data and their publication. The Sponsor is aware of its specific communication obligations placed by the Italian Law D.Lgs. 211/2003 as modified by DL 269/2003 and into law n. 326/2003.

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10. SIGNATURE PAGE

Print First and Last Name	Title	Signature	Date
Dionisio Franco Barattini	Opera CRO Medical Director Europe		
Simone Guadagna	Opera CRO BD Manager		
Raluca Gavrila	Opera CRO Clinical Project Manager		
Georgeta Burov	Opera CRO Biostatistician		
Fabio Cardinale	Scientific Supervisor		

ANNEX 1

PediaFlù®

PediaFlù®'s composition is shown in the table below.

Average contents	**Per 100 ml**	**Per 15 ml**	**Per 30 ml**
Pelagon P-70™ equal to Pelargonium sidoides d.e.	190,6 mg 133,3 mg	28,6 mg 20 mg	57,2 mg 40 mg
PropolNext® PLUS equal to propolis d.e.	77 mg 7,7 mg	11,55 mg 1,155 mg	23,1 mg 2,31 mg
Zinc	13,3 mg	2 mg	4 mg
Honey	5,5 g	825 mg	1,65 g

ANNEX 2

Collected variables

TSS – Tonsillopharyngitis severity score

Symptoms	Intensity score	Assessment
Throat pain	Absence = 0 Slight = 1 Moderate = 2 Severe = 3	
Difficulty in swallowing	Absence = 0 Slight = 1 Moderate = 2 Severe = 3	
Salivation	Absence = 0 Slight = 1 Moderate = 2 Severe = 3	
Erythema	Absence = 0 Slight = 1 Moderate = 2 Severe = 3	
Fever*	Absence = 0 Slight = 1 Moderate = 2 Severe = 3	
TSS (Tonsillopharyngitis Severity Score) = Total score of summing score for all symptoms		

* The axillary body temperature increase is rated as follows:
0 points: <37.5 °C.
1 point: 37.5 to <38.5 °C;
2 points: 38.5 to <39.5 °C;
3 points: ≥39.5 °C.

Investigator Global evaluation of treatment efficacy (IGAE)

- the investigator will assess the efficacy in the overall symptom improvement at visit 4 using a 4-point scale: 1= very good efficacy, 2 = good efficacy, 3 = moderate efficacy and 4 = poor efficacy.