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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

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ABSTRACT

Pediatrica Srl develop a dietary supplement (DSPP) with extract of *Pelargonium sidoides* (Pelagon P 70™), specific for paediatric age for the well-being of the airways. The scientific literature currently available shows that the extract of *Pelargonium sidoides* may be effective in the treatment of disorders affecting the respiratory tract. Moreover, the DSPP also contains zinc, honey, and propolis. A long tradition of use and literature support the use of zinc, propolis and honey for seasonal disease prevention and/or in the acute phase of colds. In addition to this, the specific formulation of propolis (PropolNext® PLUS) contained in the DSPP showed to be able to inhibit bacterial growth to a much greater extent if compared to simple propolis.
The DSPP is currently on the market in Italy as adjuvant in seasonal diseases and its effectiveness has been evidenced in the daily clinical practice of thousand of paediatricians in this country.
The present clinical trial was planned to confirm the results of standard clinical practice. Therefore, its aim was to explore if in paediatric patients affected by acute tonsillopharyngitis / rhinopharyngitis (ATR) a 6-day administration of the tested DSPP along with the standard of care (SoC) could improve the ATR symptomatology in comparison with patients receiving SoC alone.

1 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

2 **ClinicalTrials.gov Identifier**: NCT04899401
Study Type: Interventional
Interventional product: PediaFlù®
Indication studied: Acute tonsillopharyngitis / Rhinopharyngitis (ATP)
Design: Interventional, randomized, open label, controlled, multicentre, parallel group, superiority clinical investigation
Name and address of Sponsor: Pediatrica SRL Via Nicolodi 28/A, 57121 Livorno (LI), Italy
Name and address of CRO: Opera Contract Research Organization (Opera CRO)
10 Cozia Street, Building B 300209 Timișoara (Romania)
Principal Investigator of Coordinating Centre: Dr Maria Morariu Bordea, CMMF Dr Morariu Bordea, 28 Liviu Rebreanu Street, 300425 Timișoara (Romania)
Statement of Compliance: 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

3 **Objectives**
The primary objective was 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 trial were the assessment of the use of rescue medicine (ibuprofen or a high dose of paracetamol) and the evaluation of the overall improvement of symptoms.

Criteria for Efficacy Evaluations
Primary Efficacy Outcomes
·Tonsillitis severity score (TSS). The results were 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 of paracetamol) were compared in the two groups.
Secondary Efficacy Outcomes:
·IP compliance.
·Overall symptoms improvement through Investigator Global Assessment of Efficacy (IGAE).
Overall symptoms improvement through Patient Global Assessment of Efficacy (PGAE).

Criteria for Safety Evaluations
The safety evaluation criterion was the incidence of AE/SAE during the study; the safety was also evaluated through the Investigator Global Assessment of Safety (IGAS).

Methodology
This was an interventional, randomized, open label, controlled, multicentre, parallel group, superiority study, aimed at evaluating the performance and safety of the dietary supplement PediaFlù® along with standard of care in children with acute tonsillopharyngitis / rhinopharyngitis versus standard of care only.
The study visits were scheduled as follows:
·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 study visit.
Evaluations included:
·Tonsillitis severity score (TSS) evaluated by Investigator.
·Global Assessment of Efficacy done by Investigator to assess the overall symptoms improvement (IGAE).
·Global Assessment of Efficacy done by patient to assess the overall symptoms improvement (PGAE).
·Investigator Global Assessment of Safety (IGAS).

·Safety was assessed by monitoring adverse events (AEs), serious adverse events (SAEs), at all study visits. A rapid test for detection of beta-haemolytic streptococci or nasal and/or pharyngeal exudate culture (if Mc Isaac score is 0-1) and SARS-COV-2 was performed.

Sample Size

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®

The sample size was calculated based on the primary outcome Tonsillitis severity score (TSS) and based on the results of similar investigation.
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).

Inclusion Criteria

The following inclusion criteria were imposed:
·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-haemolytic 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

The following exclusion criteria were required:
·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 haemorrhagic 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.

Investigational Product and Posology

Investigational product: PediaFlù®, Pediatrica SRL, is a dietary supplement already marketed in Italy; its composition is based on Pelagon P-70™ (equal to *Pelargonium sidoides* d.e. 133.3 mg /100ml), PropolNext® PLUS (equal to propolis d.e. 7.7mg / 100ml), zinc (13.3 mg / 100ml), honey (5.5gr / 100ml).
Dose and mode of administration:PediaFlù® is provided as an oral solution and was administered according to

the following in Group B:
-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).

Standard of care
Standard of care was composed of the following treatments:

- Nasopharyngeal liberation through hydration with drinking fluids to support body fluid excretion, aspiration of secretions, NaCl solution for nasal irrigation, nasal sprays with seawater, nasal spray with active compound (to be used only at special indication of the medical doctor)
- Throat spray with benzydamine hydrochloride (Tantum Verde®, CSC Pharmaceuticals, 0.15%), paediatric use according to the leaflet (each spray is equivalent to 0.17 ml of solution), for 6 days:

- Children (under 6 years): 1 spray for every 4 kg of body weight, up to a maximum of 4 sprays at once, 2-6 times a day.
- Children (6-12 years): 4 sprays 2-6 times a day.

- Paracetamol (acetaminophen) (Panadol®, GlaxoSmithKline, 120 mg/5 ml) *per os*: as antipyretic (fever is defined as a body temperature >38.5°C), as needed, 10 mg/kg/dose, every 6-8 hours, according to the leaflet; maximum dosage 80 mg / kg / day.

Rescue medicine
Ibuprofen or dosage of over 30 mg/Kg/dose of paracetamol as needed, *per os*, according to product leaflet.

Statistical methods
All statistical analyses were performed using the R statistical software v4.1.0.
The overall type I error rate was preserved at 5%. All tests were two-sided. Data from unscheduled visits were not included in the analysis.
Statistical analyses were conducted on all patients 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 were evaluated preliminarily compared to data analysis. If a patient is missing information for one or more variables, even after the resolution of its query, the missing data were not replaced. If a patient has been involved in violation of inclusion/exclusion criteria, the respective data were excluded from the analysis.
Quantitative variables (i.e., demographic) if normally distributed were described through media, standard deviation (SD); variables non-normally distributed were described using median and range of interquartile. The Student's t-test and the Mann-Whitney U were employed to perform comparative analysis in accordance with 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 were finally described using frequencies and percentages and comparative analysis used the chi2 test.

4 Autorship

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5 **Keywords**
Dietary supplement, tonsillopharyngitis, rhinopharyngitis, *Pelargonium sidoides*

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