Strictly Confidential

Impact of adding Healsea® isotonic nasal spray to conventional therapies for the care of children with allergic rhinitis presenting with symptoms of acute infectious rhinitis: an observational study

CLINICAL INVESTIGATION PLAN

Study Number: LPH-2101

SYMBIOFILM-TAK

Version 2.0; 08 Sep 2021

This Clinical Investigation is being sponsored by:

Lallemand Pharma AG

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HISTORY OF CLINICAL INVESTIGATION PLAN'S UPDATES

Version	Date	Purpose of Update
1.0	**27 May 2021**	**Creation**
2.0	**08 Sep 2021**	**Update of Sites and Investigators list**

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APPROVAL FORM
STUDY: LPH-2101
CLINICAL INVESTIGATION PLAN
Version 2.0; 08 Sep 2021

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Date:
Signature:

Study's Coordinating Investigator:

Pr Andrzej EMERYK, MD, PhD

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Study's monitor:

Wojciech WĘKLAR

Date:
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Study's Statistician:

Benjamin POIRIER

Date:
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1. Table of content

PRINCIPAL INVESTIGATOR STUDY APPROVAL PAGE

STUDY: LPH-2101

CLINICAL INVESTIGATION PLAN Version:

Version 2.0, 08 Sep 2021

By signing the hereinafter form, I hereby confirm that I agree:

- To conduct the trial described in the Clinical Investigation Plan (LPH-2101) dated 27 May 2021 in compliance with GCP and the ethical principles that have their origin in the Declaration of Helsinki, with applicable regulatory requirements and with the Clinical Investigation Plan agreed upon by the sponsor and given approval/favourable opinion by the Ethics Committee;
- To document the delegation of significant study related duties and to notify the sponsor of changes in site personnel involved in the study;
- To comply with procedures for data recording and reporting;
- To permit monitoring, auditing and inspection;
- To retain the trial-related essential documents until the sponsor informs these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the availability of adequate resources, personnel and facilities for the conduct of this trial.

Principal Investigator's Name:

_____

Principal Investigator's Title:

_____

Principal Investigator's Address:

_____

_____

Principal Investigator's Signature:

Date of signature:

_____

LIST OF ABBREVIATIONS

Abbreviation	Definition
AsIgE	**A**llergen **S**pecific **IgE**
AR	**A**llergic **R**hinitis
AUC	**A**rea **U**nder the **C**urve
AE	**A**dverse **E**vent
BoV	**B**ag-**o**n-**V**alve
CA	**C**ompetent **A**uthority
CIP	**C**linical **I**nvestigation **P**lan
CRF	**C**ase **R**eport **F**orm
EC	**E**thic **C**ommittee
GDPR	**G**eneral **D**ata **P**rotection **R**egulation
IFU	**I**nstruction **F**or **U**se
IgE	**I**mmuno**g**lobulin **E**
MDR	**M**edical **D**evice **R**egulation
PI	**P**rincipal **I**nvestigator
PNF	**P**rimary **N**otification **F**orm
RAST	**R**adio**A**llergo**S**orbant **T**est
SAP	**S**tatistical **A**nalysis **P**lan
WURSS-K	**W**isconsin **U**pper **R**espiratory **S**ymptom **S**urvey for **k**ids

2. Synopsis

Sponsor:	LALLEMAND PHARMA AG
Coordinating/Principal Investigator	Pr Andrzej Emeryk, University Children Hospital, Lublin, Poland
Short Title:	**SYMBIOFILM-TAK**
CIP version:	Version 2.0 – 08 Sep 2021
Competent Authority:	N/A
Rational	Healsea® Children is a seawater-based nasal spray supplemented with a natural Symbiofilm® extract (0.02%) isolated from marine bacteria. Symbiofilm® is an exopolymeric composition with emulsifying properties, in vitro antibiofilm activity and detachment properties against various bacterial pathogens involved in respiratory tract infections. Symbiofilm® has no bacteriostatic nor bactericidal activities. Healsea® Children is indicated in the cleaning and moistening of nasal mucosa during common cold and rhinitis. The common cold is an acute viral infection of the upper respiratory tract, involving, to variable degrees, sneezing, nasal congestion and discharge (rhinorrhea), sore throat, cough, low-grade fever, headache, and malaise. It can be caused by members of several families of viruses; the most common are the more than 100 serotypes of rhinoviruses. Acute viral rhinitis is generally self-limiting. In children where the illness is not self-limiting and extends beyond 7-10 days, many agree that a bacterial infection is likely. Bacterial over infections and progression to a chronic state are favoured by the formation of biofilms, which facilitate bacterial growth and persistence as well as reducing antibiotic efficacy. Allergic diseases may play a particular role in promoting the respiratory infection recurrences. The physiological immune response is impaired in allergic subjects and allergic inflammation favours predisposition to respiratory infections. Subjects with allergic disorders may have functional defect of type 1 immune response that is relevant in fighting infections. Allergic rhinitis (AR) may affect up to 40% of the paediatric population. Nasal symptoms are caused by exposure to an allergen to which a patient is sensitized. Typical allergens include house dust mite, grass pollen, tree pollen, weed pollens, cat, dog and moulds. Allergic rhinitis can thus be seasonal or perennial, according to the relevant allergen. AR is characterized by typical nasal symptoms and IgE-mediated inflammation. The allergic inflammatory process releases many cytokines and other proinflammatory proteins. Inflammation caused by nasal allergy leads to obstruction, fluid accumulation and acute disease. If these diseases are unsuccessfully treated, a chronic state of inflammation, obstruction, and infection develops that can cause mucosal damage and, ultimately, chronic disease. For these reasons, the paediatric IgE-dependent allergic population that is more prone to common cold represents a suitable target for Healsea® Children.

	During this prospective observational study, one cohort of IgE-dependent allergic children with early symptoms of infectious rhinitis will be followed, children being treated with Healsea® Children on top of common cold conventional therapies or with conventional therapies only (excluded nasal irrigation). Conventional therapies for non-complicated infectious rhinitis are symptomatic but are not without side effects. For example, decongestant use can increase blood pressure, antihistamine intake is associated with drowsiness. Healsea® Children represents an interesting alternative that can not only improve acute infectious rhinitis symptomatology but could also limit the complication and progression to chronic state. This observational study aimed to confirm the benefit of Healsea® Children in a real life setting in children with perennial allergy.
Objectives	**Primary Objective:** - To assess the impact of both treatment modalities (Healsea® Children on top of common cold conventional therapies and common cold conventional therapies only) to reduce acute infectious rhinitis symptoms in 6-10 years old allergic children during a 10-day treatment period. **Secondary Objectives:** - To assess the impact of both treatment modalities to reduce the duration of each infectious rhinitis symptom as rated by the Wisconsin Upper Respiratory Symptom Survey for kids (WURSS-K). - To assess the impact of both treatment modalities to reduce complications of the acute phase during a 20-day follow-up phase. - To assess the impact of both treatment modalities on the intake of conventional common cold medication (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids). - To assess the impact of both treatment modalities to reduce the person to person spreading among close contacts (parents, siblings). - **Safety**: to assess systemic and local tolerance of **Healsea® Children** over the study period.
Endpoints:	**Primary Endpoint:** The primary endpoint is the AUC of the WURSS-K during first 10 days of symptoms. The WURSS-K will be assessed once daily in the evening, considering the symptoms from the morning to the evening, during D1-D10. **Secondary Endpoints:** **-** Duration of cold symptoms (items 2 to 7) will be assessed by means of the WURSS-K (assessed once daily in the evening). During treatment period, the WURSS-K will be assessed once daily in the evening, taking into account the symptoms from the morning to the evening.

	After D10, the WURSS-K will be assessed once daily until the subject feels not sick for two consecutive days. For each item, the duration is defined as the number of symptomatic days between D1 and the first day the subject reports not having the symptom for two consecutive days. To be noticed that the duration may be censored at day 30. - Number of subjects who develop respiratory complication requiring antibiotic prescription during a 20-day follow-up period. - Frequency and number of days of use of concomitant treatments that may affect common cold symptoms (antibiotics, antipyretics, systemic or local mucolytics, decongestants, antitussives, systemic and topical corticosteroids). - Number of family members in close contact developing common cold symptoms after the patient all over the study period. - **Safety**: Assessment of adverse event/incidents/ undesirable expected side effects throughout the study.
Indication:	Treatment of acute rhinitis in children 6-10 years old
Investigation Design:	**Prospective, open label, observational study** **Visit 1 (V1) – (Day 1): Screening/Inclusion** Information and provision of the information sheet to legal guardians and participants, consent and assent signatures, demographic data and medical history, ongoing medication, physical and clinical examination, inclusion/non-inclusion criteria, record of patient choice regarding Healsea® Children use. **D1-D10 (at home):** Daily completion of the electronic diary (WURSS-K, adverse events/incident/ undesirable expected side effects and concomitant medications, contamination of relatives if applicable, Healsea® Children daily administration if applicable). **D5±2 (at home): Telephone call 1** Investigator/nurse call to review patient status and study progress, adverse event/incident/undesirable expected side effects and concomitant treatments. **Visit 2 (V2) – (Day 10±2): End of treatment** End of Healsea® Children nasal spray treatment if applicable, assessment of symptoms, diary review, reporting of adverse events/incident/undesirable expected side effects. **D11-D30±5 (at home):** Daily completion of the diary (Adverse event, concomitant medications, contamination of relatives if applicable, WURSS-K if applicable, until the subject feels not sick for two consecutive days). **D20±2 (at home): Telephone call 2** Investigator/nurse call to review patient status and study progress, adverse events and concomitant treatments.

	Visit 3 (V3) – (Day 30±2): End of study Physical and clinical examination, diary review, reporting of adverse events and concomitant treatments.
Number of Subjects:	15 centers will be involved in this study. We plan to follow a cohort of **200** subjects . The recruitment will be competitive in both group, exposed to Healsea® Children or not exposed to Healsea® Children. However, when 100 patients will be recruited in one group, the recruitment will be stopped in this group but will continue in the other group until 100 patients to be enrolled.
Target Population:	Children with allergic rhinitis and symptoms of acute infectious rhinitis
Inclusion/Exclusion criteria:	**Inclusion Criteria:** Subjects will be enrolled if they meet all of the following criteria: 1. Male/Female subjects ≥6 and ≤10-year-old 2. AsIgE ≥ class 2 (RAST) or positive prick test for at least one perennial allergen 3. Acute infectious rhinitis/rhinosinusitis **for ≤48h before trial entry** 4. Patient presenting with fever ≥ 37.5 °C at screening 5. Symptoms of headache, muscle ache, chilliness, sore throat, blocked nose, runny nose, cough, sneezing with **a total score ≤9** (according to a physician-rated symptom score; scale: 0 ⟶ 3 [0: no symptom to 3: severe intensity]) 6. At least one of these symptoms: sore throat, runny nose or blocked nose (i.e., with a score ≥1) 7. Written consent obtained from parent/legal guardians 8. Written assent obtained from patient **Non-inclusion Criteria:** Subjects will not be enrolled if one of the following criteria is present: 1. Known hypersensitivity/allergy to any component of the test device 2. Medical history that is considered by the investigator as a reason for non-inclusion, 3. Severe nasal septum deviation or other condition that could cause nasal obstruction such as the presence of nasal polyps 4. History of nasal or sinus surgery that in the opinion of the investigator may influence symptom scores 5. Antibiotic intake within 2 weeks before screening 6. Systemic corticosteroids within 4 weeks before screening 7. Antihistamines intake for allergy when treatment was started from less than 4 weeks 8. Bacterial lysate intake within 6 months before screening 9. Chronic decongestant use

	10. Recent (within the previous 2 days) intake of a common cold medicine that in the opinion of the investigator may influence symptom score at screening (NSAID, nasal decongestants, cough medicines)
Number of sites:	15 sites in Poland
Treatments:	-Healsea® Children nasal spray, one puff (1-2 sec) in each nostril twice a day for 10 days on top of conventional therapies as needed or -Conventional therapies only, **nasal irrigation excluded**
Comparator Device:	Non applicable
Duration of investigation:	Duration of inclusion period: 3 months Duration of patient's participation: 30 days Total study duration: 4 months
Study Start Date:	September 2021
Statistical Analysis:	The cohort is described: continuous variables will be summarized using the mean, standard deviation, median, minimum, maximum and quartiles, categorical variables will be summarized using frequency counts and percentages. Two groups (called treatment groups for a sake of simplicity) will be extracted from the cohort according to the treatment chosen by the patient and a description of each group will be performed. Details of the statistical analyses, methods and data conventions will be described in the SAP. All statistical tests will be 2-sided and performed using a 0.05 significance level. The selection of variables in multivariate analyses will be performed using a 0.2 significance level and a stepwise method. Whole the multivariate analyses specified below involve the treatment and, in order to adjust for confounding, all the potential confounding factors as explanatory variables. The impact of the treatment chosen on the primary endpoint will be analysed by means of a multivariate regression model with the AUC of the WURSS-K during first 10 days of symptoms as dependent variable. The impact of the treatment chosen on the cold symptoms' duration will be analysed by means of a Cox model. The impact of the treatment chosen on the risk to develop respiratory complication requiring antibiotic prescription during a 20-day follow-up period will be analyzed by a multivariate logistic model. The impact of the treatment chosen on the intake of conventional common cold medication (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids) will be analyzed by multivariate Poisson regressions for the numbers of days and a multivariate logistic regression for the frequency.

	The impact of the treatment chosen on the number of family members in close contact developing common cold symptoms after the patient all over the study period will be analyzed by means of a multivariate Poisson regression. **- Safety:** All adverse events and incidents will be listed, but only treatment-emergent adverse events/incidents (non-serious + serious)/ undesirable expected side effects will be summarized. Two groups (called treatment groups) will be extracted from the cohort according to the treatment chosen by the patient. Adverse events and incidents will be summarized by the number and percentage of patients (by treatment group), classified by System Organ Class and Preferred Term as defined by MedDRA dictionary. For a given treatment group, a given adverse event will be counted treatment emergent only once per patient during the treatment period. Frequency and percentage of patients with at least one reported adverse event/ incident/ expected side effect will be tabulated by System Organ Class and by treatment group.

3. Flow Chart

	ACUTE PHASE				FOLLOW-UP		
Visit name	Screening/Inclusion	At home	Telephone call	End of treatment	At home	Telephone call	End of study
Visit Number	**V1**		**TC1**	**V2**		**TC2**	**V3**
Days/Weeks	D1	D1 – D10	D5±2	D10±2	D11 – D30±5	D20±2	D30 ± 5
Screening and General Assessments							
Information and consent process	X						
Eligibility criteria	X						
Demography and Medical history	X						
Physical and clinical examination	X			X			X
Ongoing medication	X						
Patient's choice for using Healsea® Children self-administration or not	X						
Treatment							
Acute phase (Healsea® Children or no saline irrigation as add on therapy)		X					
Assessments							
Subject e-diary (WURSS-K)		X			X*		
Adverse Events/incidents/undesirable expected side effects and concomitant medication reporting	X	X	X	X	X	X	X

* After D10, the WURSS-K will be assessed once daily until the subject feels not sick for two consecutive days if applicable.

4. Identification and description of the investigational Device

4.1 Summary description of the investigational device

4.1.1 Summary description

Healsea® Children is a CE marked nasal spray composed with an isotonic seawater solution (0.9% NaCl) and Symbiofilm® (0.02%). Symbiofilm® is a Lallemand proprietary marine postbiotic composition including an exopolysaccharide mainly composed of N-acetyl hexosamines, acidic and neutral monosaccharides.

The sponsor certifies that the Healsea® Children Medical Device:

- does not contain any human blood derivative,
- does not contain any medicinal product,
- is not manufactured using tissues of animal origin.

Healsea® Children is a nasal spray indicated in children above 6 years to clean and moisten the nose during colds and rhinitis. Healsea® Children is administered with the help of an adult for colds and rhinitis, one puff (1-2 sec) twice a day in each nostril for 10 days.

The technical performances are summarized below:

Ingredient	**Function(s)**
Isotonic Seawater solution 0.9%	- Improve nasal mucosa function - Clean the nasal cavity and eliminate allergens and infectious agents
Symbiofilm	- Enhancing the cleansing efficacy - Reducing biofilm formation

Intended clinical performances in the intended destination are:

- Cleans and moistens the nose during colds and rhinitis.
- Cleans the nasal cavity and eliminates allergens and infectious agents.

4.2 Manufacturer

Healsea® Children is a Class IIa Medical Device manufactured by Lallemand Pharma. CE marking has been obtained on 30th of March 2021. The subcontractor for the manufacturing is AURENA, Fjarrvikvagen 22, ES-653 50 Karlstad, Sweden.

4.3 Name or number of the model to permit full identification

The test device is named Healsea® Children. It is a nasal spray (100ml presentation), isotonic seawater (0.9%) supplemented with Symbiofilm® (0.02%) identified by the code article: 7640149724004.

4.4 Traceability

Traceability of the Device will be achieved through the lot number (YYMMXXX, YY for year, MM for Month and XXX internal number of the manufacturer), the manufacturing date (YYYY/MM/DD) and the expiry date (YYYY/MM/DD).

4.5 Intended purpose of the investigational device in the clinical investigation.

This is an observational study. Healsea® Children will be used in the paediatric IgE-dependent allergic population that is more prone to common cold and represents a suitable target for Healsea® Children.

Healsea® Children will be used within its intended purpose i.e., in children above 6 years to clean and moisten the nose during colds and rhinitis.

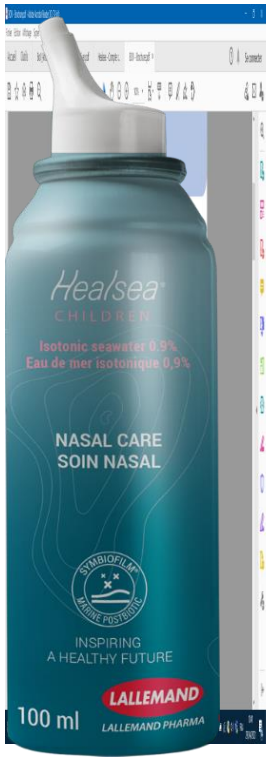
4.6 Population and indications for which the device is intended

Healsea® Children is a nasal spray indicated in children above 6 years to clean and moisten the nose during colds and rhinitis. Healsea® Children is administered with the help of an adult for colds and rhinitis, one puff (1-2 sec) twice a day in each nostril for 10 days.

4.7 Device Description

Healsea® Rescue is a nasal spray (available in 100mL) using the Bag-on-Valve (BoV) technology.

The BoV technology consists of an aerosol valve with a welded bag. The product is placed inside the bag while the propellant is filled in the space between bag and can. The product is dispensed by the propellant simply squeezing the bag when the spray button is pressed, the product is squeezed out of the bag by the compressed air/nitrogen, which creates the dispensing as a spray. Therefore, the product keeps its integrity, remaining separated from the propellant at all times. Compared to traditional aerosol spray technology, BoV has several benefits, for manufacturers, consumers and the environment. Packaging description of Healsea Children is reported in Figure 1.



***The Spray Pin:** Packaging element ensuring the delivery of the product in the patient's nose.

***The Actuator:** Pacifica Spray actuator with a flow rate of 8ml/10s pressed enables the propellant to squeeze the bag to dispense the product through the Spray Pin.

***The Valve assembly:** Packaging element ensuring the link between the Bag and the Actuator.

The Can: Standard aerosol aluminum can contain the bag and the propellant.

The Product: Isotonic seawater solution (0.9%) supplemented with Symbiofilm® 0.02%.

***The Bag:** FDA-approved laminated bag containing the product.

The Propellant: Because of the separation between product and propellant, BoV technology is used with compressed nitrogen filled between the can and the bag.

****Packaging element in contact with the product***

*Figure SEQ Figure * ARABIC 1- Packaging description of Healsea® Children*

As summarized below, Healsea® Children is intended to be used on nasal mucosa. The duration of use is 10 days.

Table 1 : Device Category / Intended Use

Type of contact	Device in contact with a surface
Type of tissues	Mucous membranes
Total duration treatment	It can be used for 10 days

4.8 Investigation Device Training/Experience

There is no need for specific training in using Healsea® Children.

A usability engineering process test according to the standard EN ISO 62366-1: 2015 was conducted with Healsea® Children with 10 people representative of the parents/legal guardians of the target population to ensure that the leaflet and the label were well understood, and that the medical device was used correctly to ensure its safe understanding and use.

The analysis of the results demonstrates that:

- The information provided by the user interface is readable and understandable by participants: the information tested was easy to understand, without interpretation.
- The observations made during the simulations of use of the device have confirmed that all safety-related handling steps are properly followed, in accordance with the instructions given in the instruction for use.

Briefly, the children (with the help of an adult if necessary) to place the nozzle into the nostril while keeping head straight. Once the nozzle is placed, to press on the nozzle for 1-2 seconds in each nostril. To let flow the excess of solution, and wipe. To clean the nozzle with tissue, soapy water rinse and dry after use.

4.9 Reference to the IFU

The IFU of Healsea® Children is provided in Appendix A.

5. Justification for the design of the clinical investigation

Although clinical evidence from well-designed trials is scarce [1], European guidelines for acute rhinitis/rhinosinusitis recommend daily nasal saline irrigation for reduction of the severity of symptoms and for speeding recovery [2]. The exact mechanisms by which nasal irrigation works are

not known. However, most of the experts agree that it is primarily a mechanical intervention leading to direct cleaning of the nasal mucosa [3] [4]. The mucus lining the nasal cavity may be softened and dislodged. The increase of mucociliary clearance is associated with a decrease of pathogens burden. Moreover, inflammatory mediators such as cytokines, prostaglandins and leukotrienes can be removed, favoring the resolution of URTIs. Nevertheless, the efficacy of such saline irrigation remains moderate [1].

Symbiofilm® is an exopolysaccharide composition with emulsifying properties and *in vitro* antibiofilm activity. Antibiofilm properties have been demonstrated with a microtiter plate assay [5]. In both models, a significant inhibition of *Staphylococcus aureus* and *Haemophilus influenzae* biofilms was observed. Detachment properties from human nasal epithelial cells of *Staphylococcus aureus* and *Pseudomonas aeruginosa* has also been demonstrated *in vitro*, suggesting an inhibition of biofilm formation at early stage in this model. The antibiofilm activity of Symbiofilm® is likely to rely on its emulsifying properties. In all models, the absence of bacteriostatic or bactericidal activities against all strains tested has been confirmed.

The technical performances of Symbiofilm® may enhance the interest of saline nasal irrigation for the treatment of acute infectious rhinitis and common cold.

The common cold is the most frequent upper respiratory tract infection (URTI), which is the most commonly treated acute problem in primary pediatric care [6]. Despite the usually benign nature of the illness, the common cold is an enormous economic burden on society in terms of visits to doctors, treatments, and absences from work, school, or day care [6][7].The common cold is an acute viral infection of the upper respiratory tract, involving, to variable degrees, sneezing, nasal congestion and discharge (rhinorrhea), sore throat, cough, low-grade fever, headache, and malaise [2]. It can be caused by members of several families of viruses. However, rhinoviruses have been consistently found to be the most common cause in all age groups, irrespective of the viral detection techniques used. Yearly, rhinoviruses account for about 30-50% of all respiratory illnesses, but during the autumn peak season these viruses can cause up to 80% of all upper respiratory infections. Coronaviruses and Influenza viruses account for about 10-15% and for 5-15% of acute infectious rhinitis respectively. Other viruses such as Respiratory Syncytial Virus, Adenoviruses and Parainfluenza viruses are less involved [7]. Acute viral rhinitis is generally self-limiting. In children where the illness is not self-limiting and extends beyond 7-10 days, many agree that a bacterial infection is likely [2]. Acute bacterial rhinosinusitis is diagnosed in a child based on several criteria: persistent upper respiratory tract symptoms more than 10 days (cough or nasal discharge or both); or recurrence of symptoms after initial improvement: fever, worsening cough, or worsening or new purulent rhinorrhea; or severe onset of symptoms like fever or purulent nasal discharge lasting more than three consecutive days associated with facial tenderness or headache. Bacterial over infections and progression to a chronic condition are favored by the formation of biofilms, which facilitate bacterial growth and persistence as well as reducing antibiotic efficacy [8][9].

Allergic diseases may play a particular role in promoting the respiratory infection recurrences. The physiological immune response is impaired in allergic subjects and allergic inflammation favours predisposition to respiratory infections [10]. Subjects with allergic disorders may have functional defect of type 1 immune response that is relevant in fighting infections [11][12]. Allergic rhinitis (AR)

may affect up to 40% of the paediatric population. Nasal symptoms are caused by exposure to an allergen to which a patient is sensitized. Typical allergens include house dust mite, grass pollen, tree pollen, weed pollens, cat, dog and moulds. Allergic rhinitis can thus be seasonal or perennial, according to the relevant allergen. AR is characterized by typical nasal symptoms and IgE-mediated inflammation. The allergic inflammatory process releases many cytokines and other proinflammatory proteins. Inflammation caused by nasal allergy leads to obstruction, fluid accumulation and acute disease. If these diseases are unsuccessfully treated, a chronic status of inflammation, obstruction, and infection develops that can cause mucosal damage and, ultimately, chronic disease [14].

For these reasons, the paediatric IgE-dependent allergic population that is more prone to common cold represents a suitable target for Healsea® Children [15][16]. During this prospective observational study, one cohort of IgE-dependent allergic children with early symptoms of infectious rhinitis will be followed, children being treated with Healsea® Children on top of common cold conventional therapies or with conventional therapies only (excluded nasal irrigation). Conventional therapies for non-complicated infectious rhinitis are symptomatic but are not without side effects [17][6]. For example, decongestant use can increase blood pressure, antihistamine intake is associated with drowsiness that can not only improve acute infectious rhinitis symptomatology but could also limit the complication and progression to chronic state.

This observational study aimed to confirm the benefit of Healsea® Children in a real life setting in children with perennial allergy.

6. Risks and Benefits of the Investigational Device and Clinical Investigation

6.1 Anticipated clinical benefit

Both groups will receive effective treatments.

Due to the presence of Symbiofilm®, the group receiving Healsea® Children is anticipated to recover more quickly from acute rhinitis than the group of children receiving only conventional therapies for the common cold.

6.2 Anticipated adverse device effects

The only anticipated adverse device effect is the feeling of nasal itching and irritation while initiating the treatment with the medical device Healsea® Children. In case of such adverse reaction, the parents/legal guardians/patients will be instructed to contact the investigator if the patient wishes to stop the nasal spray use.

6.3 Risks associated with participation in the clinical investigation

No design element, subject to safety-related questioning is identified. The instructions for use include mentions to control risks. Patients with known hypersensitivity/allergy to any component of the test device will not be enrolled in the study. The clinical procedures comprise daily completion of an electronic diary comprising a validated questionnaire (WURSS-K) [18] only.

6.4 Possible interactions with concomitant medical treatments as considered under the risk analysis

No interaction is expected. Nevertheless, patient will be instructed to respect a 60-minute minimum interval after administration of the investigational medical device before administration of another local medication e.g., decongestant or mucolytics (if permitted).

6.5 Steps that will be taken to control and mitigate the risks

In the line with *NF EN ISO 14971:2019* standard (Medical Devices – Application of risk management to medical devices), a risk analysis has been conducted to estimate the risks associated with each step of the device lifecycle. Most of the risk has been mitigated through product design and manufacturing.

The residual risk to patients who are administered this intervention is low. A list of potential risks associated with the device, procedures undertaken to minimise them, and methods used for their management is described in the device Risk Management Process File.

Considering:

- the risk analysis (ISO 14 971 activities) that demonstrates:
  - There is no longer High level risk,
  - That, the 41 Medium risk level residuals risks have an acceptable benefit-risk balance,
  - And all of the others residual risks (85) are at Low risk.
- the fact that the device Healsea® Children can be considered as safe and effective according to the Clinical Evaluation Report.

the overall residual risk is acceptable, and the benefit/risk ratio is considered satisfactory.

The verification of the implementation of risk control measures during life cycle phases of Healsea® Children is mainly performed by LALLEMAND PHARMA AG using the operating procedures currently used.

No specific risk for subject in participating in the study is identified, provided that the eligibility criteria are fulfilled. Thus, the establishment of risk acceptability thresholds is not deemed necessary although it is a requirement from the ISO 14155:2020. Nevertheless, the safety and well-being of subjects will be monitored throughout the study. Should a potential unanticipated risk be detected, the clinical investigation will be suspended, the risk assessment will be updated to adapt the risk control measures and the benefit-risk analysis.

6.6 Rationale for the benefit-risk ratio

Although infectious rhinitis is in most cases self-limiting, it impacts the children's quality of life during generally about 7-10 days. Furthermore, bacterial over infections with worsening of symptoms can occur requiring antibiotic prescription. Progression to a chronic state, i.e., chronic rhinosinusitis is also observed.

Conventional therapies for infectious rhinitis are symptomatic and not without side effect. For example, decongestant use can increase blood pressure, antihistamine intake is associated with drowsiness.

Healsea® Children represents an interesting alternative because the nasal spray could alleviate acute infectious rhinitis symptoms but also limit the complication and progression to chronic state.

Furthermore, apart from feeling of nasal itching and irritation while initiating the treatment, no adverse effect is anticipated.

7. Objectives and hypothesis of the clinical investigation

7.1 Hypothesis

Our hypothesis is that Healsea® Children nasal spray on top of conventional therapies for common cold can improve the symptomatology of acute infectious rhinitis in allergic children (6-10 years) with more efficacy than conventional therapies only without safety concerns.

7.2 Primary Objective

To assess the impact of both treatment modalities (Healsea® Children on top of common cold conventional therapies and common cold conventional therapies only) to reduce acute infectious rhinitis symptoms in 6-10 years old allergic children during a 10-day treatment period.

7.3 Secondary Objectives

- To assess the impact of both treatment modalities to reduce the duration of each infectious rhinitis symptom as rated by the Wisconsin Upper Respiratory Symptom Survey for kids (WURSS-K) [18].

- To assess the impact of both treatment modalities to reduce complications of the acute phase during a 20-day follow-up phase.

- To assess the impact of both treatment modalities on the intake of conventional common cold medication (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids).

- To assess the impact of both treatment modalities to reduce the person-to-person cold spreading among close contacts (parents, siblings).

- **Safety**: to assess systemic and local tolerance of Healsea® Children over the study period.

7.4 Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence

This is a prospective, open label, observational study. An arbitrary cohort of 200 children has been chosen. A cohort of 100-exposed and 100-not exposed patients is anticipated to allow to demonstrate the interest of using Healsea® Children in the allergic paediatric population. Indeed, 100 patients by arms are enough to detect a Cohen's effect size of 0.4 with a power of 80% and a type I error of 5%. Cohen's effect size is defined as the standardized difference between AUC in groups. Following Cohen's methodology, 0.4 is an intermediate size between a small effect (0.2) and a medium effect (0.5) and is coherent with the expected result.

The recruitment will be competitive in both group, exposed to Healsea Children or not exposed to Healsea® Children. However, when 100 patients will be recruited in one group, the recruitment will be stopped in this group but will continue in the other group until 100 patients to be enrolled.

No assumption of expected outcomes across treatment group is performed.

7.5 Risks and anticipated adverse effects that are to be assessed

No specific risk for subject in participating in the study is identified, provided that the eligibility criteria are fulfilled. Nevertheless, the safety and well-being of subjects will be monitored throughout the study.

8. Design of the clinical investigation

8.1 General

8.1.1 Design type of clinical investigation

This is a prospective, open label, observational, national (Poland), multicentre study.

During this prospective observational study, one cohort of IgE-dependent allergic children with early symptoms of infectious rhinitis will be followed, children being treated with Healsea® Children on top of common cold conventional therapies or with conventional therapies only (nasal irrigation excepted). This observational study aimed to confirm the benefit of Healsea® Children in a real life setting in children with perennial allergy.

8.1.2 Measures to be taken to minimize or avoid bias

Not applicable.

8.1.3 Primary Endpoint

The primary endpoint is the area under the curve (AUC) of the Wisconsin Upper Respiratory Symptom Survey for Kids (WURSS-K) during first 10 days of symptoms. AUC will be calculated applying the trapezoidal rule, with the y-axis, defined by daily WURSS-K scores, and the x-axis, defined as duration of illness, starting with the first symptoms and ending at day 10.

WURSS-K is a 3-dimensional structure questionnaire specifically designed for children 4 to 10 years of age [18] (appendix B). This survey has been demonstrated to be responsible, reliable, and valid for assessing illness specific symptoms and impact on quality of life during an acute infectious rhinitis in paediatric population.

It includes 6 items assessing symptoms (symptoms score: runny nose, stuffy nose, sneezing, sore throat, cough, feeling tired), 7 items assessing functional impairments (quality of life score: think, sleep, breathe, talk, walk/climb stairs/exercise, go to school, play with friends), 1 item assessing global severity. All these items are scored using visual representation of happy and sad faces to assist Likert scale ratings from 0 (absent or no impairment) through 1 (a little bad), 2 (bad) and 3 (very bad). The sum of the 14 items on a 4-point ordinal scale results in a global total score ranging from 0 (low symptoms and low functional impairment) to 42 (high symptoms and high functional impairment). One item assessing global change as compared to the day before is rated from 0 (a lot better) to 4 (a lot worse) is not included in the overall score.

Using an electronic diary, the patient will score the WURSS-K daily in the evening, taking in account the symptoms from the morning to the evening, during D1-D10. After D10, the WURSS-K will be assessed once daily until the subject feels not sick for two consecutive days.

8.1.4 Secondary Endpoints

- Duration of cold symptoms (items 2 to 7) will be assessed by means of the WURSS-K (assessed once daily in the evening).

During treatment period, the WURSS-K will be assessed once daily in the evening, taking in account the symptoms from the morning to the evening.
After D10, the WURSS-K will be assessed once daily until the subject feels not sick for two consecutive days.
For each item, the duration is defined as the number of symptomatic days between D1 and the first day the subject reports not having the symptom for two consecutive days.
To be noticed that the duration may be censored at day 30.

- Number of subjects who develop respiratory complication requiring antibiotic prescription during a 20-day follow-up period. Healsea® Children is expected to reduce acute rhinitis complications.

- **Frequency and number of days of use of concomitant treatments** that may affect common cold symptoms (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical

corticosteroids). By reducing duration of common cold symptoms, Healsea® Children will very likely reduce the use of common rescue medication.

- **Number of family members in close contact developing common cold symptoms** after the patient all over the study period. The daily use of Healsea® Children started at the onset of common cold symptoms is expected to reduce relative's contamination.

- **Safety**: Assessment of adverse events/incidents/undesirable expected side effects throughout the study.

8.1.5 Methods and timing for assessing, recording and analysing variables

The primary endpoint will be assessed and record into an electronic diary once daily in the evening, considering the symptoms from the morning to the evening, during D1-D10. After D10, the WURSS-K will be assessed once daily until the subject feels not sick for two consecutive days. To be noted that the duration may be censored at day 30. Should the children require some or lot of help to fill in the questionnaire, this will be recorded in the diary as part of the WURSS-K questionnaire.

A specific field will be designed in the electronic diary for adverse event/incidents/expected side effects and concomitant treatments recording, contamination of relative(s) and for report of Healsea® Children intake if applicable.

8.1.6 Equipment to be used for assessing the clinical variables and arrangements for the monitoring maintenance and calibration

Not applicable.

8.1.7 Any procedures for the replacement of subjects

Not applicable.

8.1.8 Investigation sites: number, location

The clinical investigation will be undertaken in 15 sites in Poland. All investigators are paediatricians and /or allergist and/or pulmonologists. The investigation does not require specific environment as it is an observational study.

8.1.9 Definition of the completion of the study

This is defined as the date of last patient last visit (LPLV).

8.2 Investigational device and comparator

The investigational device which is Healsea® Children. This is a CE marked Medical Device. Patients/parents will be allowed to use or not the investigational nasal spray. If they choose nasal symptoms to be treated with Healsea® Children, they will start the nasal spray treatment following

their inclusion visit (Visit 1). Healsea® Children will be used on the top of conventional therapies for common cold and administered with the help of an adult, spraying one puff (1-2 sec) twice a day in each nostril for 10 days.

No comparator is used in this study. Patient/parents who prefer not to use Healsea® Children will use conventional therapies for common cold only. **However, use of nasal irrigation will not be authorized for these patients.**

8.3 Subjects

The target population is allergic children with early symptoms of acute infectious rhinitis.

8.3.1 Eligibility criteria

8.3.1.1 Inclusion criteria

Subjects will be enrolled if they meet all of the following criteria:

1. Male/Female subjects ≥6 and ≤10- year old
2. AsIgE ≥ class 2 (RAST) or positive prick test for at least one perennial allergen
3. Acute infectious rhinitis/rhinosinusitis **for ≤48h before trial entry**
4. Patient presenting with fever ≥ 37.5 °C at screening
5. Symptoms of headache, muscle ache, chilliness, sore throat, blocked nose, runny nose, cough, sneezing with **a total score ≤9** (according to a physician-rated symptom score; scale: 0 → 3 [0: no symptom to 3: severe intensity])
6. At least one of these symptoms: sore throat, runny nose or blocked nose (i.e., with a score ≥1)
7. Written consent obtained from parent/legal guardians
8. Written assent obtained from patient

8.3.1.2 Non-inclusion Criteria

Subjects will not be enrolled if one of the following criteria is present:

1. Known hypersensitivity/allergy to any component of the test device
2. Medical history that is considered by the investigator as a reason for non-inclusion
3. Severe nasal septum deviation or other condition that could cause nasal obstruction such as the presence of nasal polyps
4. History of nasal or sinus surgery that in the opinion of the investigator may influence symptom scores
5. Antibiotic intake within 2 weeks before screening
6. Systemic corticosteroids within 4 weeks before screening
7. Antihistamines intake for allergy when treatment was started from less than 4 weeks
8. Bacterial lysate intake within 6 months before screening
9. Chronic decongestant use

10. Recent (within the previous 2 days) intake of a common cold medicine that in the opinion of the investigator may influence symptom score at screening (NSAID, nasal decongestants, cough medicines)

8.3.2 Criteria and procedures for subject withdrawal or lost to follow-up

8.3.2.1 Withdrawal Criteria and procedures

The reasons for a subject's premature withdrawal from the study may be the following:

- A parent can withdraw his/her consent and/or a subject can withdraw his/her assent from the study for any reason at any time, but he/she must inform the investigator. In all cases, whenever possible, the investigator should attempt to contact the patient as soon as possible for a final assessment in order to:
    - Obtain the reason(s) for withdrawal and report it/them in the Case Report Form,
    - Evaluate the patient's clinical condition,
    - If necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. In the context of COVID-19 pandemic, the diagnosis of COVID-19 during the study will justify the withdrawal of the patient from the study.

A premature end of study visit will be scheduled. Available data will be retained for the safety/efficacy analysis.

8.3.2.2 Subjects lost to follow-up

If a patient cannot be contacted to collect follow-up information even beyond the 10 days from visit 3, he/she will be considered "lost to follow-up". But before declaring that a patient is "lost to follow-up", the Principal Investigator (or his/her team) must do his/her best effort to contact patients and attempts should be made via all available routes. A certified letter should be sent to the permanent address on file.
The methods used to attempt to contact the patient should be noted in the patient medical file.

8.3.2.3 Subject replacement

It is not anticipated to replace withdrawal patients.

8.3.3 Point of enrolment

The subjects will be recruited by the sites among outpatients coming in consultation because of early symptoms of common cold.

To facilitate the enrolment, parents/legal guardians of allergic children coming for routine consultation will be informed of this clinical trial. In case of the onset of acute infectious rhinitis/rhinosinusitis symptoms, they will be invited to contact the site and to come for a consultation if they are interested. Before performing any study procedure, the investigator will give all the information pertaining to the study and the patient's legal guardians will sign the consent form if they accept their child study participation. Children will also receive an information specific to their age and will be invited to sign an assent presented by the investigator.

8.3.4 Total expected duration of the clinical investigation

The total study duration is planned to be 4 months.

8.3.5 Expected duration of each subject's participation

The duration of each patient's participation is 30 days.

8.3.6 Number of subjects required to be included in the clinical investigation

A cohort of 200 children is expected to participate in the study.

8.3.7 Estimated time needed for the enrolment

It is expected to enrol a cohort of 200 patients within 3 months.

8.3.8 Relationship of investigation population to target population

Healsea® Children will be used within its intended use. This observational study aimed to confirm the benefit of Healsea® Children in a real life setting in children with perennial allergy and early symptoms of infectious rhinitis.

8.3.9 Vulnerable, pregnant and breastfeeding population

Patient under tutorship or legal guardianship are not eligible.

Pregnant and breastfeeding women: not applicable because it is a paediatric observational study.

8.3.10 Compensation

No compensation is planned because this is an observational study. Travel expenses will be reimbursed in full on presentation of receipts attesting to such expenses for visits 2 and 3, considering that visit 1 is a routine care consultation.

8.3.11 Study procedures

The study will comprise 3 visits and 2 telephone calls.

Visit 1 (V1) – (Day 1): Screening/Inclusion

The investigator will give oral information relative to the study to parents/legal guardians and the participant. If both parents/legal guardians agree that their child participate in the study, they will receive the information sheet and will be also asked to give a written consent. In case one parent will not be available for the visit; he/she will be asked to confirm in writing that he/she agrees with the participation of the child in the study. Children will also receive an information specific to their age and will be invited to sign an assent by the investigator.

Each screened subject will be assigned a subject identifier number during screening. The subject identifier number will contain the site number and the subject number and will be assigned in numerical order at the screening visit based on chronological order of screening dates (e.g., 01-010 for the 10th subject screened at the Site #01).

The investigator or his/her delegated designee will:

- Record demographic data and medical history and ongoing medication,
- Perform a physical and clinical examination,
- Record the score of the common cold symptoms (headache, muscle ache, chilliness, sore throat, blocked nose, runny nose, cough, sneezing according a physician-rated symptom score after clinical examination of the child; (scale: 0 3 [0: no symptom, 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable), 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping]). This scoring system was developed by Jackson in 1958 and is widely used in common cold clinical trials [19],
- Verify that eligibility criteria are fulfilled,
- Record the patient choice regarding Healsea® Children use (if the patient/parents choose nasal symptoms to be treated with Healsea® Children, instructions will be given to the patient/parents for getting the test product at the end of the visit),
- Explain to the child/parents/legal guardians how to use Healsea® Children if applicable,
- Review and detail the questions of the WURSS-K,
- Explain how to use the e-diary for WURSS-K recording, how to report adverse events/ incidents/expected undesirable side effects, concomitant medications, and contamination of relatives in the e-diary. The legal guardians will access the e-diary website (https://me.vieodoc.net) using a smartphone and logging in with a randomly assigned username and Pin code. Data recorded in the e-diary will be at the same time uploaded in the e-CRF.

D1-D10 (at home):

The patients will be asked to complete the electronic diary daily (WURSS-K assessed once daily in the evening, taking in account the symptoms from the morning to the evening, adverse events/incidents/expected undesirable side effects and concomitant medications, contamination of relatives) and to report Healsea® Children intake if applicable. For the Healsea® Children treated-group, compliance will be indirectly assessed by the question: “do you use the nasal spray as

recommended (1 puff 2 sec in each nostril twice a day)?". If necessary, the parent(s) will help their child in this task.

D5 (Day 5±2, at home): Telephone call 1

The Investigator or his/her delegated designee will call the patient to review patient status and study progress, adverse event/incidents/expected undesirable side effects and concomitant treatments.

Visit 2 (V2) – (Day 10±2): end of treatment

The investigator or his/her delegated designee will:

- Perform a physical and clinical examination,
- Record the common cold symptoms if they persist,
- Validate the adverse events/incidents/expected undesirable side effects and concomitant medications reported in the e-CRF through the e-diary and report any new relevant safety event.

For patients receiving Healsea® children, the treatment will be stopped at D10. The patients for whom common cold symptoms persist, will be instructed to continue to score the WURSS-K until the subject feels not sick for two consecutive days.

D11-D30 (at home):

After D10, the WURSS-K will be assessed once daily until the subject feels not sick for two consecutive days if applicable. The patients will be asked to complete the electronic diary daily (WURSS-K if applicable, adverse events, concomitant medications, and contamination of relatives). If necessary, the parent(s) will help their child in this task.

D20 (Day 20±2, at home): Telephone call 2

The Investigator or his/her delegated designee will call the patient to review patient status and study progress, adverse event, and concomitant treatments.

Visit 3 (V3) – (Day 30±5): end of study

The investigator or his/her delegated designee will:

- Perform a physical and clinical examination,
- Record the common cold symptoms if they persist,
- Validate the adverse events and concomitant medications reported in the e-CRF through the e-diary and report any new relevant safety event.

8.3.12 Permitted and forbidden concomitant medications

All concomitant medications are authorized **except nasal irrigation for patients who do not choose to use Healsea® children.**

8.3.13 Activities performed by sponsor representatives (excluding monitoring)

The sponsor will implement and write clinical quality procedures to ensure that the clinical investigation is conducted and monitored, and that data are generated, documented, recorded, evaluated and reported in compliance with the ISO 14155:2020, the CIP, any subsequent amendment(s) and any other applicable standards and in accordance with the regulation requirements. The sponsor will ensure ongoing risk management throughout the clinical investigation and will take all measures to protect rights, safety and well-being of children who participate in the study.

The sponsor is required to report noncompliance trends and safety issues to the Ethics Committee and investigators.

The sponsor shall report on the progress and status of the clinical investigation to the Ethics Committee.

The sponsor will determine the frequency and type of audit to be performed. An audit can be used:

i) As a routine part of the sponsor's quality assurance,
ii) To assess the effectiveness of the monitoring activity,
iii) Whenever there are serious or repeated CIP deviations or suspicion of fraud,
iv) To bring an investigation site into “inspection readiness” (i.e., to prepare the investigation site for a potential regulatory inspection),
v) When requested or suggested by a regulatory authority.

8.3.14 Any known/foreseeable factors that can compromise the outcome of the clinical investigation and methods for addressing these factors

There is no known/foreseeable factor that can compromise the outcome of the clinical investigation.

8.3.15 Follow-up and medical care after completion of the study

Neither follow-up nor specific medical care for patients are foreseen after the completion of the study.

8.3.16 Potential use of samples obtained from subjects

Not applicable.

8.4 Monitoring plan

A risk-based monitoring plan included in a separate document will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Results of the risk assessment will be used to develop a risk-based monitoring plan and a supporting rationale.

8.4.1 Initiation visit

The study will only start at a site after:

- The Ethics Committee has granted approval for the conduct of the study,
- Essential documents are in place, such as CVs of the Investigators and site staff, and the Clinical Trial Agreement signed.

In agreeing to participate, the investigator undertakes to strictly comply with the study protocol, Good Clinical Practice, the Polish regulation and to MDR. The investigator also guarantees the authenticity of the data collected in the context of the study and agrees to the legal provisions for study sponsor quality control.

8.4.2 Monitoring

Study monitoring under responsibility of Lallemand Pharma by qualified staff will be performed at various stages of the study. Monitoring will include on-site visits and centralized data review to assure that the investigation is conducted according to the CIP and comply with applicable regulations and deadlines. On-site review of electronic Case Report Form (e-CRFs) will include the review of forms for completeness, clarity, and consistency with source documents available for each subject. In case of queries, the investigator should respond within agreed timelines.

The investigator must permit study-related monitoring visits, audits review by the Ethics Committee, and allow direct access to source data and source documents provided that subject confidentiality is protected. In case of an audit appointed by Lallemand Pharma, the investigator will receive written notification in advance.

9. Statistical design and analysis

9.1 Descriptive statistics

The cohort is described: continuous variables will be summarized using the mean, standard deviation, median, minimum, maximum and quartiles, categorical variables will be summarized using frequency counts and percentages.

Two groups (called treatment groups for a sake of simplicity) will be extracted from the cohort according to the treatment chosen by the patient and a description of each group will be performed.

Details of the statistical analyses, methods and data conventions will be described in the SAP.

All statistical tests will be 2-sided and performed using a 0.05 significance level.

9.2 Study population

The study population consists in all the patients included and who do not meet a “major deviation to protocol” as defined in section 12.

The safety population consists in all the patients included in this study.

The analysis of primary and secondary endpoints will be performed on study population, safety endpoint will be performed on safety population.

9.3 Primary endpoint

The primary objective will be analysed by performing a t-test (or a Wilcoxon test if the normality assumption is not acceptable) between the means AUC of WURSS-K score during first 10 days of symptoms in each group.

9.4 Secondary endpoints

The analysis of the secondary endpoints will involve multivariate analysis.

The selection of variables in multivariate analysis will be performed using a 0.2 significance level and a stepwise method. Whole the multivariate analyses specified below involve the treatment and, in order to adjust for confounding, all the potential confounding factors as explanatory variables.

The analysis of the impact of the treatment chosen on the primary endpoint will be enriched by means of a multivariate regression model with the AUC of the WURSS-K during first 10 days of symptoms as dependent variable.

The impact of the treatment chosen on the cold symptoms' duration will be analysed by means of a Cox model.

The impact of the treatment chosen on the risk to develop respiratory complication requiring antibiotic prescription during a 20-day follow-up period will be analyzed by a multivariate logistic model.

The impact of the treatment chosen on the intake of conventional common cold medication (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids) will be analyzed by multivariate Poisson regressions for the numbers of days and a multivariate logistic regression for the frequency.

The impact of the treatment chosen on the number of family members in close contact developing common cold symptoms after the patient all over the study period will be analyzed by means of a multivariate Poisson regression.

9.5 Safety

All adverse events/incidents/expected side effects will be listed, but only treatment-emergent adverse events/incidents (non-serious + serious) will be summarized.

Two groups (called treatment groups) will be extracted from the cohort according to the treatment chosen by the patient.

Adverse events/incidents/expected side effects will be summarized by the number and percentage of patients (by treatment group), classified by System Organ Class and Preferred Term as defined by MedDRA dictionary.

For a given treatment group, a given adverse event will be counted treatment emergent only once per patient during the treatment period.

Frequency and percentage of patients with at least one reported adverse event/ incident / expected side effects will be tabulated by System Organ Class and by treatment group.

10. Data management

Subject data will be entered into an electronic case report form.

10.1 Source documents

The source documents (e.g., medical file, clinical and office charts, laboratory reports…) which contain the source of data recorded in the CRF should be specified. The e-diary will be used as source document for WURSS-K, compliance, contamination of relatives if applicable.

Each subject will be assigned and identified by a unique Screening Number. Any reference made to an individual subject within the study must be done using the unique Screening Number.

10.2 Methods for data entry and collection

A validated electronic case report form (eCRF, e-Diary, VIEDOC software) will be used to collect clinical data for this study. Some of the study data will be recorded in the e-diary (ViedocMe) by the legal guardian after secure logging to the study website (https://me.viedoc.net) and will be automatically uploaded in the e-CRF:

- WURSS-K,
- Healsea® Children use if applicable,
- Adverse event/ incidents/ expected side effects and concomitant treatments,
- Contamination of relative(s) if applicable.

Lallemand Pharma is responsible for designing the e-CRF. eCRF training will be given to appropriate personnel before/at initiation of the investigation site(s). Legal guardians will be instructed how to connect to the e-diary at visit 1.

10.3 Data review

The Data Management process includes all activities related to data handling regarding:

- Set-up of eCRF and database
- Specification of on-line checks
- Data entry/Data editing
- Export of data from e-CRF to SAS
- Creation of post-entry checks and listings
- Clean-file process including execution of post-entry checks and listings
- Post clean-file tasks

Data entry will be done by investigators and other authorized personnel at the site(s). When entering data, on-line checks are encoded in the e-CRF for consistency and validation. Whenever required, queries issued from this review will be submitted to the investigator for resolution and then tracked until corrections are entered and validated.

A clean-file review meeting will be held prior to database lock.

The review process prepared by the clinical research assistant, data manager, study monitor, medical manager and statistician will be completed by a meeting (Validation Committee) to be attended by at least the following:

- Coordinating investigator,
- Study monitor,
- Sponsor Vigilance representative,
- Study Coordinator,
- Data manager,
- Statistician.

The review is also required for defining the analysis populations and validating the statistical analysis plan.

The meeting will be documented by written and signed minutes that will act as the basis for data processing by the Biometrics Department.

All decisions on the evaluability of the data from each individual subject for the statistical analysis must be made and documented before locking the database.

Data will be retained for at least 15 years after investigation closure. All data collected in the electronic Case Report Forms will be handled and archived under the responsibility of Lallemand Pharma.

10.4 Procedures for verification, validation and securing of electronic clinical data system

The VIEDOC software is installed on a server (secure Data Center) hosted at the VIEDOC company that guarantees the security, maintenance, as well as regular antivirus and firewall updates of this dedicated server. Any modification to the data is tracked, i.e., creation and changes are timestamped, and authors are recorded. Viedoc Technologies complies with the E.U. General Data Protection Regulation (GDPR).

Backups are taken, encrypted, and replicated to the paired Microsoft Azure region every five minutes. One full backup for each instance is encrypted and transferred to cold storage in a third location, read back, restored, and tested for integrity every 24 hours.

The VIEDOC electronic system from PCG Solutions is systematically validated at several levels, from program development to actual use in clinical trials:

- Unit Test / Code Review

Unit test and code review are validation activities performed by the system developers during the programming phase. Unit tests are written by the programmer while they are writing (or modifying) the source code. Unit tests are automatic test cases. All Viedoc unit tests are automatically executed every time the source code is built. PCG Solutions implements daily builds so these tests are run daily (or more often). The results of the unit testing are reported by the build tool, which is integrated into the PCG Solutions repository. The build automatically fails if any of the unit tests fail, and the source code needs to be corrected and the unit test passed before the next build will pass. Records of all builds are kept in TFS so that the history of the release build of any version of Viedoc can be examined, as well as the builds leading up to that release. The results of the unit testing are summarized in the Validation Report for the release.

Code review is performed by another member of the development team than the programmer of that source code. Code review is mandatory for high-risk implementations and encouraged even for all other source code. Risk evaluation is part of the sprint planning process. Code review is performed either using pair programming or code review sessions where more members of the team are involved. The results of the code review are immediately worked into the source code and are not separately documented.

- Function / System Test

Function and system testing are different names for the same thing at PCG Solutions. The name function test is derived from the fact that the majority of all testing performed at this level is with regards to functional requirements. The name system test simply recognizes that occasionally non-functional requirements are also tested (i.e., performance requirements). The same methodology is employed irrespective of whether the requirements are functional or non-functional.

The goal of function testing is to confirm that the implementation fulfils the requirement, i.e., to validate the product implementation against the requirements placed on the product. Function testing is performed by a different member of the system development team than the programmer and consists of exploratory testing and scripted testing.

Exploratory tests are not predefined but are rather focused on testing a given requirement using an approach of simultaneous learning, test design, test execution and test result documentation. Exploratory tests are documented in one test result object in the PCG repository, i.e., the test steps and the test results are documented together and linked to the requirement being tested. Exploratory testing is often performed first in order for the tester to develop a deeper understanding of the requirement before writing the formal scripted tests.

Scripted tests are predefined test cases with detailed preconditions, steps to be executed and expected outcomes listed. Scripted test cases are designed and written by one system developer and executed by a different system developer (neither of whom are the programmer who wrote the source code). The results of scripted tests are stored in separate test result objects linked to the test cases in the PCG repository.

All test cases and test results are stored in the PCG repository, and are linked such that test cases are linked to the requirements they test, while test results are linked to the test case they record the results of.

- Installation Qualification

The goal of installation qualification is to ensure that the correct versions of all modules that make up a release of the product have been installed correctly on the server. There are two types of installation qualification: Build Installation Qualification and Instance Installation Qualification.

Regarding Built Installation Qualification, when a new product or a new version of a product is to be released, a build for the version is delivered by the development department. Product operations are then responsible for deploying this same build on all production servers. Build installation qualification ensures that the exact content released by the development department (in terms of modules and versions of the modules) and the exact configuration of the server environment (operating system version, database version, other software infrastructure products) are included in the build. This is done by ensuring all software components are in place and of the correct version.

Regarding Instance Installation Qualification, every time a new instance of the product is setup the environment is checked to ensure that all prerequisites are met, and all components are installed.

- Operational Qualification

After completing the Installation Qualification an Operational Qualification is executed to ensure that all core functionality operates as expected. This is performed for every release of a product, and Operational Qualification is documented as part of the release documentation for that release of the product.

- Performance Qualification

The goal of performance qualification is to confirm that the delivered product is fit for use, i.e., that the product will work as intended. While function testing will typically find errors where the product implemented does not fulfil the requirement as stated, performance qualification will typically identify weaknesses where the requirements themselves are faulty (for example have been incorrectly analysed or have missed certain conditions).

Performance qualification is scenario-based, designed around using the product in the same way it will be used in a clinical research setting. Performance qualification includes a great deal of regression testing, aimed at ensuring that existing functionality is not affected in new releases. Performance Qualification is performed and documented per release of the product being validated. These documents are stored together with the other release documentation for that product.

Build Installation Qualification is performed once for every release of a product, and Instance Installation Qualification is produced once for every instance of the product. Both are documented as part of the release documentation for every release of the product.

10.5 Procedures to maintain and protect subject privacy

It is the responsibility of the sponsor to maintain a security system that prevents unauthorized access to the data, both internally and externally.

Subject privacy is protected through the VIEDOC system at different levels so as to preclude unauthorized access to data:

- Personal data other than medical are limited to a minimum and under full control of the subject.

In the e-Diary, ViedocMe, there is a possibility for the patient to register their email address and/or telephone number to receive reminders, but that information is encrypted within Viedoc and cannot be read by any user. The patient can modify or delete this personal data (the email address and telephone number) at any time. Each patient will have a username and a PIN code randomly assigned for connexion to the e-Diary.

- Only authorized persons can access the data.

The permission system is role-based, supporting the principle of least privilege, and restricting access to specific pieces of data to users on a need-to-know basis. Multi-factor authentication, as well as a sophisticated system for delegated provisioning/deprovisioning of user access, provide an additional level of security.

- The risk of data breaches is minimized by full encryption.

In addition to encryption-measures in operations environment (only encrypted endpoints served, encryption-at-rest on disk), encryption-in-transit is enforced through strict-transport-security headers for public endpoints, and sensitive data are encrypted-at-rest in database. The system is also designed to use encryption-in-transit internally between sub-systems.

- External interactions are actively protected.

Viedoc data communication between client and public endpoint is tuned to standards which in turn allows web-application-firewalls to inspect all traffic in prevent mode. Content Delivery Networks (CDN) are not used – all content and client-side code libraries are distributed directly from Viedoc servers, which is also enforced through content-security-policy headers, to ensure authenticity and prevent man-in-the-middle tampering.

Anti-malware signatures are updated in real-time as released by vendor. Web application firewalls are configured with OWASP 3.0 rules in prevent mode. All network segments are protected with firewalls that have block-all by default and only allow whitelisted traffic. Only encrypted endpoints are exposed.

There is a daily review of security bulletins. Each month a black-box vulnerability test (according to PCI-DSS standard) is performed, along with an encryption-in-transit test. A security meeting is held once a month to discuss the current security landscape and review the past month's activity and the plans for the upcoming month.

Once a year, a third-party security team is contracted to perform white-box penetration testing of the solution.

10.6 Methods for database locking at the start of analysis and storage upon completion of the clinical investigation

The validated database will be locked upon request of the Data manager following the completion of all steps required, i.e., resolution of all queries, validation of the coding, data review meeting.

10.7 Procedure for data retention

Once the Clinical Investigation Report is signed and validated, the data are archived on a dedicated hard disk file with limited access rights. This specific file is mounted on AXIODIS's OVH server with a back-up every two months as well as copied to an external disk that will be stored under seal within the premises of AXIODIS. The data are conserved for at least 10 years.

11. Amendments to the CIP

Neither the investigator nor the sponsor may alter the protocol without the authorisation of the other party.

All changes to the protocol are subject to an amendment which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are notified to the EC.

12. Deviation from Clinical Investigation Plan

In this context of observational study, the intervention is not protocolized and the study is restricted to the observation of the being of patients during the study. However, we define "Major protocol deviations" as deviations liable to prevent or change the interpretation of the results of the study. The following deviations are considered major:

- Non-compliance with the inclusion or exclusion criteria,
- No assessment of the primary efficacy criterion (WURSS-K) at D1, D5±1 and D10±1 during the treatment period,
- Intake of forbidden medication, i.e., nasal irrigation for patients who choose not to take Healsea® children.

All other cases will, a priori, be considered as minor deviations.

All protocol deviations will be managed as per the Standard Operating Procedures of the CRO.

A deviation log shall be maintained by the study sites.

All deviations will be included, as required in the final study report.

Any major deviation from the protocol that has not been previously approved by the sponsor must be reported to the sponsor within 2 working days of the deviation occurrence. Any deviations from the clinical investigation plan that are identified during routine monitoring visits will be reported to the sponsor within 24 hours of being identified.

Corrective and preventive actions and principal investigator disqualification criteria will be described in the monitoring plan.

13. Device accountability

Not applicable for an observational study.

14. Ethical consideration

14.1 Informed consent process

According to Regulation EU 2017/745, ISO 14155:2020 and applicable Polish regulations, the Principal Investigator or his/her authorized designee must explain all aspects of the clinical investigation that are relevant to the parents/guardians' decision for their child participation throughout the clinical investigation before any study. Parents/legal guardians will have the opportunity to carefully review the information document and ask questions prior to accept or not the participation of their child in the study. Although this investigation is observational, the consent will be obtained in writing by both parents/legal guardians and the study participation must be documented in the patient medical file. In case one parent will not be available for the visit, he/she will be asked to confirm in writing that he/she agrees with the participation of the child in the study. Children will also receive an information specific to their age and will be invited to sign an assent presented by the investigator. Objections raised by a child at any time during a trial should be considered. The child's will should be respected. The child should not be forced to provide reasons. The child should be informed of the possibility to freely withdraw from the trial, at any time for any reason, without any disadvantage or prejudice.

14.2 Subject confidentiality

The present study will be conducted under Regulation 2016/679/EU of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the personal data and free movement of such data (GDPR) and Act on Personal Data Protection dated 10 May 2018, effective within the territory of Poland (uniform version - Journal of Laws of 2018, item 1000).

In accordance with GDPR, the Sponsor is the "Controller" and the participating sites, monitors, data managers and statisticians are "Processors". Lallemand Pharma AG, sponsor of the study, is responsible for the processing of the study data.

Confidentiality of data shall be observed by all parties throughout the clinical investigation. All data will be secured against unauthorized access. Subject names will not be sent to the sponsor. Only the patient number will be recorded in the e-CRF, and if the patient's name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. All subject data that appear in reports and publications will be anonymised such that the privacy and confidentiality of each subject is maintained.

No data processing will be performed outside of the European Union, but the data base will be transferred to the sponsor at Massagno in Switzerland. Although outside EU, this country is recognized by the EU as offering an adequate data privacy protection.

To fulfil the requirements of source data verification, the PI will be required to obtain consent from each subject stating that they agree for their medical records to be accessed (this will form part of the consent process). To comply with the Polish Regulation and GDPR, a specific document explaining the lawfulness of personal data processing conditions and patients' rights will be signed before any study procedure by the parents/guardians.

The patients' rights are the followings:

- The right to request access to, rectification, deletion or restriction of processing concerning personal data collected during the study,
- The right to get back all data linked to the research and to forward them to another data processing manager (portability right),
- The right to withdraw consent to data collection at any time and to request a restriction of processing concerning personal data as mentioned in GDPR's article 18. However, the data processing manager keeps the ability to reject such request should this right likely make impossible or seriously compromise the achievement of the research objectives.

These rights can be exercised with the investigator or his designated representative or by contacting the Data Protection Officer appointed by Lallemand Pharma: Yannick Hervy, yhervy@lallemand.com.

14.3 Insurance policy

Lallemand Pharma has an insurance policy intended to guarantee against possible damage resulting from the investigation (Insurance Policy number).

It is advisable to underline that non-compliance with the Research Legal Conditions is a cause for guarantee exclusion.

15. Vigilance

Non-invasive procedure is planned in this observational study and Healsea® Children will be used in the intended use covered by the CE mark.

Pursuant to (EU)2017/745 Medical Device Regulation, for a post market clinical follow-up investigation of a medical device used within the intended use covered by the CE-mark, requirement of MDR articles 87 to 90 apply.

15.1 Definitions

Incident means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect (MDR 2017/745).

Serious incident means any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat (MDR 2017/745).

Serious public health threat means an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time (MDR 2017/745).

Expected and foreseeable side effects (MEDDEV 2 12-1 rev. 8)

They meet all the following criteria:

- Clearly identified in the manufacturer's labelling,
- Clinically well known as being foreseeable and having a certain qualitative and quantitative predictability when the device is used and performs as intended,
- Documented in the device master record, with an appropriate risk assessment, prior to the occurrence of the incident and,
- Clinically acceptable in terms of the individual patient benefit.

Adverse event means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether related or not related to the investigational device (MDR 2017/745).

Adverse or intercurrent events are graded as follows:

- Mild: Awareness of signs or symptoms but easily tolerated.
- Moderate: Uncomfortable enough to cause interference with usual activity.
- Severe: Incapacity with inability to work or do usual activity.

15.2 Reporting in the eCRF

All serious and non-serious incidents/serious and non-serious risk of incidents/expected side effects (except pre-existing condition but allergy) occurring during the clinical investigation will be reported in the e-CRF.

15.3 Investigator's responsibilities and processing timelines

All incidents and expected undesirable side effects will be reported to LP vigilance manager according to MDR, MEDDEV 2.12 rev 8 modalities, national requirements, ISO 14155:20 and Lallemand Pharma procedures which are described in the safety management plan. This document will be signed by the Principal Investigator, representants of the Clinical Research Organization (CRO) before study start.

As soon as the investigator will be informed of the event, he will complete a Primary Notification Form template (PNF, appendix C) and send it to LP vigilant manager and to the CRO with any relevant supportive documentation within the same day (<24h) for serious (risk)incident and within two calendar days (<48h) for non-serious incidents and expected side effects.

15.4 Sponsor responsibilities and processing timelines

The vigilance manager of Lallemand Pharma is responsible for the reporting to the Polish Health Authority (URPL) and to Ethics Committees according to local requirements.

Briefly, for serious incidents or risk of serious incident, the vigilance manager will complete a Manufacturer Incident Report (MIR). The result of the investigation conducted by the sponsor may lead to the implementation of a safety corrective action and completion of a Field Safety Correction Action (FSCA) and of a Field Safety Notice. These documents will be transmitted to the URPL in accordance with the timelines provided in the table below:

Serious Public Health Threat	Report immediately but not more than 2 days
Death or UNANTICIPATED Serious Deterioration in State of Health	Report immediately but not more than 10 days
Others (could have led to death or serious deterioration in health)	Report immediately but not more than 15 days
Every FSCA	Immediately before the measure is implemented except in case of emergency, when the vigilance manager of the sponsor has to immediately take a safety corrective action

Increase rate or severity of expected undesirable side effects and non-serious incidents will be reported to the URPL in Trend reports as per regulation requirements.

16. Suspension, premature termination and routine close out

16.1 Suspension or Premature Termination of the Clinical Investigation

Lallemand Pharma may suspend or prematurely terminate either the clinical investigation in an individual investigation site or the entire clinical investigation. The reasons will be documented. Reasons for suspension or premature termination at an investigation site may include incidences where monitoring or auditing identifies serious or repeated deviations done by an investigator. Lallemand Pharma will notify the EC of any suspension or early termination of the clinical investigation, it will also notify all other principal investigators in the event that the suspension or termination was due to safety issues.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the EC, Lallemand Pharma will suspend the clinical investigation while the risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. Should the risk not be confirmed Lallemand Pharma will, in accordance with regulations, supply relevant persons with justification and data supporting the decision to resume the clinical investigation.

16.2 Routine close out

Routine close-out procedures will be conducted ensuring that the Patients' records are complete, all documents needed for the sponsor files are retrieved, remaining clinical investigation materials are returned to the sponsor, previously identified issues have been resolved.

The expected duration of the trial is ca. 4 months from recruitment of the first participant. The end of trial is the date of the last follow up visit of the last participant.

The Principal Investigator will retain all copies of the records for a period of 15 years from the completion of the clinical investigation. In any circumstances, the Principal Investigator must contact the sponsor prior to disposing of any records related to the clinical investigation. Should the data be no longer required for regulatory purposes then the confidential destruction of said documents will be approved. Should the data be maintained for longer Lallemand Pharma will make this information available to all appropriate bodies in the same way. A list of essential documents to be maintained will be provided to each site at initiation.

Should the Principal Investigator have to move/retire, or otherwise leaves his(her) position, he(she) will provide Lallemand Pharma with the name and address of the person assuming responsibility for retention of records relating to this clinical investigation.

17. Publication policy

The information and data collected during the conduct of this clinical study are considered confidential and are used by the sponsor in connection with the development of the study treatment. This information will be disclosed by the sponsor depending on current regulations.

To allow use of the information derived from this clinical study and to ensure compliance with current regulations, the investigator must provide the sponsor with complete test results and all data collected during the study.

Only the sponsor may make study information available to physicians and to Regulatory Agencies, except as required by current regulations.

All the results of this study including data and reports are the property of the sponsor.

In the event that the sponsor chooses to publish study data, the manuscript must be provided to the author(s) at least 30 days prior to the expected date of submission to the intended publisher.

The investigator(s) can reserve the right to publish or present study data; if so, the manuscript or abstract must be provided to the sponsor for review at least 30 days prior to the expected date of submission to the intended publisher or of planned presentation.

In addition, if necessary, (the) investigator(s) shall withhold publication for an additional 60 days, to allow the filing of a patent application, or to allow the sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of study results by each site shall be made only as part of a publication of the study results obtained by all sites performing the protocol, once the study is completed and finalised.

A description of the clinical investigation is registered in https://www.clinicaltrials.gov/. The content will be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation and made publicly available.

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19. List of Appendix

Appendix A: Instruction for Use of Healsea® Children

Appendix B: WURSS-K

Appendix C: PNF

Appendix A: Instruction For Use

Healsea®
CHILDREN
NASAL CARE

Discover Healsea®!
Healsea® is a range of medical devices in nasal spray form with seawater from the Swedish Gullmarn Fjords ensuring a high level of purity.
It contains an innovative extract, Symbiofilm®, isolated from the marine biosphere of the deep seas of Panarea islands in Sicily. Symbiofilm® was discovered in a protected ecosystem ensuring a unique marine biodiversity.
Healsea® is a natural care preservative free allowing to clean the fragile nasal mucosa.

Healsea® CHILDREN is the ideal solution for children who suffer from common cold or flu.
Symbiofilm® is a marine postbiotic, which contains unique exopolysaccharides, an important natural component, enhancing the cleansing efficiency of **Healsea® CHILDREN**. Symbiofilm® reduces the development of biofilm from respiratory pathogenic microorganisms, and improves the nasal microbiome quality, contributing to an increased resistance against viral and bacterial respiratory tract infections.
Healsea® CHILDREN cleans the nasal cavity and eliminates allergens and infectious agents.

INDICATION
Healsea® CHILDREN is a nasal spray indicated in children above 6 years to clean and moisten the nose during colds and rhinitis.

DIRECTIONS FOR USE
Healsea® CHILDREN shall be administered in children with the help of an adult.
For colds and rhinitis: one puff (1-2 sec) twice a day in each nostril for 10 days.

COMPOSITION
Isotonic seawater solution (salinity 0.9%), Symbiofilm®.

CONTRAINDICATIONS
Do not use in children under 6 years.
Do not use in case of hypersensitivity or allergy to one or several components.

STORAGE AND WASTE RECOMMENDATIONS
Store at room temperature and not above 30°C.
See the expiry date on the box or the spray bottle.
Ask your pharmacist to throw out the spray bottle after use. These measures contribute to protect the environment.

PRECAUTIONS OF USE
- Keep out of reach of children.
- If symptoms persist more than 10 days, ask for advices to your doctor or pharmacist.
- The bottle shall be used by only one person for hygiene reason and to avoid the transmission of pathogenic agents that could be in contact with the nozzle.
- Keep away from heat, hot surfaces, sparks, flames or sunlight.
- As the bottle is pressurised, do not pierce or burn even after use.
- Do not smoke while using the spray.

Lallemand Pharma AG - Via Selva 2 - 6900 Massagno - Switzerland
Distributed by:

Confidential - Mockup - Not intended for use

UNDESIRABLE EFFECTS
Feeling of itching and irritation can occur while initiating the treatment. In case of undesirable effects, contact your doctor.

BAG ON VALVE TECHNOLOGY
The Bag on Valve technology warrants a perfect airtight of the bag containing the seawater-based solution. This technology permits to dispense a preservative free solution.

How to use Healsea® CHILDREN?
1. Place the nozzle smoothly into the nostril while keeping head straight.
2. Once the nozzle is placed, press on the nozzle for 1-2 sec in each nostril. Let flow the excess of solution and wipe.
3. Clean the nozzle with tissue, soapy water, rinse and dry after every use.

Symbiofilm® has been scientifically documented *in vitro* for its physical properties helping to reduce the biofilm formation by pathogens. Learn more about biofilms by flashing this QR code!

First authorization date of CE marking: YYYY/MM/DD
CE 0459
Publication date : YYYY/MM/DD_R0

LALLEMAND
LALLEMAND PHARMA

Appendix B: WURSS-K (English version)

Wisconsin Upper Respiratory Symptom Survey For Kids
Daily Symptom Report

Day:	Date:	Time:	ID:

Please fill in one circle for each question:

	Not sick 	A little sick 	Sick 	Very sick 
How sick do you feel today?	O	O	O	O

How bad are your cold symptoms? (Overall, since yesterday)

	Do not have this 	A little bad 	Bad 	Very bad 
Runny nose	O	O	O	O
Stuffy nose	O	O	O	O
Sneezing	O	O	O	O
Sore throat (hurts to swallow)	O	O	O	O
Cough	O	O	O	O
Feeling tired	O	O	O	O

Since yesterday, how **hard** has it been to:

	Not at all 	A little hard 	Hard 	Very hard 
Think	O	O	O	O
Sleep	O	O	O	O

Breathe	O	O	O	O
Talk	O	O	O	O
Walk, climb stairs, exercise	O	O	O	O
Go to school	O	O	O	O
Play with friends	O	O	O	O

Compared to yesterday, I feel my cold is…

A lot better	A little better	The same	A little worse	A lot worse
				
O	O	O	O	O

I completed this page: ☐ all by myself ☐ with some help ☐ with a lot of help

Who helped you? _____

WURSS-K© (Wisconsin Upper Respiratory Symptom Survey) 2014
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Appendix C: Primary Notification Form

Date of the report: ……
Type of report: initial/Follow up
Recorded by (name and position) : …….
Reference number:
Information on reporter:

Contact name :	
Health professional :	☐ YES ☐ NO
Address :	
Country :	
Phone :	
Fax : Email :	

Support : Mail / Phone / Fax / Email / Other
(1) Delete as appropriate

Product concerned by notification :

Product Name :	
Country :	
Batch number :	
Expiry date :	
Classification :	
Quantity concerned :	

Consumer information :
Age :
Gender :
Remedial action :
Outcome :

Detailed description the incident :

Date of the incident occurred:	

Seriousness criteria : Incident description narrative: Usage of the medical Device/frequency of use :	

INVESTIGATION

☐ Date : .....
☐ Manager : .....

Elements to control during investigation :	
Risks identification :	
Recurrence study / Impact on other batches ?	

Field Safety Corrective Action (FSCA), preventive actions, corrections, and corrective actions

FSCA

☐ Date : .....

☐ Manager : .....

Nature of the FSCA :	
Control of the FSCA implemantation :	
Control of the FSCA effectiveness:	

Preventive actions

☐ Date : .....
☐ Manager : .....

Nature of preventives actions :	
Control of the preventive actions' implementation :	
Control of the preventives actions' effectiveness :	

Corrective actions

☐ Date : .....

☐ Manager : .....

Nature of corrective actions :	
Control of the corrective actions' execution :	
Control of the corrective actions' implementation :	

Corrections :

☐ Date : .....

☐ Manager : .....

Nature of corrections :	

Closure

☐ Date of investigation conclusion : .....

☐ Manager : .....

☐ Signature :