Strictly Confidential

Efficacy and safety of Healsea® Babykids in the treatment of acute infectious rhinitis symptoms in children

CLINICAL INVESTIGATION PLAN

Study Number: LPH-2202

Short Title: BASICC

Version 1.1; 2023.02.02

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
Version 1	**2022-12-14**	**Initial version**
Version 1.1	**2023-02-02**	**Correction of a typography (7.1.3) & addition of two sites**

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STUDY: LPH-2202
CLINICAL INVESTIGATION PLAN Version:
1.1 – 2023-02-02

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Table of Contents

PRINCIPAL INVESTIGATOR STUDY APPROVAL PAGE
STUDY: BASICC-LPH 2202
CLINICAL INVESTIGATION PLAN Version:
Version 1.1 – 2023.02.02

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

- To conduct the trial described in the Clinical Investigation Plan (LPH-2202) Version 1 dated 2022-12-14 in compliance with GCP, 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

AE	**A**dverse **E**vent
ARSSQ	**A**cute **R**hinitis **S**ymptoms **S**everity **Q**uestionnaire
CA	**C**ompetent **A**uthority
CIP	**C**linical **I**nvestigation **P**lan
CRF	**C**ase **R**eport **F**orm
CRO	**C**linical **R**esearch Organization
EEC	**E**uropean **E**conomic **C**ommunity
EC	**E**thics **C**ommittee
FAS	**F**ull **A**nalysis **S**et
GDPR	**G**eneral **D**ata **P**rotection **R**egulation
GP	**G**eneral **P**ractitioner
IFU	**I**nstruction **F**or **U**se
LPLV	**L**ast **P**atient **L**ast **V**isit
MDCG	**M**edical **D**evices **C**oordination **G**roup
MDR	**M**edical **D**evice **R**egulation
MedDRA	**Med**ical **D**ictionary for **R**egulatory **A**ctivities
NSAID	**N**on-**S**teroidal **A**nti-**I**nflammatory **D**rugs
PI	**P**rincipal **I**nvestigator
PMCF	**P**ost-**M**arket **C**linical **F**ollow-up
PNF	**P**rimary **N**otification **F**orm
PP	**P**er **P**rotocol
PT	**P**referred **T**erm
SAE	**S**erious **A**dverse **E**vent

SAP	**S**tatistical **A**nalysis **P**lan
SOC	**S**ystem **O**rgan **C**lass
TEAE	**T**reatment **E**mergent **A**dverse **E**vent
URTI	**U**pper **R**espiratory **T**ract **I**nfection

1. Synopsis

Sponsor:	LALLEMAND PHARMA AG
Coordinating Investigator:	**Assoc. Prof. Rada Markova**
Title:	**Efficacy and safety of Healsea® Babykids in the treatment of acute infectious rhinitis symptoms in children**
Short Title	**BASICC (BAbykids Spray In Common Cold)**
CIP version:	Version 1-2022-12-14
Competent Authority:	Bulgarian Drug Agency / Central Ethics Committee
Rationale:	**Healsea® Babykids** is an isotonic saline solution based nasal spray supplemented with a natural Symbiofilm® extract (0.04%) 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. Symbiofilm® also protects *in vitro* human nasal epithelial cells viability after Rhinovirus, Adenovirus, coronavirus OC43 and flu infection. **Healsea® Babykids** is a nasal spray indicated in children above 2 years to clean and moisten the nose during colds 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. The aim of this study is to demonstrate that **Healsea® Babykids** alleviates symptoms of the acute rhinitis phase with better efficacy than isotonic saline solution used as Placebo.
Objectives:	**Primary Objective:** - To assess the efficacy of **Healsea® Babykids** on the overall health status score of the Acute Rhinitis Symptoms Severity Questionnaire (ARSSQ) in 2-6 years old children during a treatment period of 7 to 10 days as compared to Placebo. **Secondary Objectives:** - To assess the impact of **Healsea® Babykids** on the duration of each infectious rhinitis symptom and on quality of life as compared to Placebo.

	- To assess the impact of **Healsea® Babykids** on the intake of conventional common cold medication (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids) as compared to Placebo. - **Safety**: to assess systemic and local tolerance of **Healsea® Babykids** over the study period.
Endpoints:	**Primary Endpoint:** The primary endpoint is the AUC of the global score of the Acute Rhinitis Symptoms Severity Questionnaire (ARSSQ) over the first 11 days of symptoms. The ARSSQ will be assessed once daily in the evening from Day 1 to Day 8 and, if needed, until complete resolution of all symptoms for 2 consecutive days ("not sick" at question 1 of the ARSSQ). Due to the study schema, data may be censored at Visit 2 (between Day 15 and Day 18 after inclusion). **Secondary Endpoints:** - **Duration of each cold symptom** as reported in questions 2 to 7 of the ARSSQ (refer to table 1). For each separate symptom, the duration is defined as the number of days between Day 1 and the first day the parent reports the patient not having this symptom ("Not present") for 2 consecutive days. As mentioned for primary endpoint, duration may be censored at Visit 2. - **Duration of quality-of-life impairment** as reported in questions 8 to 10 of the ARSSQ. For each separate activity, the duration is defined as the number of days between Day 1 and the first day the parent reports no impact on the patient quality of life ("No impact") for 2 consecutive days. As mentioned for primary endpoint, duration may be censored at Visit 2. - **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). - **Safety**: Assessment of adverse event related to acute rhinitis and incidents throughout the study.
Indication:	Treatment of acute rhinitis in children 2-6 years old
Investigation Design:	**Prospective, Double-Blind Placebo controlled randomized trial** The study will comprise 2 parts: - Part 1 (D1-D11): treatment of the acute phase • with **Healsea® Babykids**, 2 puffs in each nostril 2 times per day with a minimum of 7-day-treatment period (14 intakes of Healsea® Babykids) up to 10 days (20 intakes of the investigational device). or • with **isotonic nasal spray (Placebo)**, 2 puffs in each nostril 2 times per day with a minimum of 7-day-treatment period (14 intakes of Placebo) up to 10 days (20 intakes of the investigational device). - Part 2 (up to D15/D18): follow-up phase. **Visit 1 (V1) - (Day 1): Screening/Inclusion/Randomization**

	Information and provision of the information sheet to legal guardians/parents of participants, consent signature, demographic data and medical history, ongoing medication, inclusion/non-inclusion criteria, physical and clinical examination, baseline assessment of the ARSSQ, randomization, diary presentation, treatment dispensation of **Healsea® Babykids** Nasal Spray or **Placebo** (**Isotonic nasal spray)** (according to randomization list). **D1-D8 up to D1-D11 (at home**): Daily completion of the paper diary (questionnaire, adverse events/incidents and concomitant medications), **Healsea® Babykids /Placebo** nasal spray treatment daily administration. **Between D8 and D11 (at home):** End of **Healsea® Babykids/Placebo** nasal spray treatment. **Up to D15/D18 (at home):** Daily completion of the diary (adverse events/incidents, concomitant medications, ARSSQ if applicable, until the subject feels not sick for two consecutive days). **Visit 2 (V2) – (Day 15-18): end of study** Diary review, reporting of adverse event/incidents/, compliance, ARSSQ completion if "not sick" is not ticked for 2 consecutive days in the previous days.
Number of Subjects:	It is planned to enroll a cohort of **200** subjects.
Target Population:	Children with symptoms of acute infectious rhinitis
Permitted and prohibited concomitant medication	Permitted concomitant medications during the study: ○ Antipyretics ○ Systemic and/or local mucolytics ○ Local decongestants (to be taken away from nasal score assessment, 2 hours minimum) ○ Systemic antihistamines only if taken for more than 4 weeks at screening or started at/after screening ○ Local and systemic corticosteroids ○ Antitussive ○ Antibiotics Non-permitted concomitant medications: ○ Saline nasal spray
Inclusion/Exclusion criteria:	**Inclusion Criteria:** Subjects will be enrolled if they meet all of the following criteria: 1. Male/Female subjects >2 and ≤6-year-old 2. Acute infectious rhinitis/rhinosinusitis **for ≤48h before trial entry** 3. Patient presenting with fever ≥ 37.5 °C at screening

	4. Subjects with nasal congestion (blocked / stuffy nose) rated at least as moderate on the Acute Rhinitis Symptoms Severity Questionnaire, based on evaluation by the investigator 5. Subjects showing at least moderate grade for at least one of the following additional signs of acute rhinitis: runny nose, nasal crust (dry mucus), sneezing and cough 6. Written consent obtained from parent/legal guardians **Non-inclusion Criteria:** Subjects will not be enrolled if <u>one</u> 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. Chronic decongestant use 8. Recent (within the previous 2 days) intake of a common cold medicine that in the opinion of the investigator may influence ARSSQ score at screening (NSAID, nasal decongestants, cough medicines)
Number of sites:	8 sites in Bulgaria
Test Device:	**Healsea® Babykids** nasal spray, class I
Comparator Device:	Isotonic nasal spray used as Placebo
Duration of investigation:	Duration of inclusion period: 3 months Duration of patient's participation: up to 18 days Total study duration: 4 months
Study Start Date:	February 2023
Statistical Analysis:	Variables will be described according to the appropriate summary statistics, e.g.: • Number and percentages of subjects in each category for categorical data. For tabular summaries of percentages, the denominator (e.g. number of subjects with non-missing data) will be displayed. • Number of observations, mean, standard deviation, median, and range for continuous data. • Number of observations, number of events, median time for time to event data. When calculating treatment effects (e.g. differences, hazard ratios, odds ratios) and when using treatment arm as a covariate in regression modelling, the Placebo arm will be used as the reference group. Details of the statistical analyses, methods and data conventions will be described in the Statistical Analysis Plan.

	All statistical tests will be 2-sided and performed using a 0.05 significance level. A multivariate regression model of the AUC of the global score of the ARSSQ during the first 11 days will be used to analyse the primary endpoint. A Cox survival regression model will be used to analyse the secondary endpoints of duration of cold symptoms and of impact of quality of life. A multivariate Poisson regression model will be used to analyse the secondary endpoint related to the number of days of use of conventional common cold medications (overall and by therapeutic class). A multivariate logistic regression model will be used to analyse the secondary endpoint related to the use (yes/no) of conventional common cold medications (overall and by therapeutic class). **-Safety:** Adverse events/incidents will be summarized by the number of occurrences, the number and percentage of patients by treatment group, classified by System Organ Class and Preferred Term as defined by MedDRA dictionary. Only treatment-emergent events will be analysed.
Expected benefits:	**Healsea® Babykids** nasal spray is expected to reduce the symptoms of acute rhinitis without any safety concern.

2. Flow Chart

	Acute phase		Follow-up phase	
Visit name	Screening/Inclusion	At home	At home	End of study
Visit Number	**V1**			**V2**
Days	D1	D1 to D11	D12 to End of study	D15-D18
Informed consent	X			
Eligibility criteria	X			
Demography and Medical history ***	X			
Physical and clinical examination	X			X
Baseline assessment of the Acute Rhinitis Symptoms Severity Questionnaire	X			
Ongoing medication	X			
Randomization	X			
Treatment (Healsea® Babykids or Placebo)	X*	X#		
Subject paper diary (Acute Rhinitis Symptoms Severity Questionnaire**)	———	———	———	———
Adverse events/incidents and concomitant medication reporting	———	———	———	———
Compliance				X

* Treatment dispensation
** ARSSQ to be completed with the investigator on site at screening and at the end of the study if the patient still has symptoms ("not sick" not ticked for 2 consecutive days in the previous days). After day 8, until complete resolution of symptoms for 2 consecutive days (question 1 of the questionnaire).
# Treatment from D1 to D8 and up to D11.
*** Medical History - Relevant medical history in connection to infectious acute rhinitis, allergic rhinitis, nasal disorders and asthma back to 2 years

3. Identification and description of the investigational device and of the Placebo

3.1 Summary description

3.1.1 The investigational device

Healsea® Babykids is a CE marked nasal spray composed with an isotonic saline solution (0.9% NaCl) and Symbiofilm® (0.04%) (Table 1). Symbiofilm® is a Lallemand proprietary marine postbiotic composition including an exopolysaccharide mainly composed of N-acetyl hexosamines, acidic and neutral monosaccharides.

Table 1 : Qualitative and quantitative composition of Healsea® Babykids

Ingredient	Concentration (g/L)
NaCl	9 g/L
Symbiofilm®	0.4 g/L
Purified Water	QS 1L

Healsea® Babykids is a class I medical device (in accordance with the rule 5 of the annex IX of European Council Directive 93/42/EEC).
In accordance with annex IX of European Council Directive 93/42/EEC, the medical device classification is based on the following characteristics:
- Duration of continuous use: Short-term (60 min to 30 days)
- Type of device: Invasive, with respect to body orifice, non-active, not surgically inserted, no implantable device
- Location of action: Nasal cavity

The primary packaging is a plastic bottle with atmospheric pump in 20 ml format.

Healsea® Babykids is a nasal spray indicated in children above 2 years to clean and moisten the nose during colds and rhinitis. Healsea® Babykids shall be administered in children with the help of an adult. One-two sprays, twice a day in each nostril during 10 days.

The technical performances are summarised below:

Table 2 : Technical performances of Healsea® Babykids

Component	**Function(s)**
Isotonic Saline 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

3.1.2 The comparator

The comparator is an isotonic saline nasal spray (same primary and secondary packaging) used as Placebo.

Ingredient	Concentration (g/L)
NaCl	9g/L
Purified Water	QS 1L

3.2 Manufacturer

Healsea® Babykids is a class I Medical Device manufactured by Lallemand Pharma. The device is CE marked (17 May 2021). The subcontractor for the manufacturing is C.O.C Farmaceutici Srl, Via Chiesa Sud, 156 C/D/E/F/G – 41016 Rovereto s/ Secchia - Novi di Modena (MO) - Italy

Clinical batches (Healsea® Babykids and Placebo) are manufactured by C.O.C Farmaceutici and the blinding of the investigational devices is ensured by Creapharm, ZA Air-Space Avenue de Magudas, CS 2007, 33185 Le Haillan, Email : contact@creapharm.com.

The Lallemand AG identifier numbers are the following: 75014DJMM (20/04/2022) for Healsea® Babykids and 75014DJMQ (22/07/2022) for the Placebo (Isotonic saline nasal solution).

3.3 Name or number of the model to permit full identification

Because the Investigational Device and the Placebo will be used in a blinded manner, a single lot number will be attributed to the devices.

3.4 Traceability

The traceability of the Investigational Device and of the Placebo will be insured during the clinical study according to the SOP “Investigational Products Management” of the CRO.

3.5 Intended purpose of the devices in the clinical investigation

This is a post market clinical investigation, and the devices will be used in the treatment of acute infectious rhinitis.

3.6 Population and indications for which the device is intended

The target population of the study is children of 2-6 years with acute infectious rhinitis. The only contraindication is hypersensitivity to one or several of the components. This is a non-inclusion criterion.

Healsea® Babykids will be used within its intended purpose i.e., in children to clean and moisten the nose during colds and rhinitis, and to clean the nasal cavity and eliminate allergens and infectious agents.

The comparator is a saline isotonic nasal spray considered as inert Placebo i.e., neutral for the nasal mucosa. Nevertheless, nasal irrigation with isotonic saline solution is known to have some efficacy in reducing common cold symptomatology.

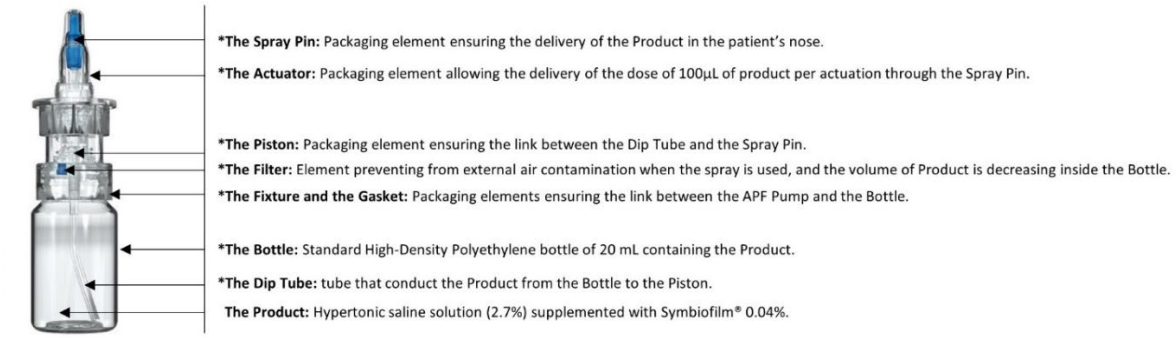
3.7 Devices description

3.7.1 Investigational device

Healsea® Babykids is a nasal spray (available in 20mL) using the APF (Advanced Preservative-Free) technology. This is a spray pump consisting of a white high density polyethylene bottle and a manual polyolefine/homopolymer polypropylene actuator holding the nozzle spraying the solution in the nostrils. A single activation propels a volume of 100 ± 20 µliters of solution.

This is a non-sterile device. The primary packaging is described in Figure 1.

Figure 1: The spray pump



The sponsor certified that the Healsea® Babykids Medical Device:
- does not contain any human blood derivative,
- does not contain any medicinal product,
- is not manufactured using tissues of animal origin.

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

Table 3: Contact with body and total duration treatment

Type of contact	Device in contact with a surface
Type of tissues	Mucous membranes

Total duration treatment	It can be used for 10 days

Healsea® Babykids and the **Placebo** need to be indistinguishable in the context of a blinded study. The subcontractor in charge of the blinding will stick a black-out label on both primary packagings then stick a white label with the mentions requested by the regulation.

3.7.2 The comparator

The Placebo is a nasal spray (available in 20mL) using the same technology as those described above for the investigational device (Figure 1).

This is a non-sterile device.

3.7.3 Primary and secondary packaging and labelling

The primary packaging is a white vial (Figure 2)

Figure 2: primary packaging

The secondary packaging is a white cardboard box.

A white label is sticked on the primary packaging with the following mentions:

LPH-2202- Study BASICC

Saline isotonic solution 0,9% and Symbiofilm 0.04% (Healsea® Babykids) or isotonic nasal saline solution (Placebo).
Nasal spray, nasal route, vial 20 ml
Posology: two sprays, twice a day in each nostril during a treatment period of 7 to 10 days

Batch number: _____ Investigator: _____

Treatment:_____ Patient: _____

Expiry Date (mm/yyyy): __/_____ Site: _____

For Clinical Investigation use only

A white label is sticked on the secondary packaging with the following mentions:

LPH-2202- Study BASICC

Saline isotonic solution 0,9% and Symbiofilm 0.04% (Healsea® Babykids)
or isotonic nasal saline solution (Placebo).
Nasal spray, nasal route, vial 20 ml
Posology: two sprays, twice a day in each nostril during a treatment period of 7 to 10 days

Batch number: _____ Investigator: _____

Treatment:_____ Patient: _____

Expiry Date (mm/yyyy): __/_____ Site: _____

Please refer to the leaflet- Store at room temperature up to 30°C- Keep out of the reach of children

For Clinical Investigation use only

Sponsor: **Lallemand Pharma AG**
Via Selva 2, 6900 Massagno, Switzerland
Tel: +41 91 980 46 13

3.8 Investigation Device training/ experience

In real life setting, there is no need for specific training in using **Healsea® Babykids**.
A usability engineering process test according to the standard EN ISO 62366-1:2015 was conducted on Healsea® Babykids with 10 people representatives 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.

Nevertheless, Healsea® Babykids and the comparator will be specially conditioned for this controlled and blinded study. An IFU leaflet is included in each secondary packaging: on one face, the IFU of Healsea® Babykids, on the other face, the IFU of Healsea® Placebo (see 3.9). During the site initiation visit, the investigator will be briefly trained how to use the study devices. After the enrolment, the investigator will instruct each parents/legal guardians on how to use the nasal spray on their child.

3.9 Reference to the IFU

An IFU leaflet is included in each secondary packaging: on one face, the IFU of Healsea® Babykids, on the other face, the IFU of Healsea® Placebo (See appendix A).

4. Justification for the design of the clinical investigation

The common cold is the most frequent upper respiratory tract infection (URTI), which is the most commonly treated acute problem in primary pediatric care (1). 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). The common cold is caused by a variety of viruses. Improvements in viral detection techniques during the past two decades, including various viral antigen detection methods and particularly the advent of PCR-based assays, have substantially increased the rates of viral detection in clinical specimens. The relative proportions of different viruses in the cause of the common cold vary depending on several factors, such as age, season, and viral sampling and detection methods. 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 (2).

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 (2,3). 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 favoured by the formation of biofilms, which facilitate bacterial growth and persistence as well as reducing antibiotic efficacy (4,5). Despite the usually benign nature of the illness, the socioeconomic impact of acute rhinitis is well established: visits to GP, additional prescriptions and over prescription of antibiotics, absence from work, school or day care (1).

Although clinical evidence from well-designed trials is scarce (6), European and American guidelines for acute rhinosinusitis recommend daily nasal saline irrigation for reduction of the severity of symptoms and for speeding recovery (2,7). The exact mechanisms by which nasal irrigation works are not fully elucidated. However, most of the experts agree that it is primarily a mechanical intervention leading to direct cleansing of the nasal mucosa (8,9). 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. Although the impact of the salt concentration of the saline solution on all these parameters is still debated, the efficacy of saline irrigation remains moderate (6).

The Healsea® products are a saline-based nasal spray line supplemented with a natural Symbiofilm™ extract (0.02% to 0.04%) isolated from the marine flora of the deep seas of the Panarea Islands, in Sicily. Healsea® Babykids is an isotonic saline solution (0.9%) with Symbiofilm™ (0.04%).

Symbiofilm™ is an exopolysaccharide composition secreted by *Bacilllus licheniformis* LP-T14, a Lallemand Pharma proprietary strain, with *in vitro* antibiofilm activity and detachment properties against various bacterial pathogens involved in respiratory tract infections, i.e *Haemophilus influenzae type b, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus and streptococcus pneumoniae*. Antibiofilm effects of Symbiofilm™ have been reported *in vitro*, using microtiter plate-based model and human nasal epithelial cells. The antibiofilm activity of Symbiofilm™ is likely to rely on its emulsifying properties. Symbiofilm™ (400 µg/ml) has also been demonstrated to protect *in vitro* human nasal epithelial cells viability after Adenovirus, Rhinovirus, Coronavirus OC43 and Flu infections.

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

The aim of this investigation is to demonstrate that thanks to the antibiofilm and antiviral properties of Symbiofilm™, isotonic saline solution and Symbiofilm™ alleviate symptoms of the acute rhinitis phase with better efficacy than isotonic saline solution without Symbiofilm™.

To demonstrate the efficacy of Healsea® Babykids in common cold, a Double Blind Randomized Controlled Study will be performed. The efficacy of the test product will be assessed by comparison with an isotonic saline nasal spray.

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

5.1 Anticipated clinical benefit

Healsea® Babykids is an isotonic saline solution (0.9%) with Symbiofilm™ (0.04%).

Healsea® Babykids is indicated in children above 2 years to clean and moisten the nose during colds and rhinitis.

The exact mechanisms by which classic saline 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.

The supplementation of the saline solution with Symbiofilm™ impacts the performance of the device. Indeed, Symbiofilm™ has also been demonstrated to protect in vitro human nasal epithelial cells viability after Adenovirus, Rhinovirus, Coronavirus OC43 and Flu infection.

Therefore, isotonic saline solution and Symbiofilm™ may act in a synergistic manner to alleviate symptoms of the acute rhinitis phase resulting in better efficacy than isotonic saline solution without Symbiofilm™ used as Placebo. As a consequence, patients receiving daily administrations of **Healsea® Babykids** are expected to recover more rapidly from common cold than those receiving the Placebo.

Subjects who receive Placebo will not benefit from as effective a treatment although nasal administrations of isotonic saline are well described as cleansing and hydrating the nasal mucosa. Nevertheless, these subjects will receive all concomitant treatments necessary in the context of acute rhinitis with the exception of other saline solutions.

5.2 Anticipated adverse device effects

There is no expected side effect in using Healsea® Babykids nor the Placebo.

No adverse effect is expected with **the Placebo**.

5.3 Risk associated with the participation in the clinical investigation

The assessments planned in the clinical investigation are questionnaires with no associated risk.

5.4 Possible interaction with concomitant treatments as considered under the risk analysis

No interaction is expected. Nevertheless, parents/legal guardians 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) on their child.

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

5.5.1 Healsea® Babykids

In 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 12 Medium risk level residual risks have an acceptable benefit-risk balance,
- And all the others residual risks (62) are at Low risk.
- Healsea® Babykids can be considered as safe and effective

and regarding the evaluation of benefit/risk profile, as detailed in the Clinical evaluation report, considering:

- The clinical data of the equivalent device (Physiomer® Spray Hygiène du nez)
- The currently available data on products use for the treatment of nasal cold and flu symptoms and the prevention of upper respiratory tract infections

it can be concluded that the benefit/risk ratio of Healsea® Babykids is acceptable, in compliance with essential requirements.

5.5.2 Placebo

Isotonic saline nasal solutions are well known for cleansing and hydrating the nasal mucosa without any safety concern. No risk analysis has been conducted to estimate the risk associated with each step of this device lifecycle. Anyway, the residual risk for the Placebo is expected to be lower than for Healsea® Babykids since this latter contains Symbiofilm® and isotonic saline solution and therefore represents the worst case. Thus, the Placebo used during this study can also be considered as safe.

5.5.3 Mitigation of risk during the clinical investigation

Although no obvious specific risk is identified for subjects participating in the study, and according to the requirements of ISO 14155:2020, some specific points have been identified requiring particular attention to guarantee the safety and the well-being of the subject.

As the study will be conducted in a blinded manner in minors, stringent risk acceptability thresholds per site are defined in the Study Risk Management Plan. Because of the paediatric population of the study, any issue with the informed consent process, any major protocol deviation or any serious incident are deemed unacceptable and shall trigger an immediate action plan.

More generally, the number of unreported incident/serious incident or adverse event per site, the timelines for materiovigilance/vigilance reporting to sponsor, the dispensation issues (number of devices delivered different from the number reported in the e-CRF), inadequate process to ensure the traceability of the investigational product, number of patient diary not collected at V2 shall be tracked according to the risk management plan in which risk acceptability thresholds are defined.

All issues shall be tracked according to the risk management plan and shall trigger an immediate action plan if the threshold is reached.

Should a potential unanticipated risk be detected, an action plan will be implemented with no delay.

5.6 Rational 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 to 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 are not without side effect. For example, decongestant use can increase blood pressure, antihistamine intake is associated with drowsiness.

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

Furthermore, there is no expected side effect.

6. Objectives and hypotheses of the clinical investigation

6.1 Hypothesis

Our hypothesis is that Healsea® Babykids nasal spray can improve the symptomatology of acute rhinitis with more efficacy than an isotonic saline nasal spray used as Placebo.

6.2 Primary Objective

To assess the efficacy of Healsea® Babykids on the overall health status score of the Acute Rhinitis Symptoms Severity Questionnaire (ARSSQ) in 2-6 years old children during a treatment period of 7 to 10 days as compared to Placebo.

6.3 Secondary Objectives

- To assess the impact of **Healsea® Babykids** on the duration of each infectious rhinitis symptom and on quality of life as compared to Placebo.
- To assess the impact of **Healsea® Babykids** on the intake of conventional common cold medication (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids) as compared to Placebo.
- Safety: to assess systemic and local tolerance of **Healsea® Babykids** over the study period.

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

This is a PMCF study. The primary endpoint is a customized symptom and quality of life questionnaire. An arbitrary cohort of 200 children has been chosen. A cohort of 100 children in the Healsea® Babykids arm and 100 children in the Placebo arm is anticipated to allow to demonstrate the interest of using Healsea® Babykids in the acute infectious rhinitis. Indeed, 100 patients by arm 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. According to 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 Placebo arm will be used as the reference group.

The recruitment will be performed using a 1:1 randomization ratio.

6.5 Risks and anticipated adverse effects that are to be assessed

No specific risk for subject participating in the study is identified, provided that the eligibility criteria are fulfilled. The safety and well-being of subjects will be monitored throughout the study and a Risk Management Plan has defined stringent risk acceptability thresholds (see 5.5.3).

7. Design of the clinical investigation

7.1 General

7.1.1 Design type of clinical investigation

This is a two-arm, double-blind, parallel group, randomized controlled trial (RCT).

The primary endpoint ARSSQ will be assessed once daily. After D8, the ARSSQ will be assessed once daily until the subject feels not sick for two consecutive days.

7.1.2 Measures to be taken to minimize or avoid bias

Randomization:
The random product attribution will be performed after checking that the eligibility criteria are fulfilled, thus minimizing the selection bias. Each site will receive several treatment blocks in accordance with the randomization table generated by Axiodis (blocks of 4). During the V1 visit, the investigator will deliver a product (active or placebo) to the patient in chronological order using the list of treatments allocated to the respective site. This method allows to maintain the 1:1 balance in a multicentric study.
Example: the site 01 received 3 treatment blocks, i.e. 12 treatments, number 001 to 012. For the patient 01-001, the investigator will deliver the treatment 001. The site 02 received 3 treatments blocks, i.e 12 treatments, number 013 to 025. For the patient 02-001, the investigator will deliver the treatment 013.

Blinding and unblinding:
The randomization list will be drawn up using a validated software and before the beginning of the study, by a statistician (at Axiodis) not involved in the study. The master randomization list will be stored confidentially until the study blind is broken at the end of study.
The randomization list will be:

- Transmitted by the Axiodis statistician to the person in charge of the product preparation, Creapharm
- Uploaded into the patient unblinding module of the eCRF

During the whole study and in the absence of unblinding, neither the investigators nor the subjects nor the staff involved (CRO, sponsor…) will be aware whether the product is Healsea® Babykids or the Placebo. Every effort will be made to maintain the blind during the study as well as during the follow-up period.
Both Medical Devices (Healsea® Babykids and Placebo) will be indistinguishable: same aspect, same packaging and same labelling of the vials.
The unblinding will occur after the database locking, at the end of the study. The statistician responsible for the randomization list will be in charge of the unblinding.

Emergency Unblinding:
In case of a medical emergency where knowledge of the blinded treatment is necessary for the treatment of an adverse event/incident, the investigator shall perform the unblinding via the unblinding module of the eCRF. The investigator shall send an e-mail informing about the unblinding with patient ID, date and reason of unblinding (**the name of patient not to be communicated for GDPR compliance**) to:

- The CRO in charge of the study coordination: etudes@bgclinicals.com
- The sponsor (officelp@lallemand.com and rbelloti@lallemand.com (vigilance manager))
- The statistician if charge of the randomisation list

The date and the reason for the unblinding will be indicated in the e-CRF and in the source document of the study.

7.1.3 Primary Endpoint with methods and timing for assessing recording and analysing variables

The AUC of the global score of the Acute Rhinitis Symptoms Severity Questionnaire (ARSSQ) during first 11 days of symptoms will be compared between both groups.

ARSSQ is a non-validated customized questionnaire (Appendice 1). It includes 10 items assessing symptoms, functional impairments, and global severity. Each item is scored from 0 (not present/no impact/ not sick) to 3 (severe, severe impact and very sick) for symptoms, functional impairment and global severity respectively. Parents/legal guardians will respond to questions according to the evolution of their child's symptoms. This questionnaire is based on the most common symptoms reported for children with common cold and on functional impairments easily evaluable by parents. In order to evaluate the time dependent efficacy of active/placebo, an AUC computation will be carried out.

The ARSSQ assessment will be completed in a paper diary once daily in the evening, taking into account the symptoms from the morning to the evening, within D2-D8 period. After D8, the ARSSQ will be assessed once daily until resolution of all symptoms for 2 consecutive days (question 1 of the questionnaire “not sick” ticked). At D1, the ARSSQ will be completed during the screening/inclusion visit V1. If the patient still has symptoms at V2, (“not sick” not ticked for 2 consecutive days in the previous days), the questionnaire will be also completed during the visit.

To be noticed that the duration may be censored at the end of study participation (visit V2, between day 15 and D18 after inclusion).

7.1.4 Secondary Endpoints with methods and timing for assessing, recording and analysing variables

- **Comparison of duration of each cold symptom (questions 2 to 7 of the ARSSQ)** in both groups.

For each separate symptom, the duration is defined as the number of days between Day 1 and the first day the parent/legal guardian reports the patient not having this symptom ("Not present") for 2 consecutive days.
As mentioned for primary endpoint, duration may be censored at Visit 2.

- **Comparison of duration of quality-of-life impairment (questions 8 to 10 of the ARSSQ)**.
For each separate activity, the duration is defined as the number of days between Day 1 and the first day the parent/legal guardian reports no impact on the patient quality of life ("No impact") for 2 consecutive days.
As mentioned for primary endpoint, duration may be censored at Visit 2.

- **Comparison of the frequency and number of days of concomitant treatments use that may affect common cold symptoms** (antibiotics, antipyretics, systemic or local mucolytics, decongestants, antitussives, systemic and topical corticosteroids).
By reducing duration of the common cold symptoms, Healsea® Babykids will very likely reduce the use of common rescue medication. Concomitant treatments use will be reported in the paper diary by parents/legal guardians throughout the study, validated by the investigator at the end of the study visit before being reported in the e-CRF.

- Safety: Assessment of adverse event related to acute rhinitis and incidents throughout the study in both groups.
Adverse events/incidents will be reported in the paper diary by the parent , validated by the investigator at the end of study visit before being reported in the e-CRF.

7.1.5 Equipment to be used for assessing the clinical investigation variables

No specific equipment is required for the conduct of the study.

7.1.6 Any procedures for the replacement of subjects

Not applicable.

7.1.7 Investigation sites: number, location

The clinical investigation will be conducted in 8 sites in Bulgaria. All investigators are familiar with acute infectious rhinitis and study procedures.

7.1.8 Definition of the completion of the study

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

7.2 Investigational device and comparator

7.2.1 Description of the exposure to the investigational device

The investigational device will be **Healsea® Babykids.** This is a CE marked Medical Device used for acute rhinitis and administered by spraying 2 puffs in each nostril 2 times per day with a minimum of 7-day-treatment period (14 intakes of the investigational device) up to 10 days (20 intakes of the investigational device). *The patient should stop taking the investigational device before D11 only if the question 1 "not sick" of the ARSSQ is ticked YES for 2 consecutive days.*

7.2.2 Description and justification of the choice of the comparator

Clinical batches are manufactured by C.O.C Farmaceutici and the blinding of the investigational devices is ensured by Creapharm, ZA Air-Space Avenue de Magudas CS 200733185 Le Haillan, Email: contact@creapharm.com.

The comparator is an isotonic saline nasal spray indistinguishable from the **Healsea® Babykids** product.

We hypothesize that isotonic saline solution and Symbiofilm™ will be more effective that the isotonic saline solution for achieving the principal action, i.e. reduction of the duration of acute rhinitis symptoms.
We have chosen isotonic saline solution as Placebo which can be considered as inert solution; nevertheless, nasal irrigation with isotonic saline solution is known to have some efficacy in reducing common cold symptomatology. Posology, instructions for use, contraindications, precaution of use and labelling are identical to those for Healsea® Babykids.

7.3 Subjects

The target population is children (>2, ≤6 years) with early symptoms of common cold / acute infectious rhinitis.

7.3.1 Eligibility Criteria

7.3.1.1 Inclusion Criteria

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

1. Male/Female subjects >2 and ≤6-year-old
2. Acute infectious rhinitis/rhinosinusitis **for ≤48h before trial entry**
3. Patient presenting with fever ≥ 37.5 °C at screening
4. Subjects with nasal congestion (blocked / stuffy nose) rated at least as moderate on the Acute Rhinitis Symptoms Severity Questionnaire, based on evaluation by the investigator
5. Subjects showing at least moderate grade for at least one of the following additional signs of acute rhinitis: runny nose, nasal crust (dry mucus), sneezing and cough
6. Written consent obtained from parent/legal guardians

7.3.1.2 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. Chronic decongestant use
8. Recent (within the previous 2 days) intake of a common cold medicine that in the opinion of the investigator may influence ARSSQ score at screening (NSAID, nasal decongestants, cough medicines)

7.3.1.3 Withdrawal Criteria and procedures

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

- A parent/legal guardian can withdraw his/her consent 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 parent/legal guardian 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, incident 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. The monitor will be immediately informed by phone or e-mail A letter or report explaining the withdrawal will be forwarded to the monitor as soon as possible.

In these cases, a premature end of study visit will be scheduled. Available data will be retained for the safety/efficacy analysis.

It should be noted that COVID-19 is not an exclusion criterion. Nevertheless, the investigator may consider on a case-by-case basis that a subject should be withdrawn from the study prematurely.

7.3.1.4 Subject lost to follow-up

If a parent/legal guardian cannot be contacted to collect follow-up information even beyond the 7 days from visit 2, the patient 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 parent/legal guardian and attempts should be made via all available routes.
The methods used to attempt contacting the parent/legal guardian should be noted in the patient medical file.

7.3.1.5 Subject replacement

It is not anticipated to replace withdrawal patients.

7.3.2 Point of enrolment and randomization

The subjects will be recruited by the sites among outpatients coming in consultation because of early symptoms of common cold.
The study participation can be proposed to parents/legal guardians of children coming for consultation.
In order to facilitate the enrolment, the site may choose to inform parents/legal guardian of this clinical investigation before this visit.

Before performing any study procedure, the investigator will give all the information pertaining to the study. Parents/legal guardians will have the opportunity to carefully review the information document and ask questions prior to accepting or not to participate in the study. The children will also receive an information specific to their age. The subject will be enrolled in the study just after the consent signature.

7.3.3 Total expected duration of the clinical investigation

The total study duration is planned to be 4 months.

7.3.4 Expected duration of each subject's participation

The duration of each patient's participation is up to 18 days.

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

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

7.3.6 Estimated time needed for the enrolment

Based on the number of participating sites, an enrolment period of 3 months is considered sufficient to enrol the cohort of 200 patients.

7.3.7 Relationship of investigation population to target population

Healsea® Babykids will be used within its intended use, in children above 2 years with acute infectious rhinitis. This post-market clinical investigations aims to demonstrate that isotonic saline solution and

Symbiofilm™ act in a synergistic manner to alleviate symptoms of the acute rhinitis phase resulting in better efficacy than isotonic saline solution without Symbiofilm™.

7.3.8 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.

7.3.9 Compensation

A compensation of 200 BGN for costs resulting from participation in the clinical investigation (transportation, absence of work…) will be paid to the parents of each patient having completed the study (diary completion and availability for visits).

7.4 Procedures

7.4.1 Description of clinical investigation-related procedures

The clinical investigation is divided into 2 parts:

- **Part 1 (D1-D11)**: treatment of the **acute phase** with Healsea® Babykids/Placebo, with a minimum of 7-day-treatment period (14 intakes of investigational device) up to 10 days (20 intakes of investigational device).
- **Part 2 (up to D15/D18)**: **follow-up phase**.

The clinical investigation comprises 2 visits.

Visit 1 (V1) - (Day 1): Screening/Inclusion/Randomization

Parents/legal guardians of children with symptoms of acute infectious rhinitis for ≤48h will go to the site for the screening/inclusion visit (visit 1). The investigator will give oral information relative to the study and will answer all questions relative to the study participation. Appropriate information using drawings will be also delivered to the child. 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 should 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. Each screened subject will be assigned a subject identifier number during screening that will be used on all subject documentation. 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, medical history and ongoing medication.
- Perform a physical and clinical examination.
- Instruct the parents/legal guardian of the patient to complete the baseline ARSSQ questionnaire, The investigator/designee will then rate patient nasal congestion symptoms and additional signs of acute rhinitis (runny nose, nasal crust, sneezing, cough)

- Verify that eligibility criteria are fulfilled.
- Explain to the parents/legal guardians how to complete every day the paper diary ARSSQ recording, how to report concomitant medications, adverse events/incidents.
- Remind the parents/legal guardians to return the device for assessment of compliance to the treatment at V2 and to bring back the paper diary at the study end.

The investigator will provide the parents/legal guardians with the device according to the site specific treatment list, in order to respect the 1:1 randomization (blocks of 4). The investigator will explain how to use it.

NB: The first use of the device will be performed in the evening of the Day 1.

D1-D8 up to -D11 (at home):

The Parent/legal guardian will be asked to complete the ARSSQ in the diary, once daily in the evening. The symptoms occurring from the morning to the evening should be taken into consideration. The ARSSQ shall be scored at least from D1 to D8. Adverse events/incidents and concomitant medications are to be reported during the whole period

Between D8 and D11 (at home):

End of Healsea® Babykids/Placebo nasal spray.

- *NB: The last study nasal spray intake will be performed* **between D8 and D11** *in the morning. The patient should stop taking the investigational device before D11 only if the question 1 "not sick" of the ARSSQ is ticked YES for 2 consecutive days.*

Up to D15/D18 (at home):

Parents/legal guardians will continue to complete the paper diary daily (incidents/adverse events/expected undesirable sides effects, concomitant medications). For patients for whom common cold symptoms persist, parents/ legal guardians will be instructed to continue to complete the ARSSQ, until the subject feels not sick for two consecutive days.

Visit 2 (V2) – (Day 15-Day 18): end of study

The investigator or his/her delegated designee will:

- Perform a physical and clinical examination.
- Collect the patient diary.
- Review the paper diary to validate adverse events pertinent in the context of the common cold, incidents linked to medical device use and concomitant medications reported by the parents/legal guardians. Complete the e-CRF accordingly and report any new relevant safety events.
- Ask parents/legal guardians to complete the ARSSQ if the patient still has symptoms.
- Assess the compliance to the treatment by weighing the device bottle returned by the parents/legal guardians. If a nasal spray is not returned or lost, the investigator will ask the

parents/legal guardians to specify the number of missed nasal spray uses and will report the data into the e-CRF.

7.4.2 Concomitant Medication

7.4.2.1 Permitted concomitant medications during the study:

- Antipyretics
- Systemic and/or local mucolytics
- Local decongestants (to be taken away from nasal score assessment, 2 hours minimum)
- Systemic antihistamines only if taken for more than 4 weeks at screening
- Antitussive
- Antibiotics
- Local or systemic corticosteroids
-

7.4.2.2 Non-permitted concomitant medications:

- Saline nasal spray

7.4.3 Activities performed by sponsor representatives (excluding monitoring)

The sponsor has delegated to the CRO the provision of tasks relative to the project management, medical writing, clinical operations, data management and statistics, and site(s) oversight. These delegated tasks have been established through a Study Management Plan, signed by both parties.

The CRO will rely on its in-force Quality Management System 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 CRO will ensure the management of ongoing risk in close collaboration with the sponsor throughout the clinical investigation and will take all measures to protect rights, safety and well-being of patients who participate in the study.

Tasks still under sponsor responsibility:

- Reporting of non-compliance trends and safety issues to the Ethics Committee/Competent Authorities and investigators.
- Triggering audit to be performed if applicable.

7.4.4 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.

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

The patients will receive all treatments needed if the common cold is not cured or in case of complication or safety issues. In this case, the patient will be followed until the end of the issue.

7.4.6 Potential use of samples obtained from subjects

Not applicable.

7.5 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.

7.5.1 Initiation visit

The study will only start at a site after:

- The Ethics Committee has granted approval and the Competent Authority has been notified 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 Bulgarian regulation and to MDR. 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.

7.5.2 Monitoring

Study monitoring delegated by Lallemand Pharma AG to the CRO will be performed at various stages of the study. Monitoring will include on-site visits and centralized data review to ensure 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, investigators should respond within agreed timelines.

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

7.5.3 Routine Close-out

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

7.5.4 Retention of Documentation

Principal Investigators will retain all copies of the records for a period of 10 years from the completion of the clinical investigation. In any circumstances, PIs 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 AG 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 a PI have to move/retire, or otherwise leaves his(her) position, he(she) will provide Lallemand Pharma AG with the name and address of the person assuming responsibility for records relating to this clinical investigation.

8. Statistical design and analysis

The statistical analysis will be detailed in the Statistical Analysis Plan. This section provides a summary.

8.1 Analysis population

The safety population consists in all the patients included in this study who will have used the nasal spray at least once.

Full Analysis Set (FAS): all subjects who will have used the nasal spray at least once and with at least one post-baseline efficacy data.

Safety endpoints will be assessed on the safety population.

The analysis of primary and secondary endpoints will be performed on the FAS population.

8.2 Baseline Characteristics

Variables will be described according to the appropriate summary statistics, e.g.:
• Number and percentages of subjects in each category for categorical data. For tabular summaries of percentages, the denominator (e.g. number of subjects with non-missing data) will be displayed.
• Number of observations, mean, standard deviation, median, and range for continuous data.
• Number of observations, number of events, median time for time to event data.

When calculating treatment effects (e.g. differences, hazard ratios, odds ratios) and when using treatment arm as a covariate in regression modelling, the Placebo arm will be used as the reference group.

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

8.3 Primary endpoint

In order to analyze the primary endpoint, a multivariate regression model of the AUC of the global score of the ARSSQ during the first 11 days will be used.

8.4 Secondary endpoints

A Cox survival regression model will be used to analyse the secondary endpoints of **duration of cold symptoms and of impact on quality of life**.

A multivariate Poisson regression model will be used to analyse the secondary endpoint related to the **number of days of use of conventional common cold medications** (overall and by therapeutic class).

A multivariate logistic regression model will be used to analyse the secondary endpoint related to the **use (yes/no) of conventional common cold medications** (overall and by therapeutic class).

-Safety: Adverse events/ incidents will be summarized by the number of occurrences, the number and percentage of patients by treatment group, classified by System Organ Class and Preferred Term as defined by MedDRA dictionary. Only treatment-emergent events will be analysed.

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.

8.5 Sample Size calculation and justification

See 6.4

8.6 Rationale for the number of procedures to be performed by a single user

Only non-burdensome and non-invasive procedures are planned in the study investigation, mainly a short questionnaire. Two visits are scheduled to assess the study criteria.

8.7 Interim analysis

Not applicable.

8.8 Management of bias (randomization, blinding)

See section 7.1.2

8.9 Management, justification, and documentation of missing data, including drop-outs

For subject who stop completing the ARSSQ before D11 (see 7.4), the Last Observation Carried Forward (LOCF) imputation will be used. Other missing data for the primary endpoint (ARSSQ) will be estimated by interpolation.

8.10 Procedures for reporting any deviation(s) from the original statistical analysis plan

Any deviation(s) from the original statistical analysis plan will be reported in the final statistical analysis plan and in the clinical investigation report.

9. Data Management

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

9.1 Source documents

The source documents (e.g., medical file, clinical and office charts, study worksheets, log for compliance data…) which contain the source of data being recorded in the eCRF should be specified. The paper diary will be used as source document for ARSSQ, concomitant treatments and adverse events/incidents reported by parents/legal guardians.

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.

9.2 Methods for data entry and collection

A validated electronic case report form (eCRF, 21 CFR Part 11 compliant) will be used to collect clinical data for this study. Some of the study data will be recorded in the paper diary by parents/legal guardians:

- Daily ARSSQ
- Adverse events/incidents
- Concomitant treatments

Investigators will validate adverse events pertinent in the context of the common cold, incidents linked to medical device use and concomitant medications reported in the paper diary. They will complete the e-CRF accordingly.

The sponsor is responsible for designing the e-CRF. eCRF training will be provided to appropriate personnel before/at initiation of the investigation site. Parents/legal guardians will be instructed how to complete the paper diary during visit V1.

9.3 Procedure used for eCRF tracking, data review, database cleaning and issuing/resolving data queries.

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 database
- 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 sites. When entering data, on-line checks are encoded in the eCRF 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 data blind review meeting will be held prior to database lock.

The data review meeting prepared by the project manager, data manager, study monitor, medical manager and statistician will be attended by at least the following:

- Coordinating investigator,
- Study monitor,
- Sponsor Vigilance representative,
- Project managers from the sponsor and from the CRO,
- 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 10 years after investigation closure. All data collected in the electronic Case Report Forms will be handled and archived under the responsibility of Lallemand Pharma.

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

The EXAGIS software is installed on a Linux server (secure Data Center) hosted at the OVH 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. Software access is restricted to authorized users using individual encrypted passwords. Data processing via SAS software (SAS Institute, Cary, NC, USA) is carried out on a Windows 2012 R2 production server at OVH, using direct access by SAS or MySQL Workbench.

9.5 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 EXAGIS system at different levels to preclude unauthorized access to data:

- Only authorized persons can access the data:

Access to the database is restricted to authorized users using individual encrypted passwords. For all co-workers (from remote or on-site), an identification via a VPN is mandatory. Then, access to each server is always done through an authentication with a login and a personal password.

- The risk of data breaches:

The risk is minimized by full encryption and controlled access.

- External/internal interactions are actively protected:

A standard operating procedure (SOP) details all processes implemented for ensuring network security. This SOP mentioned the following subjects: system update, antivirus, antimalware, VPN management, user access accounts, password policy, training and awareness of coworkers, and data transfer security with partners/clients.

9.6 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.

9.7 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.

10. Amendments to the CIP

Investigators should not implement any changes of the protocol without agreement by the sponsor.

All changes to the protocol are subject to an amendment which must be dated and signed by the sponsor and Principal Investigators and must appear as an amendment to the protocol.

Substantial amendments are notified to the EC and CA.

11. Deviation from Clinical Investigation Plan

A major protocol violation is a deviation that has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study. In this PMCF study, the following deviations are considered major:

- Non-compliance with the inclusion or exclusion criteria,
- No assessment of the primary efficacy criterion (ARSSQ) at D1, D5±1 and D8-1 during the treatment period,
- Intake of wrong treatment, i.e, wrong treatment given to the patient after randomization
- A compliance to study product intake below 80% or greater than 120%
- Intake of forbidden medication, i.e., nasal irrigation

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 site.

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.

In case of major deviation, corrective and preventive actions will be implemented as per Study Deviation Management plan and Risk management plan.

12. Device accountability

The device accountability will be performed all over the study according to the SOP “Investigational Product Management” of the CRO. Briefly, sites will complete an accountability log after each receipt of the Medical Device and dispensation to parents/legal guardians. The CRA in charge of the site

monitoring will check the accountability log at each visit. At V2, the compliance will be assessed by weighing the device brought back by the parents/legal guardians.

Return of unused or expired investigational devices to the sponsor will be tracked using a specific record.

13. Ethical consideration

13.1 Informed Consent

According to Regulation EU 2017/745, ISO 14155:2020 and applicable Bulgarian regulations, the Principal Investigator or his/her authorized designee must explain all aspects of the clinical investigation that are relevant to the parents/legal guardians' decision for their child participation throughout the clinical investigation before any study procedure.
In order to ensure that the parents/legal guardians are fully informed the investigator must explain the nature of the clinical investigation, including any risks and benefits, its purpose and procedures, and expected duration of involvement in the clinical investigation. It must be made clear to the parents/legal guardians that participation of their child in the clinical investigation is voluntary and a decision not to participate will not affect their child right to the most appropriate treatment/care or affect the relationship with the doctor. Patients/legal guardians will have the opportunity to carefully review the information document and ask questions prior to accepting or not to participate in the study.
As this investigation is interventional, the consent shall be obtained in writing by both parents (except in specific situations as divorce with sole custody, widowhood) and the study participation must be documented in the patient medical file. But considering the specifics of the population, the children are not chronically ill, and that the screening/inclusion in the study can't be pre-planned, the written consent of only one parent at the screening visit is deemed acceptable with some conditions. Indeed, in case one parent would not be available for the visit, an oral consent (phone call) must be collected by the investigator during the visit and documented in the patient medical file. The second parent will be asked to sign the consent form at the earliest opportunity and to send it by e-mail to the investigator or to provide it on the next visit. The original of ICF with the signature of both parents shall be filed in the patient medical file.
In accordance with the "Ethical considerations for clinical trials on medicinal products conducted with minors" (Rev.1; 18 Sep 2017), no written assent will be collected for the children, because written assent is evaluated not to be obtainable before the school age (6-7 years). But, because children from the age of 3-4 years have some capacity of understanding, age- and maturity-appropriate information will be delivered by the investigator and the parents. Since textual information is not usable by most of these children, visual information using drawings will be used to ensure that the child is properly informed. The agreement of a child should be requested systematically, even if the assent is not legally required. Their refusal or dissent should be respected.
Parents/legal guardians reserve the right to withdraw from the clinical investigation at any time, irrespective of their initial consent. Objections raised by a child at any time during the trial should also

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.

13.2 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 about the personal data and free movement of such data (GDPR) and PERSONAL DATA PROTECTION ACT, in force as from 1 January 2002.

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 eCRF, 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.

To fulfil the requirements of source data verification, the PI will be required to obtain consent from each parent/legal guardian stating that they agree for their child's medical records to be accessed (this will form part of the consent process). To comply with 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.

13.3 Insurance policy

Lallemand Pharma AG has an insurance policy intended to guarantee against possible damage resulting from the investigation.

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

14. Vigilance

14.1 General

Healsea® Babykids will be used in the intended use covered by the CE mark in this PMCF study.

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 (materiovigilance).

Nevertheless, if a causal relationship between a serious adverse event and an investigational procedure has been established, the safety reporting laid down in Article 80 of the MDR. Since the electronic system referred to in Article 73 (Eudamed) will not be available and fully functional at the date of study start, the procedures for safety reporting will be performed according to modalities described in the MDCG 2020-10/1 and -10/2.

All modalities of safety reporting will be detailed in a Safety Management Plan signed by the sponsor's vigilant, the Principal Investigators, the local CRA in charge of the monitoring and a representant of the CRO.

14.2 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.

Serious adverse event (SAE) (MDR Article 2(58))**:**

Any adverse event that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
   i. life-threatening illness or injury,
   ii. permanent impairment of a body structure or a body function,
   iii. hospitalisation or prolongation of patient hospitalisation,
   iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
   v. chronic disease,
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

14.3 Reporting in the eCRF

At V2, the investigator will validate the adverse events/incidents and concomitant medications reported in the paper diary by questioning the parent/legal guardian of the patient.

All serious and non-serious incidents/serious and non-serious risk of incidents/serious and non-serious adverse event (pertinent in the context of the common cold, additional study procedures and of the medical device use) occurring during the clinical investigation will be reported in the eCRF.

14.4 Investigator's responsibilities and processing timelines

14.4.1 Materiovigilance

All incidents will be reported to LP vigilance manager according to MDR, MEDDEV 2.12 rev 8 modalities, national requirements, ISO 14155:2020 and Lallemand Pharma procedures which are described in the safety management plan. This document will be signed by the Principal Investigators of all participating sites, representants of the Clinical Research Organization (CRO), CRA in charge of the monitoring and the Vigilant Manager, before the study start.

As soon as the investigator will be informed of the event, he/she will complete a Primary Notification Form template (PNF, appendix C) and send it to the sponsor (officelp@lallemand.com and/or fax +41 91 980 4615 (as back-up method) and to the Vigilance manager Roberta Belotti (rbelotti@lallemand.com), to the CRO (etudes@bgclinicals.com and/or fax: +33 561 561 956), to the EU representative Michel Huc (michel.huc@aspe-conseil.eu), and to the local CRAs (marina@convex.bg and r.dimitrova.convex.bg) with any relevant supportive documentation within the same day (<24h) for serious (risk) incident and within two calendar days (<48h) for non-serious incidents.

14.4.2 Vigilance reporting according to Article 80 of the MDR

Although not expected in this investigation with no invasive procedure, the following events are considered reportable events in accordance with MDR Art. 80(2):

- a) Any serious adverse event that has a causal relationship with the investigation procedure or where such causal relationship is reasonably possible.
- b) Any new findings in relation to any event referred to in point a)

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality as per definitions of the MDCG 2020-10/1 rev 1 specified in the safety management plan:

1. Not related
2. Possible
3. Probable
4. Causal relationship

Only causality level 1 (i.e. “not related”) is excluded from reporting.

Any serious adverse event that has a causal relationship with an investigational procedure will be reported by the investigator to the sponsor (officelp@lallemand.com and/or fax +41 91 980 4615 (as back-up method) and to the Vigilance manager Roberta Belotti (rbelotti@lallemand.com), to the CRO (etudes@bgclinicals.com and/or fax: +33 561 561 956), to the EU representative Michel Huc (michel.huc@aspe-conseil.eu), and to the local CRA (marina@convex.bg) and r.dimitrova@convex.bg **immediately, but not later than 3 calendar days** after investigation site study personnel’s awareness of the event. To this end, the investigator will complete the *“SAE form”* (appendix D).

14.5 Sponsor responsibilities and processing timelines

14.5.1 Materiovigilance

The vigilance manager of Lallemand Pharma is responsible for the reporting to the Bulgarian Competent Authority.

Briefly, for serious incidents or risk of serious incident, the vigilance manager will complete a Manufacturer Incident Report. 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 Corrective Action (FSCA) and of a Field Safety Notice. These documents will be transmitted to the Bulgarian Competent Authority and to the Ethics Committee (ekki@bda.bg) 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 status of health	Report immediately but not more than 10 days using electronic Manufacturer Incident Report Form (+ paper version for the EC)
Others (could have led to death or serious deterioration in health)	Report immediately but not more than 15 days using electronic Manufacturer Incident Report Form (+ paper version for the EC)
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, using the electronic FSCA form

Increase rate of non-serious incidents will be reported to the Bulgarian Competent Authority in Trend reports as per regulation requirements.

Responsibilities of sponsor are detailed in the Safety Management Plan.

14.5.2 Vigilance according to Article 80

Any serious adverse event that has a causal relationship with an additional procedure or a causal relationship reasonably possible, will be reported by the sponsor to the Bulgarian CA and the Ethics Committee as follows:

Any serious adverse event that has a causal relationship with the additional procedure or a causal relationship reasonably possible, will be reported to the Bulgarian CA by the sponsor as follows: Imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for patients/subjects or a new finding to it	Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. The excel file provided by the MDCG 2020-10/2 rev1 is to be used.
Other reportable events or a new finding/update to it	Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event. The excel file provided by the MDCG 2020-10/2 rev 1 is to be used.

15. Suspension, or premature termination of the Clinical Investigation

Lallemand Pharma AG may suspend or prematurely terminate the clinical investigation. The reasons shall be documented. Reasons for suspension or premature termination at an investigation site may include occurrences where monitoring or auditing identifies serious or repeated deviations on the part of an investigator. Lallemand Pharma AG will notify the Regulatory Authority as appropriate and ensure that the EC is notified of any suspension or early termination of the clinical investigation.

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

EC or Regulatory Authority may suspend or prematurely terminate participation of one site or of all the participating sites.

The patients will receive all treatments needed in case of complication or safety issues. In this case, the patient will be followed until the end of the issue.

16. 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 investigator(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.

17. References

Medical Device Directive 93/42/EEC (MDD)
"Clinical Investigation of medical devices for human subjects" – Good clinical practice ISO 14155:2020

Ethical considerations for clinical trials on medicinal products conducted with minors Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use Revision 1 18 September 2017

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List of Appendix

Appendix A: Instructions for Use (IFU)

Appendix B: Acute Rhinitis Symptoms Severity Questionnaire

Appendix B: Primary Notification Form (PNF)

Appendix C: Serious Adverse Event (SAE) form

Appendix A: IFU

HEALSEA®BABYKIDS

INDICATION **Healsea® babykids** is a nasal spray indicated in children above 2 years to clean and moisten the nose during colds and rhinitis	**UNDESIRABLE EFFECTS**. In case of undesirable effects, contact your doctor.
COMPOSITION Isotonic saline solution (salinity 0.9%), Symbiofilm®.	**STORAGE AND WASTE RECOMMENDATION** Store at room temperature and not above 30°C. See the expiry date on the box or the bottle. Ask your pharmacist to throw out the bottle after use. These measures contribute to protect the environment.
DIRECTION OF USE Healsea® BABYKIDS shall be administered in children with the help of an adult. One-two sprays twice a day in each nostril for 10 days or as recommended by your doctor or pharmacist.	**TECHNOLOGY** The spray pump APF (Advanced Preservative Free) uses a technology that permits to dispense a preservative free solution.
PRECAUTION 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.	**HOW TO USE HEALSEA® BABYKIDS?** 1. Place the nozzle smoothly into the nostril while keeping head straight. 2. Once the nozzle is placed, press on the nozzle 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.
CONTRAINDICATION Do not use in children and adolescents under 2 years. Do not use in case of hypersensitivity or allergy to one or several components.	

Healsea® BABYKIDS is a nasal spray containing isotonic saline solution mixed with an innovative extract, Symbiofilm®, isolated from the marine biosphere.
Healsea® BABYKIDS is a natural care preservative free allowing to clean and moisten the nasal mucosa.
Symbiofilm® is a marine postbiotic, which contains exopolymeric substances, that enhances mechanically the cleansing efficiency of isotonic water.
Symbiofilm® reduces the development of biofilm from respiratory pathogenic microorganisms by mechanical action as well as the mucosal adhesion and helps reducing the spreading of viruses in-vitro.
Healsea® BABYKIDS is the ideal solution for children who suffer from colds or rhinitis by cleaning the nasal cavity and eliminating allergens and infectious agents.

Lallemand Pharma AG
Via Selva 2
6900 Massagno
Date: Switzerland

Learn more about biofilms by flashing this QR code!

Publication 2021/12/10_R1

EC REP

ASPE CONSEIL
21, chemin de la Favasse
31140 Aucamville – FRANCE

LALLEMAND PHARMA

PLACEBO

INDICATION **The Medical Device** is a nasal spray indicated in children above 2 years to clean and moisten the nose during colds and rhinitis	**UNDESIRABLE EFFECTS**. In case of undesirable effects, contact your doctor.
COMPOSITION Isotonic saline solution (salinity 0.9%)	**STORAGE AND WASTE RECOMMENDATION** Store at room temperature and not above 30°C. See the expiry date on the box or the bottle. Ask your pharmacist to throw out the bottle after use. These measures contribute to protect the environment.
DIRECTION OF USE The Placebo shall be administered in children with the help of an adult. One-two sprays twice a day in each nostril for 10 days or as recommended by your doctor or pharmacist.	**TECHNOLOGY** The spray pump APF (Advanced Preservative Free) uses a technology that permits to dispense a preservative free solution.
PRECAUTION 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.	**HOW TO USE THE PLACEBO?** 1. Place the nozzle smoothly into the nostril while keeping head straight. 2. Once the nozzle is placed, press on the nozzle 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.
CONTRAINDICATION Do not use in children and adolescents under 2 years. Do not use in case of hypersensitivity or allergy to one or several components.	

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Appendix B: Acute Rhinitis Symptoms Severity Questionnaire (English version)

Please, tick the box that corresponds to your child's situation

Q1: How sick does your child feel today:

Not sick ☐	A little sick ☐	Sick ☐	Very sick ☐

Q2-Q7: How do you evaluate the intensity of the following symptoms of your child?

Symptoms	Not present	mild	moderate	severe
Runny nose	☐	☐	☐	☐
Stuffy nose/blocked nose	☐	☐	☐	☐
Yellow/green discharge	☐	☐	☐	☐
Nasal crust (dry mucus)	☐	☐	☐	☐
Sore throat (hurts to swallow)	☐	☐	☐	☐
Sneezing/cough	☐	☐	☐	☐

Q8-Q10: How do you evaluate the impact of the common cold on your child's activities?

Activity	No impact	Mild impact	Moderate impact	Severe impact
Sleeping	☐	☐	☐	☐
Breathing	☐	☐	☐	☐
Playing/going to the nursery or to school	☐	☐	☐	☐

Appendix C: Primary Notification Form

This form is to be completed immediately and no later than 24h (in case of any SERIOUS safety issue) or 48h (in case of any NON-SERIOUS safety issue).

Protocol title:	Acronym:
Sponsor code:	Site number: ☐☐☐☐ Country:
Competent authority(ies) reference number:	Transmission date: ☐☐ ☐☐ ☐☐ ddmmyy

1. Date, type and classification of incident report			
Incident codification:	First notification: ☐	Follow-up: ☐	Final: ☐
Date of the incident	☐☐ ☐☐ ☐☐ ddmmyy		
Reporter awareness date	☐☐ ☐☐ ☐☐ ddmmyy		
Classification/type of the incident	☐ Serious public health threat ☐ Death ☐ Expected undesirable side effect	☐ Unanticipated serious deterioration in state of health ☐ Non serious incident	

2. Patient information	
Birthdate: ☐☐ ☐☐☐☐ mmyyyy Height: ☐☐☐ cm ☐☐☐ cm ☐☐☐ cm ☐☐☐ cm	Gender: Male ☐ Female ☐ Unknown ☐ Non applicable ☐ Weight: ☐☐☐ , ☐ Kg
List any of the patient's prior condition of medication that may be relevant to this incident:	

3. Medical Device information

UDI device identifier / Eudamed ID: ☐ not applicable	Basic UDI-DI/Eudamed-DI: ☐ not applicable	UDI production identifier: ☐ not applicable

Medical device name (brand, trade, proprietary or common name) & SKU:	
Class of risk:	
Batch number	
Expiry date (yyyy/mm):	☐☐☐☐/☐☐
Other details:	

4. Incident information

Intended use of the medical device:

Date of first use: ☐☐ ☐☐ ☐☐ ddmmyy

Date of last use: ☐☐ ☐☐ ☐☐ ddmmyy

Frequency of use:_____

Description of the incident: Provide a comprehensive description of the incident, including (1) what went wrong with device (if applicable) and (2) a description of health effects (if applicable), i.e. clinical signs, symptoms …):

Outcome & Health Impact:

☐ death ☐ life threatening ☐ hospitalization (initial or prolonged)
☐ required intervention to prevent permanent damage ☐ disability or permanent damage
☐ congenital abnormality/birth defect

☐ no serious outcome

☐ other, please specify:

Remedial actions taken by investigator, patient, or user subsequent:

5. Reporter information
☐ Distributor ☐ Patient ☐ Healthcare professional: _____ ☐ Investigator *(in case of the safety issue has been occurred during a clinical investigation)* ☐ Other, please specify: _____ For any follow-up please kindly indicate the contact details: Name and Surname: _____ Email: _____ Phone number:_____ Fax: _____ Date: Signature: _____ _____

Appendix D: SAE form

This form is to be used when a causal relationship between the serious adverse event and the additional investigational procedure is suspected (art 80.5 and 80.6).
This form is to be completed immediately and no later than 3 days after the investigation site personnel have been made aware of the event and sent immediately to the Clinical Study Monitor by mail marina@convex.bg and r.dimitrova.convex.bg , to BG ClinicalS etudes@bgclinicals.com, FAX: no +33 561 531 956 and to the sponsor officelp@lallemand.com and/or fax: +41 91 980 4615 (as back-up method) and to the Vigilance Manager Roberta Belotti (rbelotti@lallemand.com) and the EU representative (michel.huc@aspe-conseil.eu).

Protocol title: Efficacy and safety of Healsea® Babykids in the treatment of acute infectious rhinitis symptoms in children	Acronym: BASICC
Sponsor code: LPH-2202	Competent Authority(ies) reference number:
Transmission date: ☐☐ ☐☐ ☐☐ ddmmyy	Site number: ☐☐☐☐ Country:Bulgaria

SAE# (*to be completed by the sponsor*) ☐☐	First notification: ☐	Follow-up: ☐	Final: ☐

1. Subject information			
Birthdate: ☐☐ ☐☐☐☐ mmyyyy Height: ☐☐☐ cm		Gender: Male ☐ Female ☐ Other ☐ Weight: ☐☐☐ , ☐ Kg	
Investigational arm:	☐test group	☐comparison group	☐blinded

2. Description of the SAE	
The serious adverse event resulted in: ☐ Death (whatever may be the cause) Serious deterioration in the health of the subject, that resulted in any of the following: ☐ In-patient hospitalisation or prolongation of existing hospitalisation (*) ☐ Life threatening illness or injury ☐ Permanent impairment to a body structure or a body function	☐ Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function ☐ Chronic disease ☐ Foetal distress, foetal death or congenital physical or mental impairment or birth defect
Description of the SAE: (if clinical nature, indicate the diagnosis or the major symptoms)	

Date of the procedure leading to the SAE: ☐☐ ☐☐ ☐☐ ddmmyy	
SAE onset date: ☐☐ ☐☐ ☐☐ ddmmyy	☐ not capture
SAE stop date: ☐☐ ☐☐ ☐☐ ddmmyy	☐ on going
Or date of death if SAE "fatal" ☐☐ ☐☐ ☐☐ ddmmyy	
Summary description (study procedure, significant medical history, progression of event, available laboratory results, study procedure): (*) Except hospitalisations with durations and goal planned in the protocol or scheduled before study participation	

3. Mesures taken following the SAE

The event led to:

☐ Prescription of corrective or symptomatic medication / medical device (specify name, dosage):
……

☐ Other,specify:
……
……

4. Outcome

☐ Not recovered/Not resolved ☐ Recovering/Resolving ☐ Recovered/Resolved
☐ Recovered/Resolved with sequelae ☐ Unknown
☐ Fatal: in case of death, has an autopsy been conducted? ☐ Yes ☐ No

5. Investigator causality assessment with the study procedure (investigator's assessment to be done as soon as possible)

☐ Not related	☐ Possible	☐ Probable	☐ Causal relationship

Comments:
……

Enclose in the notification the results of carried out examination, reports of hospitalisation, etc…

6. Submitter information
☐ Investigator ☐ Other, please specify: _____ Name: _____ e-mail: _____ Phone number: _____ Fax: _____ Date: ☐☐ ☐☐ ☐☐ ddmmyy Signature: