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Efficacy and safety of Healsea® hypertonic nasal spray 2.7 % in the treatment of acute infectious rhinitis in adults

CLINICAL INVESTIGATION PLAN

Study Number: LPH-2201

Short Title: TEACHER

Version 1.0; 2022.10.03

This Clinical Investigation is being sponsored by:

Lallemand Pharma AG

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Switzerland

Represented by Dr Frédéric Durmont

Principal Investigator:

Dr Emil Kolev

Convex 1991 Ltd, Sofia, Bulgaria

HISTORY OF CLINICAL INVESTIGATION PLAN'S UPDATES

Version	Date	Purpose of Update
Version 1.0	**2022.10.03**	**Initial version**

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APPROVAL FORM
STUDY: LPH-2201
CLINICAL INVESTIGATION PLAN Version:
1.0 – 2022.10.03

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Date:
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Principal Investigator:

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PRINCIPAL INVESTIGATOR STUDY APPROVAL PAGE

STUDY: TEACHER-LPH 2201

CLINICAL INVESTIGATION PLAN Version:

Version 1.0-2022-10-03

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

- To conduct the trial described in the Clinical Investigation Plan (LPH-2201) Version 1 dated 2022-10-03 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
CA	**C**ompetent **A**uthority
CIP	**C**linical **I**nvestigation **P**lan
CRF	**C**ase **R**eport **F**orm
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
Principal Investigator:	Dr Emil Kolev
Title:	**Efficacy and safety of Healsea® hypertonic nasal spray 2.7% in the treatment of acute infectious rhinitis in adults**
Short Title	**T**esting the **E**fficacy in **A**dults with **C**old of **HE**alsea **R**escue*: **TEACHER**
CIP version:	2022-10-03
Competent Authority:	Bulgarian Drug Agency
Rationale:	Upper respiratory tract infections (URTIs) and sino-nasal symptoms are very frequent, especially during the fall and the winter. The common cold is caused by a variety of viruses such as human rhinoviruses and influenza viruses. The incidence of acute rhinitis/rhinosinusitis is very high, estimated to occur from 2 to 5 times per year in the average adult. However, the natural course of acute rhinitis in adults is favorable since 75% of persons have a reduction or resolution of symptoms within 7 days. Only 0.5 to 2.0% of subjects develop secondary bacterial sinusitis requiring antibiotic prescription. 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 socioeconomic impact of acute rhinitis is well established: visits to GP, additional prescriptions and over prescription of antibiotics, workdays lost. Although clinical evidence from well-designed trials is scarce, European and American guidelines for acute rhinosinusitis recommend daily nasal saline irrigation for reduction of the severity of symptoms and for speeding recovery. The exact mechanisms by which nasal irrigation works are not known. However, most of the experts agree that it is primarily a mechanical intervention leading to direct cleansing of the nasal mucosa. Hypertonic saline solutions are generally considered as more effective than isotonic saline solutions in reducing nasal symptoms in the acute phase. Nevertheless, the efficacy of such solution remains moderate. **Healsea® Rescue*** is a CE-marked class I medical device. This is a saline-based nasal spray supplemented with a natural Symbiofilm™ extract (0.04%) isolated from the marine bacteria *Bacillus licheniformis T14*. The nasal solution is hypertonic (NaCl 2.7%). Symbiofilm™ is an exopolysaccharide with emulsifying properties and *in vitro* antibiofilm activity and detachment properties against various bacterial pathogens. Symbiofilm™ also protects *in vitro* human nasal epithelial cells viability after Rhinovirus, Adenovirus, Coronavirus OC43 and Flu infection. The aim of this study is to demonstrate that hypertonic 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™ used as Placebo.

Objectives:	**Primary Objective:** - To compare the efficacy of **Healsea® Rescue* and Placebo** to improve the Quality of Life through symptoms of acute infectious rhinitis reduction in adults during a 7-day treatment period. **Secondary objectives:** - To compare the efficacy of **Healsea® Rescue* and of the Placebo** to reduce the duration of each infectious rhinitis symptoms rated by the WURSS 21 - To compare the efficacy of **Healsea® Rescue* and of the Placebo** to reduce the use of concomitant medication (antipyretics, systemic or local mucolytics, decongestants, antitussives, antibiotics) - To compare the subject overall assessment on efficacy of **Healsea® Rescue*** and of the **Placebo**. - **Safety**: to assess systemic and local tolerance of **Healsea® Rescue*** over the study period.
Endpoints:	**Primary Endpoint:** **The primary endpoint is the AUC** of Wisconsin Upper Respiratory Symptom Survey (WURSS-21) during first 8 days of symptoms. The WURSS-21 will be assessed once daily during D1-D8. **Secondary Endpoints:** **- AUC of the symptoms sub-score (items 2-11) and Quality of Life sub-score (items 12-20) of the WURSS-21** during first 8 days. **- Duration of cold symptoms** in both groups assessed by means of the WURSS-21. For each item, the duration is defined as the number of symptomatic days between D1 and the first day the subject reports not having the symptom for two consecutive days. Notice that the duration may be censored at day 13-day 15. - **Frequency and number of days of use of concomitant treatments** that may affect common cold symptoms (antipyretics, systemic or local mucolytics, decongestants, antitussives, antibiotics). **- Subject satisfaction** regarding ease of use, efficacy, local tolerance and taste at the end of study visit (V2) using a **4-points categorical scale** and of **Global subject feedback on treatment use** ("will you recommend the prescribed treatment for treatment of acute rhinitis?"). - **Safety**: Assessment of adverse events/incidents/foreseeable side effects throughout the study in both groups
Indication:	Treatment of acute rhinitis
Investigation Design:	**Double-Blind Placebo controlled randomized trial** The study will comprise 2 parts: - Part 1 (D1-D8): treatment of the acute phase

	• with **Healsea® Rescue***, 2 puffs in each nostril 2 times per day during 7 days (14 intakes of the investigational device). or • with **isotonic nasal spray (Placebo)**, 2 puffs in each nostril 2 times per day during 7 days (14 intakes of the Placebo). - Part 2 (D9-D13/15): follow-up phase. **Visit 1 (V1) - (Day 1): Screening/Inclusion/Randomization** Information and consent, demographic data and medical history, ongoing medication, physical and clinical examination (including COVID-19 antigen test), inclusion/non-inclusion criteria, randomization, e-diary presentation (including the first study questionnaire completion), reporting of adverse events, dispensation of **Healsea® Rescue*** Nasal Spray or **Placebo** (**Isotonic nasal spray)** (according to randomization list). **D1-D8 (at home**): Daily completion of the electronic diary (questionnaire, adverse events/incidents and concomitant medications), **Healsea® Rescue* /Placebo** nasal spray treatment daily administration. **D8 (Telephone call):** End of **Healsea® Rescue*/Placebo** nasal spray treatment. **D9-D13/15 (at home):** Daily completion of the electronic diary (adverse events/incidents, concomitant medications, WURSS-21 if applicable, until the subject feels not sick for two consecutive days). **Visit 2 (V2) – (Day 13-15): end of study** Physical and clinical examination (including COVID-19 antigen test), diary review, reporting of adverse events and incidents, compliance, subject satisfaction, WURSS-21 completion if the patient has not ticked "not sick" for 2 consecutive days in the previous days.
Number of Subjects:	A sample of **180** subjects (90 subjects per group) will be needed to provide 80% power with a 1-sided test at a 0.05 significance level to detect a difference between Healsea® Rescue* and Placebo groups AUC of 30%. Assuming that approximately 10% of subjects may drop-out the study, **200** will be randomly assigned at a ratio 1:1 to **Healsea® Rescue*** and **Placebo** (100 subjects per group).
Target Population:	Adults with acute infectious rhinitis
Permitted and prohibited concomitant medication	<u>Permitted concomitant medications during the study:</u> ○ Antipyretics except NSAID ○ 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 Non-permitted concomitant medications: ○ Local or systemic corticosteroids ○ NSAID ○ Saline nasal spray
Inclusion/Exclusion criteria:	**Inclusion Criteria:** Subjects will be enrolled if they meet all of the following criteria: 1. Male/Female subjects >18 years 2. Acute infectious rhinitis/rhinosinusitis **for ≤48h before trial entry** 3. Symptoms of headache, muscle ache, chilliness, sore throat, blocked nose, runny nose, cough, sneezing with **a score ≤9** (according to a self-rated symptom score; scale: 0 → 3 [0: no symptom to 3: severe intensity]) 4. At least one of these symptoms: sore throat, runny nose or blocked nose (i.e. with a score ≥1) 5. Willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the information consent form 6. Patient with a smartphone and an internet connection. **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 or any current disease 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 or local corticosteroids (nasal route or inhalation) within 4 weeks before screening 7. Antihistamines intake for allergy when treatment was started from less than 4 weeks 8. Chronic decongestant use 9. Recent (within the previous 2 days) intake of a common cold medicine that in the opinion of the investigator may influence symptom score at screening (NSAID, nasal decongestants, cough medicines) 10. Pregnant/Lactating female or absence of efficient contraception
Number of sites:	1 site in Bulgaria
Test Device:	**Healsea® Rescue*** nasal spray, class I

Comparator Device:	Isotonic nasal spray used as Placebo
Duration of investigation:	Duration of inclusion period: 5 months Duration of patient's participation: up to 15 days Total study duration: 5.5 months
Study Start Date:	November 2022
Statistical Analysis:	Continuous variables will be summarized using the mean, standard deviation, median, minimum, maximum and quartiles. Categorical variables will be summarized using frequency counts and percentages. All statistical tests will be 1-sided and performed using a 0.05 significance level. **Analysis of Primary endpoint:** For the primary criterion analysis, AUC for the WURSS-21 will be compared between Healsea® Rescue* group and Placebo group using a Student's t-test. If the usual applicability assumptions for the Student's t-test are not met, a Mann-Whitney test will be used. **Analyses of Secondary endpoints:** -The analysis of the primary endpoint will be completed by an analysis of the AUC for each of the WURSS-21 components (symptoms and Quality-of-Life). -Duration endpoints will be summarized using the medians, with 95% CIs for the medians by group. Results for **Healsea® Rescue*** group and **Placebo group** will be compared using Wilcoxon-Mann-Whitney test. -The number of days of use of concomitant treatments in each group will be compared by means of chi-square test or exact Fisher test. -The subject general satisfaction in each group will be compared by means of chi-square test. The global subject feedback on treatment use in each group will be compared by means of exact Fisher test. **-Safety:** All adverse events/incidents will be listed, but only treatment-emergent adverse events (non-serious + serious) will be summarized. Adverse events/incidents will be summarized by the number and percentage of patients (by treatment group), classified by System Organ Class and Preferred Term as defined by MedDRA dictionary. For a given treatment group, a given adverse event will be counted treatment emergent only once per patient during the treatment period. Frequency and percentage of patients with at least one reported adverse event/incident will be tabulated by System Organ Class and by treatment group.
Expected benefits:	**Healsea® Rescue*** nasal spray is expected to reduce the symptoms of acute rhinitis without any safety concern.

2. Flow Chart

	Acute phase		Telephone call	Follow-up	
Visit name	Screening/Inclusion	At home		At home	End of study
Visit Number	**V1**		***TC1***		**V2**
Days/Weeks	D1	D1-D8	D8	D9-End of study visit	D13-D15
Informed consent	X				
Eligibility criteria	X				
Demography and Medical history	X				
Physical and clinical examination	X				X
COVID-19 antigen test	X				X
Ongoing medication	X				
Randomization	X				
Treatment (**Healsea® Rescue*** or Placebo) (14 intakes)		X			
Telephone call (End of **Healsea® Rescue*** or Placebo)			X		
Subject e-diary and WURSS 21	X*	X		X[$]	X*
(Serious) Adverse Events/ (serious) incidents and concomitant medication reporting	X	X		X	X
Satisfaction Questionnaire					X
Compliance					X

[$] After D8, WURSS-21 until complete resolution of symptoms for 2 consecutive days.

*WURSS-21 to be completed with the investigator on site at screening and at the end of the study if the patient still has not ticked “not sick” for 2 consecutive days in the previous days.

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

3.1 Summary description

3.1.1 The investigational device

Healsea® Rescue* is a CE marked nasal spray composed with a hypertonic saline solution (2.7% 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 Rescue**

Ingredient	Concentration (g/L)
NaCl	27 g/L
Symbiofilm®	0.4 g/L
Purified Water	QS 1L

Healsea® Rescue* 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® Rescue* is indicated in adults over 18 years in the treatment of symptoms of acute respiratory tract infections: rhinitis or rhinosinusitis, reduces swelling of the nasal mucosa.
One-two sprays, twice a day in each nostril during 7 days or as recommended by the doctor or pharmacist.

The technical performances are summarised below:

*Table 2 : Technical performances of Healsea Rescue**

Component	**Function(s)**
Hypertonic saline solution 2.7 %	- 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® Rescue* 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® Rescue* 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: 75015DJMN (20/04/2022) for Healsea Rescue* 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 adults with acute infectious rhinitis. The only contraindication is hypersensitivity to one or several of the components. This is a non-inclusion criterion.

Healsea® Rescue* will be used within its intended purpose i.e., in adults for the treatment of symptoms of acute respiratory tract infections, rhinitis or rhinosinusitis, and for reduction of the swelling of the nasal mucosa.

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.

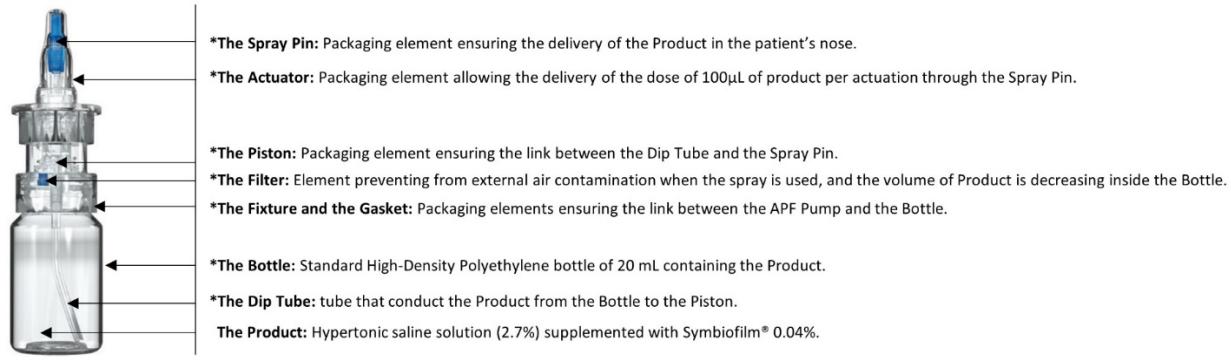
3.7 Devices description

3.7.1 Investigational device

Healsea® Rescue* 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® Rescue* 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® Rescue* is intended to be used on nasal mucosa. The duration of use is 7 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 7 days

Healsea Rescue* and the **Placebo** need to be indistinguishable in the context of a blinded study. The subcontractor in charge of the blinding will remove the label of Healsea® Rescue* and replace it by 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-2201 / TEACHER

Saline hypertonic solution 2.7% and Symbiofilm 0.04% (Healsea® Rescue) or isotonic nasal saline solution (Placebo).
Nasal spray, nasal route, vial 20 ml
Posology: two sprays, twice a day in each nostril during 7 days

Patient: _____ Investigator: _____

Batch number: _____ Site: DCC Convex EOOD
11 A Sinanishko ezero str.
1680 Sofia, Bulgaria

Treatment: _____ Expiry Date (mm/yyyy): _ _ / _ _ _ _

For Clinical Investigation use only

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

LPH-2201 / TEACHER

Saline hypertonic solution 2.7% and Symbiofilm 0.04% (Healsea® Rescue)
or isotonic nasal saline solution (Placebo).
Nasal spray, nasal route, vial 20 ml
Posology: two sprays, twice a day in each nostril during 7 days

Patient: _____ Investigator: _____

Batch number: _____ Site: DCC Convex EOOD
11 A Sinanishko ezero str.
1680 Sofia, Bulgaria

Treatment: _____ Expiry Date (mm/yyyy): _ _ / _ _ _ _

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® Rescue***.
A usability engineering process test according to the standard EN ISO 62366-1: 2015 was conducted with a product from the same range, Healsea® Babykids (same type of pump, worse case because of the paediatric population) 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 Rescue* and the comparator will be specially conditioned for this controlled and blinded study. A IFU leaflet is included in each secondary packaging: on one face, the IFU of Healsea® Rescue*, 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 patient on how to use the nasal spray.

3.9 Reference to the IFU

A IFU leaflet is included in each secondary packaging: on one face, the IFU of Healsea® Rescue*, on the other face, the IFU of Healsea® Placebo (See appendix 1).

4. Justification for the design of the clinical investigation

Upper respiratory tract infections (URTIs) and sinonasal symptoms are very frequent, especially during the fall and the winter. 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 common cold respectively. Other viruses such as Respiratory Syncytial virus, Adenoviruses and Parainfluenza viruses are less involved [1].

Viral upper respiratory infection can extend into the paranasal sinuses and 90% of subjects with viral upper respiratory tract infections have concurrent acute sinusitis [2]. The incidence of acute rhinitis/rhinosinusitis is very high, estimated to occur from 2 to 5 times per year in the average adult. However, the natural course of acute rhinitis in adults is favorable since 75% of persons have a reduction or resolution of symptoms within 7 days [2] [3]. Only 0.5 to 2.0% of subjects develop secondary bacterial sinusitis requiring antibiotic prescription. The most common pathogens in adults with acute bacterial sinusitis are Streptococcus pneumoniae, Haemophilus influenzae, Moraxella

catarrhalis and Streptococcus aureus [4] [5]. 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 socioeconomic impact of acute rhinitis is well established: visits to GP, additional prescriptions and over prescription of antibiotics, workdays lost [3].

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] [3]. 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 [7] [8]. 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, hypertonic saline solutions are generally considered as more effective than isotonic saline solutions in reducing nasal symptoms in the acute phase [9] [10]. Nevertheless, the efficacy of such 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® Rescue* is an hypertonic saline solution (2.7%) 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. *In vitro* data suggest that due to its physico-chemical properties, Symbiofilm™ acts in synergy with hypertonic saline solution to interfere with the binding of the viruses on the host cell surface.

The aim of this investigation is to demonstrate that thanks to the antibiofilm and antiviral properties of Symbiofilm™, hypertonic 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™.

To demonstrate the efficacy of Healsea® Rescue* 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® Rescue* is a hypertonic saline solution (2.7%) with Symbiofilm™ (0.04%).

Healsea® Rescue* is indicated in adults over 18 years for the treatment of symptoms of acute respiratory tract infections (rhinitis or rhinosinusitis).

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, hypertonic 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™. As a consequence, patients receiving daily administrations of **Healsea® Rescue*** 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

The only expected adverse event is the feeling of itching and irritation while initiating the treatment with the investigational medical device **Healsea® Rescue***. In case of such adverse reaction, the patients will be instructed to report the incident into the e-diary and to contact the investigator if the patient wishes to stop the nasal spray use.

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

5.3 Risk associated with the participation in the clinical investigation

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

Two nasopharyngeal swabs are planned for SARS-CoV- 2 antigen detection, at screening and at end of study. This sampling method is routinely performed without safety concern.

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

No interaction is expected. Nevertheless, patients 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).

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

5.5.1 Healsea Rescue*

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 residuals risks have an acceptable benefit-risk balance,
- And all the others residual risks (62) are at Low risk.
- Healsea® Rescue* 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 (Hysan® Salin-Spray)
- 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 Rescue* 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 Rescue* since this latter contains Symbiofilm® and hypertonic 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 subject participating in the study, and according to the requirements of ISO 14155: 2020, some specific points have been identified requiring specific attention to guarantee the safety and the well-being of the subject.

As the study will be conducted in a blinded manner, stringent risk acceptability thresholds are defined in the Study Risk Management Plan. Any issue with the dispensation (wrong device delivered) or inadequate process to ensure the traceability of the investigational product is deemed unacceptable and shall trigger an immediate action plan.

More generally, the number of unreported incident/serious incident or adverse event/foreseeable expected side effect per site, the timelines for materiovigilance/vigilance reporting to sponsor shall be tracked according to the risk management plan and risk acceptability threshold are defined.

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 patient's quality of life during generally about 7 days. Furthermore, bacterial over-infections with worsening of symptoms can occur requiring antibiotic prescription. Progression to a chronic state, i.e. chronic rhinosinusitis is also observed.

Conventional therapies for infectious rhinitis are symptomatic and not without side effect. For example, decongestant use can increase blood pressure, antihistamine intake is associated with drowsiness. Healsea® Rescue* represents an interesting alternative because this nasal spray can alleviate infectious rhinitis symptoms but also limit the complication and progression to chronic state.

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

6. Objectives and hypotheses of the clinical investigation

6.1 Hypothesis

Our hypothesis is that Healsea® Rescue* 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

The primary objective is to compare the efficacy of **Healsea® Rescue*** and of **Placebo** to improve the Quality of Life through symptoms of acute infectious rhinitis reduction in adults during a 7-day treatment period.

6.3 Secondary Objectives

- To compare the efficacy of **Healsea® Rescue* and Placebo** to reduce the duration of each infectious rhinitis symptoms rated by the WURSS 21.
- To compare the efficacy of **Healsea® Rescue* and Placebo** to reduce the use of concomitant medication (systemic antibiotics, antipyretics, mucolytics, decongestants).
- To compare the subject overall assessment on efficacy of **Healsea® Rescue*/Placebo**.
- Safety: to assess systemic and local tolerance of **Healsea® Rescue*** over the study period.

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

A non-pharmaceutical product (Influcid®) used as add-on treatment for Upper Respiratory Tract Infections has been demonstrated to reduce from about 30% the WURSS-21 AUC in comparison with standard treatment alone [11]. Considering that the **Healsea® Rescue*** also exerts its action via a non-pharmacologic mechanism, we consider that a 30% reduction of the WURSS-21 AUC is deemed a suitable effect size in this clinical investigation.

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 only expected adverse event is the feeling of itching and irritation while initiating the treatment with the investigational medical device **Healsea® Rescue*.** 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 will be assessed once daily during the treatment period. After D8, the WURSS-21 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 the eligibility criteria are fulfilled, thus minimizing the selection bias. During the V1 visit, each subject will be randomly assigned to a product (active or placebo) with a 1:1 allocation in accordance with the blocked randomization table generated by Axiodis. The investigator or designee will allocate a treatment number according to the randomization for eligible subjects via the eCRF.

Blinding and unblinding:
The randomization list will be drawn up by Axiodis using a validated software and before the beginning of the study, by a statistician 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 Axiodis to the responsible of the product preparation, Creapharm
- Uploaded into the patient enrolment module of the eCRF

In case of dysfunction of the Medical Device, it will be possible to attribute a new randomisation number to the patient and a new identical treatment (in a blinded manner) using the eCRF back-up randomisation module.
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® Rescue* 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 Device (Healsea® Rescue* 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 person 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 randomization management interface 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 data manager if charge of the randomisation list

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

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

The AUC of Wisconsin Upper Respiratory Symptom Survey (WURSS-21) during first 8 days of symptoms will be compared between both groups.

WURSS-21 is a validated 3-dimensional structure questionnaire [12]. This survey has been demonstrated to be responsive, and valid to assessing the severity and functional impact of the common cold. It includes 10 items assessing symptoms (symptoms score, (items 2 to 11), 9 items assessing functional impairments (quality of life score, (items 12 to 20).) and 2 items assessing respectively global severity and global change. Brown et al. [13] support the practice of using, for AUC computation, a simply summed daily global illness severity score to represent the overall symptomatic and functional impairments arising from acute upper respiratory infection.

The WURSS-21 will be assessed in an e-diary once daily in the evening, taking into account the symptoms from the morning to the evening, during D2-D8 (day of the end of treatment). At D1, the WURSS-21 will be completed during the visit. After D8, the WURSS-21 will be assessed once daily until the subject feels not sick for two consecutive days.

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

--**AUC of the symptoms sub-score (items 2-11) and Quality of Life sub-score (items 12-20) of the WURSS-21 during first 8 days**

- Duration of cold symptoms in both groups assessed by means of the WURSS-21.

For each item, the duration is defined as the number of symptomatic days between visit V1 and the first day the subject reports not to have this symptom for two consecutive days.

To be noticed that the duration may be censored at the end of study participation (visit V2). Should the patient have not ticked “not sick” for 2 consecutive days at the end of study visit, a WURSS-21 will be completed by the patient during the visit.

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

- **Subject satisfaction** regarding ease of use, efficacy, local tolerance and taste at end of study visit (V2) using a **4-points categorical scale** and of the **Global subject feedback** on treatment use ("will you recommend the prescribed treatment for treatment / prevention of acute rhinitis?").
Although subjective, these endpoints are pertinent because Healsea® Rescue* is an OTC product which does not require physician prescription.

- **Safety**: Assessment of adverse events and incidents throughout the study in both groups. Adverse events/incidents will be reported in the e-diary by the patient, 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 1 site 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® Rescue***. This is a CE marked Medical Device used for acute infectious rhinitis and administered by spraying 2 puffs in each nostril 2 times per day during 7 days (14 intakes of the investigational device).

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® Rescue*** product. Posology, instructions for use, contraindications, precaution of use and labelling are identical to those for Healsea® Rescue*.
We hypothesize that hypertonic saline solution and Symbiofilm™ will act in a synergistic manner for achieving the principal action, i.e. reduction of the duration of acute rhinitis symptoms. Placebo is classically defined as a pharmaceutically inert substance. This definition can of course be extended to the present study evaluating the Medical Device Healsea® Rescue*. Thus, we have chosen isotonic saline solution which can be 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.

7.3 Subjects

The target population is subjects 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 >18 years
2. Acute infectious rhinitis/rhinosinusitis **for ≤48h before trial entry**
3. Symptoms of headache, muscle ache, chilliness, sore throat, blocked nose, runny nose, cough, sneezing with **a score ≤9** (according to a self-rated symptom score; scale: 0 → 3 [0: no symptom to 3: severe intensity])
4. At least one of these symptoms: sore throat, runny nose or blocked nose (i.e., with a score ≥1)
5. Willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the information consent form
6. Patient with a smartphone and an internet connection.

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 or any current disease 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 or local corticosteroids (nasal route or inhalation) within 4 weeks before screening
7. Antihistamines intake for allergy when treatment was started from less than 4 weeks
8. Chronic decongestant use
9. Recent (within the previous 2 days) intake of a common cold medicine that in the opinion of the investigator may influence symptom score at screening (NSAID, nasal decongestants, cough medicines)
10. Pregnant/Lactating female or absence of efficient contraception

7.3.1.3 Withdrawal Criteria and procedures

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

- A subject 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 patient as soon as possible for a final assessment in order to:
    - Obtain the reason(s) for withdrawal and report it/them in the Case Report Form,
    - Evaluate the patient's clinical condition,
    - If necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.

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

- Significant study product non-compliance
- 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 fax. 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. A SARS-COV-2 test will be performed at the beginning and at the end of the study to identify the subpopulation of patients with COVID-19.

7.3.1.4 Subject lost to follow-up

If a patient cannot be contacted to collect follow-up information even beyond the 7 days from visit 2, he/she will be considered "lost to follow-up". But before declaring that a patient is "lost to follow-up", the Principal Investigator (or his/her team) must do his/her best effort to contact patients and attempts should be made via all available routes. A certified letter should be sent to the permanent address on file.
The methods used to attempt contacting the patient 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 site is a healthy volunteer centre. The clinical research center will inform potential subjects (identified in the center database) of the objectives and procedures of the clinical investigation by sending emails and performing phone calls. Also, flyers describing the clinical trial will be sent and displayed in pharmacy stores and in general practitioners' offices. In case of the onset of acute infectious rhinitis, interested subjects will be invited to contact the site and to come for a consultation. Before performing any study procedure, the investigator will give all the information pertaining to the study and patient will sign the consent form if he/she accepts study participation. 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 5.5 months.

7.3.4 Expected duration of each subject's participation

The duration of each patient's participation is up to 15 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

An enrolment period of 5 months is considered sufficient to enrol the cohort of 200 patients.

7.3.7 Relationship of investigation population to target population

Healsea® Rescue* will be used within its intended use, in adults with acute infectious rhinitis. This post-market clinical investigations aims to demonstrate that hypertonic 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 are not eligible although the investigational device is not contraindicated in this population.

7.3.9 Compensation

A compensation of 310 euros for costs resulting from participation in the clinical investigation (transportation, absence of work…) will be paid to each patient who complete the study (e-diary completion and availability for visits and telephone call).

7.4 Procedures

7.4.1 Description of clinical investigation-related procedures

The clinical investigation is divided into 2 parts:
- Part 1 (D1-D8): treatment of the acute phase with Healsea® Rescue* or Placebo.
- Part 2 (D9-D13/15): follow-up phase.

The clinical investigation comprises 2 visits and 1 telephone call.

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

Subjects 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. The patient will receive the information sheet. If the subject agrees to participate in the study, he/she will be asked to give a written consent.

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., 001-010 for the 10th subject screened at the Site #001).

The investigator or his/her delegated designee will:

- Record demographic data, medical history and ongoing medication.
- Perform a physical and clinical examination. A pharyngeal nasal swab will be performed by the investigator or by the delegated study nurse to check for absence or presence of SARS-CoV2.
- Verify that eligibility criteria are fulfilled.
- Record the score of the common cold symptoms (headache, muscle ache, chilliness, sore throat, blocked nose, runny nose, cough, sneezing according to a physician-rated symptom score after clinical examination; (scale: 0 → 3 [0: no symptom, 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable), 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping]). This scoring system was developed by Jackson in 1958 and is widely used in common cold clinical trials [14].
- Review and detail the question of the WURSS-21.
- Allocate a treatment number for eligible subjects via the eCRF.
- Explain how to complete every day the e-diary for WURSS-21 recording, how to report concomitant medications, adverse events/incidents/expected undesirable side effects. The patient will access the e-diary application using a smartphone.

  NB: The first WURSS-21 will be completed by the subject on site during this visit after the randomization of the patient.
- Remind the patient to return the device for assessment of compliance to the treatment at V2.

The investigator will provide the patient with the device according to the treatment number as per randomization and explain how to use it. The investigator will also prime the pump bottle to identify a

possible malfunction before the patient leaves the site. In case of dysfunction, a new randomisation number and a new treatment will be attributed to the patient using the eCRF back-up randomisation module.

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

D1-D8 (at home):

The patient will be asked to complete the electronic diary daily (WURSS-21 assessed once daily in the evening, taking into account the symptoms from the morning to the evening, adverse events/incidents/expected undesirable side effects and concomitant medications).

D8 (Telephone Call):

The investigator or his/her delegated designee will call the patient to remind him/her to stop the treatment.

- *NB: The last study nasal spray intake will be performed in the morning of the Day 8.*

D9-D13/15 (at home):

Patients will continue to complete the electronic diary daily (incidents/adverse events in relation with the common cold, concomitant medications). The patient for whom common cold symptoms persist, will be instructed to continue to complete the WURSS-21, until the subject feels not sick for two consecutive days.

Visit 2 (V2) – (Day 13-15): end of study

The investigator or his/her delegated designee will:

- Perform a physical and clinical examination. A pharyngeal nasal swab will be performed by the investigator or by the delegated study nurse to check for absence or presence of SARS-CoV2.
- Validate adverse events pertinent in the context of the common cold and of additional study procedures /incidents linked to medical device use and concomitant medications reported in the e-diary and complete the e-CRF accordingly and report any new relevant safety events.
- Ask the patient to complete the WURSS-21 if he/she still has symptoms.
- Assessed the compliance to the treatment by weighting the device returned by the subject. In case of nasal spray dysfunction and attribution of a new treatment using the back-up randomization list, the compliance will be assessed by weighting both devices. If a nasal spray is lost, the investigator will ask the patient to specify the number of missed nasal spray use and will report the data into the e-CRF.
- Ask the patient to complete a satisfaction questionnaire.

7.4.2 Concomitant Medication and/or Treatments

7.4.2.1 Permitted concomitant medications during the study:

- Antipyretics except NSAID
- 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

7.4.2.2 Non-permitted concomitant medications:

- Local or systemic corticosteroids
- NSAID
- 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. The investigator also guarantees the authenticity of the data collected in the context of the study and agrees to the legal provisions for study sponsor quality control.

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, the investigator should respond within agreed timelines.

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

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

The Principal Investigator will retain all copies of the records for a period of 10 years from the completion of the clinical investigation. In any circumstances, the PI 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 the 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 taken at least one puff of the nasal spray.

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

Safety endpoint will be performed on safety population.

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

8.2 Baseline Characteristics

Continuous variables will be summarized using the mean, standard deviation, median, minimum, maximum and quartiles. Categorical variables will be summarized using frequency counts and percentages.

All statistical tests will be 1-sided and performed using a 0.05 significance level.

8.3 Primary endpoint

For the primary criterion analysis, AUC for the WURSS-21 will be compared between Healsea® Rescue* group and Placebo group using a Student's t-test. If the usual applicability assumptions for the Student's t-test are not met, a Mann-Whitney test will be used.

8.4 Secondary endpoints

-The analysis of the primary endpoint will be completed by an analysis of the AUC for each of the WURSS-21 components (symptoms and Quality-of-Life).

-Duration endpoints will be summarized using the medians, with 95% CIs for the medians by group. Results for **Healsea® Rescue*** group and Placebo group will be compared using Wilcoxon-Mann-Whitney test.

-The number of days of use of concomitant treatments in each group will be compared by means of chi-square test or exact Fisher test.

-The subject general satisfaction in each group will be compared by means of chi-square test. And the global subject feedback on treatment use in each group will be compared by means of exact Fisher test.

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

Adverse events/incidents/expected side effects will be summarized by the number and percentage of patients (by treatment group), classified by System Organ Class and Preferred Term as defined by MedDRA dictionary.
For a given treatment group, a given adverse event will be counted treatment emergent only once per patient during the treatment period.
Frequency and percentage of patients with at least one reported adverse event/ incident / expected side effects will be tabulated by System Organ Class and by treatment group.

8.5 Sample Size calculation and justification

A sample of **180** subjects (90 subjects per group) will be needed to provide 80% power with a 1-sided test at a 0.05 significance level to detect a difference between Healsea® Rescue* and Placebo groups AUC of 30% [12].

Assuming that approximately 10% of subjects may drop-out the study, **200** subjects will be randomly assigned at a ratio 1:1 to Healsea® Rescue* and Placebo (100 subjects per group).

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, such as quality of life or satisfaction questionnaires. Two visits are scheduled to assess the study criteria. The phone call is performed to ensure that the patient has stopped the treatment after 14 continuous intakes.

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

Missing data for the primary endpoint (WURSS-21) 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 statistical analysis plan and in the clinical investigation report.

9. Data Management

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

9.1 Source documents

The source documents (e.g., medical file, clinical and office charts, log for compliance data…) which contain the source of data recorded in the CRF should be specified. The e-diary will be used as source document for WURSS-21, concomitant treatments and adverse events/incidents reported by patient.

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 a validated and GCP/GDPR compliant e-diary by the patient after secure logging to the study website and will be automatically uploaded in the e-CRF:

- WURSS-21,
- Adverse event/incidents/expected side effects and concomitant treatments,

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

9.3 Procedure used for CRF 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
- Creation of post-entry checks and listings
- Clean-file process including execution of post-entry checks and listings
- Post clean-file tasks

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

A data blind review meeting will be held prior to database lock.

The review process 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 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

The investigator 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 the Principal Investigator 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 (WURSS-21) at D1, D4±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, the site will complete an accountability log after each receipt of the Medical Device and delivery to subject. The CRA in charge of the site monitoring will check the accountability log at each visit. At V2, the accountability log will be completed with the weight of the returned device by the subject.

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 subject's decision before any study procedure. In order to ensure

that the subject is fully informed the investigator must explain to each patient 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 patient that participation in the clinical investigation is voluntary and a decision not to participate will not affect their right to the most appropriate treatment/care or affect the doctor-patient relationship. Participants 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 and the study participation must be documented in the patient medical file. Patients reserve the right to withdraw from the clinical investigation at any time, irrespective of their initial consent.

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 e-CRF, and if the patient’s name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. All subject data that appear in reports and publications will be anonymised such that the privacy and confidentiality of each subject is maintained.

No data processing will be performed outside of the European Union.

To fulfil the requirements of source data verification, the PI will be required to obtain consent from each subject stating that they agree for their medical records to be accessed (this will form part of the consent process). To comply with 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 guaranteed exclusion.

14. Vigilance

14.1 General

Healsea® Rescue* 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 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 e-diary by questioning the patient.

All serious and non-serious incidents/serious and non-serious risk of incidents/expected side effects /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 e-CRF.

14.4 Investigator's responsibilities and processing timelines

14.4.1 Materiovigilance

All incidents and expected undesirable side effects will be reported to LP vigilance manager according to MDR, MEDDEV 2.12 rev 8 modalities, national requirements, ISO 14155:2020 and Lallemand Pharma procedures which are described in the safety management plan. This document will be signed by the Principal Investigator, representants of the Clinical Research Organization (CRO), 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 B) 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 CRA (marina@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 and expected side effects.

14.4.2 Vigilance reporting according to Article 80 of the MDR

The following events are considered reportable events in accordance with MDR Art. 80(2):

- any serious adverse event that has a causal relationship with the investigation procedure or where such causal relationship is reasonably possible.

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 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) **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 C).

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

Increase rate or severity of expected undesirable side effects and non-serious incidents will be reported to the 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 if applicable 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 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 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 author(s) at least 30 days prior to the expected date of submission to the intended publisher.

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

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

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

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

17. References

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

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List of Appendix

Appendix A: Instructions for Use (IFU)

Appendix B: Primary Notification Form (PNF)

Appendix C: Serious Adverse Event (SAE) form

Appendix A: IFU

HEALSEA® RESCUE

INDICATION **Healsea® RESCUE** is a nasal spray indicated in adults over 18 years in the treatment of nasal symptoms of acute rhinitis and rhinosinusitis, reduces swelling of the nasal mucosa.	**UNDESIDERABLE EFFECTS** Feeling of itching and irritation can occur while initiating the treatment. In case of undesirable effects, contact your doctor.
COMPOSITION Hypertonic saline solution (salinity 2.7%), 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 One-two sprays twice a day in each nostril for 7 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 7 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® RESCUE?** 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 18 years. Do not use in case of hypersensitivity or allergy to one or several components.	

Healsea® RESCUE is a nasal spray containing hypertonic saline solution mixed with an innovative extract, Symbiofilm®, isolated from the marine biosphere.
Healsea® RESCUE is a natural care preservative free allowing to treat nasal symptoms of acute rhinitis and rhinosinusitis.
Symbiofilm® is a marine postbiotic, which contains exopolymeric substances, that enhances mechanically the cleansing efficiency of hypertonic 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® RESCUE is the ideal solution to ensure an efficient cleansing, moisturizing and decongestion of the nasal mucosa by osmotic action.

Lallemand Pharma AG
Via Selva 2
6900 Massagno
Switzerland

Learn more about biofilms by flashing this QR code!

Publication date:
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 adults over 18 years in the treatment of nasal symptoms of acute rhinitis and rhinosinusitis, reduces swelling of the nasal mucosa.	**UNDESIDERABLE EFFECTS** Feeling of itching and irritation can occur while initiating the treatment. 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 One-two sprays twice a day in each nostril for 7 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 7 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® 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 18 years. Do not use in case of hypersensitivity or allergy to one or several components.	

Lallemand Pharma AG
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EC REP

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LALLEMAND PHARMA

Appendix B: 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: [to be completed]	Acronym: [to be completed]
Sponsor code: [to be completed]	Site number: ☐☐☐☐ Country:
Competent authority(ies) reference number: [to be completed]	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	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:

_____ _____

Strictly Confidential

Appendix C: 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 to BG ClinicalS etudes@bgclinicals.com, FAX: no +33 561 531 956, 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® hypertonic nasal spray 2.7 % in the treatment of acute infectious rhinitis in adults	Acronym: TEACHER
Sponsor code: **LPH-2201**	Competent Authority(ies) reference number:
Transmission date: ☐☐ ☐☐ ☐☐ ddmmyy	

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:	☐ Healsea® Rescue	☐ Placebo	☐ 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: