ALX-009-CL-038
STUDY SYNOPSIS

Title	Randomized, double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics after single ascending doses or multiple ascending doses of hypothiocyanite ($OSCN^-$), / bovine Lactoferrin (bLF), or their combination (ALX-009) in healthy male volunteers and patients suffering from cystic fibrosis (CF) and non-CF bronchiectasis (NCFBE).
Study products	$OSCN^-$/ bLF / ALX-009
Protocol No.	ALX-009-CL-038 CRO ref: OP092815.ALX / OP092915.ALX EudraCT number: 2014-002401-38
Phase	I
Sponsor	ALAXIA SAS 30 rue Edouard Nieuport 69008 LYON - FRANCE
Coordinating Investigator	Isabelle DURIEU, MD Centre de référence Mucoviscidose Groupement Hospitalier Sud Hospices Civils de Lyon 165 Chemin du Grand Revoyet 69310 Pierre-Bénite – FRANCE
Number of study centers	Study Parts I, II, III and IVa: Single center study Study Part IVb: Multicenter international study
Subjects	103 subjects in total: - Part I: 42 healthy male subjects - Completed - Part II: 16 healthy male subjects - Completed - Part III: 7 CF patients (completed) and 14 healthy male subjects - Part IV: 12 healthy male subjects (IVa) and 12 CF and/or NCFBE patients (IVb)
Rationale of the clinical trial	ALX-009 is composed of 2 endogenous substances ($OSCN^-$/Lactoferrin) with antimicrobial properties mimicking the innate immune system The purpose of ALX-009 is to compensate, with local administration of $OSCN^-$ and bovine Lactoferrin (bLF), the pathological deficit of CF patients in these compounds, therefore restoring their broncho-pulmonary immune defense system and fighting against lung infection, in particularly infections caused by Gram(-) bacteria resistant to available antibiotics.
Benefit-risk considerations	At this early development stage, there are no demonstrated risks or benefits for ALX-009. The theoretical benefit in fighting against multi-drug resistant Gram(-) lung infections, overweigh the theoretical risk for bovine lactoferrin induced immunogenicity.

Study Design	<u>Study Part I: OP092815.ALX; cohorts 1, 2 and 3 (Completed)</u> This is a phase I, single-center, double-blind, placebo-controlled, randomized, parallel groups, single ascending dose study in healthy male volunteers. Single inhaled doses of each tested product or placebo will be tested separately in 3 different single doses (SD) in healthy volunteers. Each cohort will include 14 subjects ($OSCN^-$ n=6; bLF n=6; placebo n=2), 42 subjects in total. <u>Study Part II: OP092915.ALX; cohorts 4 and 5 (Completed)</u> This is a phase I, single-center, double-blind, placebo-controlled, randomized, parallel groups, single and multiple ascending dose study in healthy male volunteers. All subjects will receive one single nebulization of the tested combinations of test products or placebo and then multiple doses of the tested combinations or placebo (tid during 7 days). Each cohort will include 8 subjects (ALX-009 n=6; placebo n=2), 16 subjects in total. <u>Study Part III: OP092915.ALX; cohorts III-1, III-2 and III-3</u> This is a phase I, multicenter, double-blind, placebo-controlled, randomized, parallel group, multiple ascending doses study in healthy male volunteers and in CF patients. All subjects/patients will receive multiple nebulized doses of each products tested separately or placebo (bid during 7 days), at 3 different doses. Each cohort will include 7 subjects/patients ($OSCN^-$ n=3; bLF n=3; placebo n=1), 21 volunteers in total. <u>Study Part IV: OP092915.ALX; cohorts IV-1, IV-2 and IV-3</u> - <u>Cohorts IV-1a, IV-2a and IV-3a:</u> This is a phase I, single-center, double-blind, placebo-controlled, randomized, parallel group, multiple ascending doses study in healthy male volunteers. All subjects will receive multiple nebulized doses of combination of the tested products or placebo (bid during 7 days) at 3 different doses. Each cohort will include 4 subjects (ALX-009 n=3; placebo n=1), 12 subjects in total. - <u>Cohorts IV-1b, IV-2b and IV-3b:</u> This is a phase I, multicenter, double-blind, placebo-controlled, randomized, parallel group, multiple ascending doses study in CF and NCFBE patients. All patients will receive multiple nebulized doses of combination of the tested products or placebo (bid during 7 days) at 3 different doses. Each cohort will include 4 patients (ALX-009 n=3; placebo n=1), 12 subjects in total.
Study Objectives	<u>Study Part I: OP092815.ALX; cohorts 1, 2 and 3 (Completed)</u> Primary Objective: • To evaluate the safety and tolerability of products tested separately ($OSCN^-$ and bLF) after single administration at different doses. Secondary Objectives: • To determine the high dose combination (defined as the combination of the highest tolerated dose of $OSCN^-$ and the highest tolerated dose of bLF) and the low dose combination (defined as the combination of second highest tolerated doses of each of the two tested products); • To determine the PK parameters of bLF (in blood and sputum) and SCN^- (in blood, urine and sputum) after single administration of different doses; • To determine the effects on pharmacodynamics parameters.

	Study Part II: OP092915.ALX; cohorts 4 and 5 (Completed) Primary Objective: • To evaluate the safety and tolerability of bLF and $OSCN^-$ combination after single and multiple administrations at different doses. Secondary Objectives: • To determine the highest tolerated dose of bLF and $OSCN^-$ combination • To determine the PK parameters of the combination of bLF (in blood and sputum) and SCN^- (in blood, urine and sptutum) after single and multiple administrations of different doses of the combination • To determine the effects on pharmacodynamics parameters. Study Part III: OP092915.ALX; cohorts III-1, III-2 and III-3 Primary Objective: To evaluate the safety and tolerability of each product tested separately ($OSCN^-$ and bLF) after multiple administrations at different doses, in CF patients (cohort III-1) and healthy male volunteers (cohorts III-2 and III-3). Secondary Objectives: • To determine the combination ratio(s) to be tested in study part IV (cohorts 9, 10 and 11) • To determine the PK parameters of bLF (in blood and sputum) and SCN^- (in blood, urine and sptutum) after multiple administrations of the products tested separately • To determine the effects on pharmacodynamics parameters • To determine the effects of each compound at the tested doses on sputum microbiology (CF patients only – cohort III-1). Study Part IV: OP092915.ALX; cohorts IV-1, IV-2 and IV-3 o Cohorts IV-1a, IV-2a and IV-3a: Primary Objective: • To evaluate the safety and tolerability of bLF and $OSCN^-$ combination after multiple administrations at different doses of the selected ratio(s), in healthy male volunteers . Secondary Objectives: • To determine the PK parameters of bLF (in blood and sputum) and SCN^- (in blood, urine and sptutum) after multiple administrations of the combination in healthy male volunteers; • To determine the effects on pharmacodynamics parameters; o Cohorts IV-1b, IV-2b and IV-3b: Primary Objective: • To evaluate the safety and tolerability of bLF and $OSCN^-$ combination after multiple administrations at different doses of the selected ratio(s), in CF and NCFBE patients. Secondary Objectives: • To determine the PK parameters of bLF (in blood and sputum) and SCN^- (in blood, urine and sputum) after multiple administrations of the combination in CF and NCFBE patients;

	• To determine the effects on pharmacodynamics parameters; • To determine the effects of combination at the tested doses on sputum microbiology.

Investigational Medicinal Treatment	Name of the compound:	**Bovine Lactoferrin (bLF)**
	Pharmaceutical form:	Solution for inhalation
	Description:	Presented as a lyophilized powder to be diluted in NaCl 0.9 % prior administration in order to obtain a clear and pale pink solution.
	Dose per administration:	40 mg, 80 mg or 160 mg in NaCl 0.9% qs 10 mL
	Timing for administration:	Administration will take place in sitting position. Part I: Single administration on D1 at T0h Part III: Repeated administrations from D1 to D7 bid at T0h and T8h.
	Name of the compound:	**$OSCN^-$ solution**
	Pharmaceutical form:	Solution for inhalation 3.65 mM
	Description:	Produced extemporaneously as a clear and colourless solution
	Dose per administration:	0.65 mg, 1.25 mg or 2.25 mg + NaCl 0.9% qs 10 mL.
	Timing for administration:	Administration will take place in sitting position. Part I: Single administration on D1 at T0h Part III: Repeated administrations from D1 to D7 bid at T0h and T8h.
	Name of the compound:	**NaCl 0.9% (Placebo)**
	Pharmaceutical form:	Solution for inhalation
	Dose per administration:	10 mL
	Timing for administration:	Part I: Single administration on D1 at T0h in sitting position Part II: Single administration on P1D1 at T0h in sitting position and repeated tid administrations from P2D1 to P2D7 a T0h, T6h and T12h in sitting position. Parts III and IV: Repeated administrations from D1 to D7 bid at T0h and T8h.
	Name of the compound:	**ALX-009**
	Pharmaceutical form:	Solution for inhalation
	Description:	Combination of the $OSCN^-$ solution and bLF, prepared before administration, clear and pale pink solution.
	Dose per administration:	bLF 40 mg, 80 mg or 160 mg + $OSCN^-$ 0.65 mg, 1.25 mg or 2.25 mg + NaCl 0.9% qs 10 mL.
	Timing for administration:	Part I: Single administration on D1 at T0h in sitting position Part II: Single administration on P1D1 at T0h in sitting position and repeated tid administrations from P2D1 to P2D7 at T0h, T6h and T12h in sitting position.

	Part IV: Repeated administrations from D1 to D7 bid at T0 and T8h. For study parts III and IV, right before each administration of study products, subjects/patients will be administered two puffs of Salbutamol (suspension for inhalation, pressurised inhaler), corresponding to two doses of 100 µg of salbutamol.
Main Evaluation Criteria	**Study Part I: OP092815.ALX; cohorts 1; 2 and 3 (Completed)** Primary evaluation criteria: • Safety parameters: physical examination, vital signs, spirometry, adverse events, concomitant treatments, ECG, 24h-holter and laboratory examinations. Secondary evaluation criteria: • The following parameters will be determined for bLF concentration and SCN^- concentration from blood, sputum and, for SCN^- only, in urine: C_{max}, AUC_{0-t}, T_{max} and $t_{1/2}$. • Concentration of immunological/inflammation parameters will be determined in sputum (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10 and TNF-α) and in blood (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10, TNF-α, SC5b-9 and total IgE). **Study Part II: OP092915.ALX; cohorts 4 and 5 (Completed)** Primary evaluation criteria: • Safety parameters: physical examination, vital signs, spirometry, adverse events, concomitant treatments, ECG, 24h-holter and laboratory examinations. Secondary evaluation criteria: • The following parameters will be determined for bLF concentration and SCN^- concentration from blood, sputum and, for SCN^- only, in urine: C_{max}, AUC 0-t, T_{max} and $t_{1/2}$. • Concentration of immunological/inflammation parameters will be determined in sputum (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10 and TNF-α) and in blood (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10, TNF-α, SC5b-9 and total IgE). **Study Part III: OP092915.ALX; cohorts III-1, III-2 and III-3** Primary evaluation criteria: • Safety parameters: physical examination, vital signs, spirometry, oxygen saturation, adverse events, concomitant treatments, ECG, 24h-holter and laboratory examinations. Secondary evaluation criteria: • The following parameters will be determined for bLF concentration and SCN^- concentration from blood, sputum and, for SCN^- only, in urine: C_{max}, AUC_{0-t}, T_{max} and $t_{1/2}$. • Concentration of immunological/inflammation parameters will be determined in sputum (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10 and TNF-α) and in blood (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10, TNF-α, SC5b-9 and total IgE).

	• For CF patients only (cohort III-1): o A total count and a quantitative assessment of the following species in sputum will be performed: *Staphylococcus aureus*, *Staphylococcus aureus* MRSA, *Pseudomonas aeruginosa*, *Pseudomonas aeruginosa* MDR, *Haemophilus influenzae*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia complex*, *Aspergillus fumigatus* and *Aspergillus terreus*. o Collection of sputum volume **<u>Study Part IV: OP092915.ALX; cohorts IV-1, IV-2 and IV-3</u>** <u>Primary evaluation criteria:</u> • Safety parameters: physical examination, vital signs, spirometry, oxygen saturation, adverse events, concomitant treatments, ECG, holter and laboratory examinations. <u>Secondary evaluation criteria:</u> • The following parameters will be determined for bLF concentration and SCN^- concentration from blood, sputum and, for SCN^- only, in urine: C_{max}, AUC_{0-t}, T_{max} and $t_{1/2}$. • Concentration of immunological/inflammation parameters will be determined in sputum (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10 and TNF-α) and in blood (anti-bLF Ab, IL-1β, IL-6, IL-8, IL-10, TNF-α, SC5b-9 and total IgE). • For CF and NCFBE patients only (IV-1b, IV-2b and IV-3b): o A total count and a quantitative assessment of the following species in sputum will be performed: *Staphylococcus aureus*, *Staphylococcus aureus* MRSA, *Pseudomonas aeruginosa*, *Pseudomonas aeruginosa* MDR, *Haemophilus influenza*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia complex*, *Aspergillus fumigatus* and *Aspergillus terreus*. o Collection of sputum volume
Inclusion criteria	**<u>Inclusion criteria for healthy volunteers:</u>** 1- Healthy male subject, aged between 18 and 50 years inclusive. 2- Non-smoker subject since at least one week and able not to smoke during the whole study. 3- Subject's Body Mass Index (BMI) between 18 and 30 kg/m^2 inclusive. 4- Subject considered as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination). 5- Subject with Normal Blood Pressure (BP) and Heart Rate (HR) at the screening visit after 10 minutes in supine position: - 95 mmHg ≤ Systolic Blood Pressure (SBP) ≤ 140 mmHg, - 50 mmHg ≤ Diastolic Blood Pressure (DBP) ≤ 90 mmHg, - 45 bpm ≤ HR ≤ 80 bpm, - Or considered NCS by investigator. 6- Subject with Normal ECG recording on a 12-lead ECG at the screening visit: - 120 < PR < 210 ms, - QRS < 120 ms, - QTcF ≤ 430 ms, - No sign of any trouble of sinusal automatism,

	- Or considered NCS by investigator. 7- Subject with laboratory parameters within the normal range of the laboratory (haematological, blood chemistry tests, urinalysis). Individual values out of the normal range can be accepted if judged clinically non relevant by the Investigator. 8- Subject with normal dietary habits. 9- Subject having given a written informed consent prior to selection. 10- Subject covered by Health Insurance System and / or in compliance with the recommendations of National Law in force relating to biomedical research. **<u>Inclusion criteria for cystic fibrosis and non-CF bronchiectasis patients:</u>** 1- Patient suffering from cystic fibrosis defined as a positive sweat chloride test or CF-causing mutations, documented in the patient's medical record or patient suffering from non-CF and non COPD bronchiectasis with a diagnosis confirmed by a chest CT scan demonstrating bronchiectasis in 1 or more lobes documented in the patient's medical record. 2- Patient aged between 18 and 50 years inclusive. 3- Subject's Body Mass Index (BMI) between 18 and 30 kg/m^2 inclusive. 4- Subject in a stable state (No exacerbation or initiation of intravenous antibiotics in the last month). 5- FEV_1 more than or equal to 60% of predicted normal value. 6- Patient microbiological status compatible with the site segregation policy 7- Subject with Normal Blood Pressure (BP) at the screening visit after 10 minutes in supine position according to the investigator. 8- Subject with Normal ECG according to the investigator: - $120 < PR < 210$ ms, - $QRS < 120$ ms, - $QTcF \leq 430$ ms for male, $QTcF \leq 450$ ms for female, - No sign of any trouble of sinusal automatism, - Or considered NCS by investigator. 9- Subject with laboratory parameters within the normal range of the laboratory (haematological, blood chemistry tests, urinalysis). Individual values out of the normal range can be accepted if judged clinically non relevant by the Investigator, or acceptable in the context of the underlying disease. 10- Females of childbearing potential: commitment to consistently and correctly use an highly effective method of birth control for the duration of the trial and for 1 month after the last study drug administration, defined as: - Oral, intravaginal or transdermal combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation; - Oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; - Intrauterine device or intrauterine hormone-releasing system; - Bilateral tubal occlusion; - Or sexual abstinence, considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Females of non-childbearing potential: either surgically sterilized or at least 1 year postmenopausal (amenorrhoea duration at least 12 months).

	Male patients should use a condom with partners of childbearing potential for 90 days after the last study drug administration. 11- Subject having given a written informed consent prior to selection. 12- Subject covered by Health Insurance System and / or in compliance with the recommendations of National Law in force relating to biomedical research. 13- When required by the site, a PCR test for Covid 19 should be performed between D-3 and D-1 and the negative result presented to site staff at D-1 (Inclusion visit).
Non-inclusion criteria	**<u>Non-inclusion criteria for healthy volunteers</u>** 1- Any history or presence of cardiovascular, pulmonary, gastro-intestinal, hepatic, renal, metabolic, haematological, neurologic, psychiatric, systemic or infectious disease. 2- Subject with uncontrolled diabetes. 3- Frequent headaches and / or migraines, recurrent nausea and / or vomiting. 4- Symptomatic hypotension whatever the decrease of blood pressure or asymptomatic postural hypotension defined by a decrease in SBP or DBP equal to or greater than 20 mmHg within two minutes when changing from the supine to the standing position. 5- Blood donation (including in the frame of a clinical trial) within 2 months before administration. 6- General anaesthesia within 3 months before administration. 7- Presence or history of drug hypersensitivity, or any allergic disease. 8- Subject with known bronchial hyper-reactivity to drug inhalation (for Part III and Part IV only). 9- Any known contra-indications to inhaled salbutamol (for Part III and Part IV only). 10- Subject with bronchial hyper-reactivity, defined by a positive response to bronchodilator with FEV1 increase ≥ 200 mL (for Part III and Part IV only). 11- Medical history of reactions to cow's milk proteins. 12- Unable to abstain from intensive muscular effort. 13- Subject who cannot be contacted in case of emergency. 14- Any drug intake (except paracetamol) during the last month prior to the first administration. 15- History or presence of drug or alcohol abuse (alcohol consumption > 40 grams / day). 16- Excessive consumption of beverages with xanthine bases (> 4 cups or glasses / day). 17- Positive Hepatitis B surface (HBs) antigen or anti Hepatitis C Virus (HCV) antibody, or positive results for Human Immunodeficiency Virus (HIV) 1 or 2 tests. 18- Positive results of screening for drugs of abuse. 19- Subject who, in the judgment of the Investigator, is likely to be non-compliant or uncooperative during the study, or unable to cooperate because of a language problem, poor mental development. 20- Subject in the non-inclusion period of a previous study. 21- Subject under administrative or legal supervision. 22- Subject who would exceed the maximum authorized indemnities (according to national applicable regulation) for his/her participation in biomedical research, including the indemnities for the present study

	<u>Non-inclusion criteria for cystic fibrosis and non-CF bronchiectasis patients:</u> 1- Presence of cardiovascular, gastro-intestinal, hepatic, renal, metabolic, haematological, neurologic, psychiatric, systemic or infectious disease other than those related to the underlying disease. 2- Frequent headaches and / or migraines, recurrent nausea and / or vomiting. 3- Symptomatic hypotension whatever the decrease of blood pressure or asymptomatic postural hypotension defined by a decrease in SBP or DBP equal to or greater than 20 mmHg within two minutes when changing from the supine to the standing position. 4- Blood donation (including in the frame of a clinical trial) within 2 months before administration. 5- General anaesthesia within 3 months before administration. 6- History of drug-induced severe hypersensitivity reaction or severe allergic disease. 7- Clinical history of hypersensitivity reaction to cow's milk protein. 8- Unable to abstain from intensive muscular effort. 9- Subject who cannot be contacted in case of emergency. 10- Use of any of the prohibited medications as detailed in the concomitant medication section. 11- Subject with known bronchial hyper-reactivity to drug inhalation. 12- Any known contra-indication to inhaled salbutamol. 13- Subject with bronchial hyper-reactivity, defined by a positive response to bronchodilator with FEV1 increase ≥ 200 mL. 14- Active allergic bronchopulmonary aspergillosis currently treated. 15- Medical history of allergic bronchopulmonary aspergillosis in the past 2 years. 16- History or presence of drug or alcohol abuse (alcohol consumption > 40 grams / day). 17- Excessive consumption of beverages with xanthine bases (> 4 cups or glasses / day). 18- Positive Hepatitis B surface (HBs) antigen or anti Hepatitis C Virus (HCV) antibody, or positive results for Human Immunodeficiency Virus (HIV) 1 or 2 tests; or PCR test positive for Covid 19 performed according to local practice. 19- Positive results of screening for drugs of abuse. 20- Positive pregnancy test or breastfeeding patients. 21- Subject who, in the judgment of the Investigator, is likely to be non-compliant or uncooperative during the study, or unable to cooperate because of a language problem, poor mental development. 22- Subject in the non-inclusion period of a previous study. 23- Subject under administrative or legal supervision. 24- Subject who would exceed the maximum authorized indemnities for his/her participation in biomedical researches (according to national law), including the indemnities for the present study.
Study Duration	<u>Study Part I: OP092815.ALX; cohorts 1; 2 and 3 (Completed)</u> Screening within 21 days prior to the first administration. Hospitalization for 3 days (D-1 morning to D2 morning). End of study visit at D7. Expected duration: approximately 4 weeks for each participating subject

	<u>Study Part II: OP092915.ALX; cohorts 4 and 5 (Completed)</u> Screening within 21 days prior to the first administration. First Hospitalization for 3 days (P1D-1 morning to P1D2). Ambulatory visit at P1D7. P1D7 can occur the same day as P2D-1. Second hospitalisation for 9 days (P2D-1 morning to P2D8 morning) Wash out of at least 7 days between P1D1 and P2D1 End of study visit at P2D14. Expected duration: approximately 6 weeks for each participating subject <u>Study Parts III and IV: OP092915.ALX; cohorts III-1, III-2, III-3 and IV-1, IV-2 and IV-3 (Ongoing)</u> ▪ Screening within 21 days prior to the first administration. ▪ Administrations period: - Either on-site stay for 8 days (D-1 morning to D8 morning) - Or, presence at the site required : o D-1 : on-site visit for eligibility check o D1 and D7: on-site for approximately 13 hours o D2 to D6 : on-site for approximately 9 hours o D8: on-site visit for controls at the end of administration period ▪ End of study visit at D14. Expected duration: approximately 5 weeks for each participating subject/patient.
Statistics	**Safety** <u>Adverse events (for each part)</u> AEs will be coded according to the Medical Dictionary for Regulatory Activity (MedDRA). The non-treatment emergent AEs will be summarised by System Organ Class and Preferred Term for the safety set. The treatment emergent AEs will be summarised by Primary System Organ Class, Preferred Term and dose group (and received dose subgroup for cohort 5 and study parts III and IV if needed) for the safety set. It will consist in the evaluation of the number of AEs and the number of subjects reporting these AEs. <u>Physical examination, ECG and vital signs (for each part)</u> Physical examination, ECGs and vital signs recorded during the study will be individually listed and quantitative parameters will be summarised using descriptive statistics. For vital signs and ECG, values and clinically potentially significant abnormalities will be described for each parameter by dose group (and received dose subgroup for cohort 5 and study parts III and IV if needed) and overall, at screening, inclusion, baseline (D1 pre-dose), each scheduled time point and at the end of the study. Change between the value at baseline and the value at each scheduled time point and the end of study visit will be described for each parameter by dose group (and received dose subgroup for cohort 5 and study parts III and IV if needed) and overall. <u>Laboratory parameters (haematology, biochemistry, urinalysis)</u>

	- Study Part I: Values, position according to laboratory range and clinical assessment will be described for each parameter by dose group and overall, at screening, baseline (D-1), D2 (CRP only) and at the end of the study. Change between the value at baseline and the value at D2 (CRP only) and end of study visit will be described for each parameter by dose group and overall. - Study Part II: Values, position according to laboratory range and clinical assessment will be described for each parameter by dose group (and received dose subgroup for cohort 5 if needed) and overall, at screening, baseline (P1D-1), P1D2 (CRP only), P1D7, P2D-1, P2D4, P2D7 and at the end of the study (P2D14). Values, position according to laboratory range and clinical assessment will be described for each parameter of thyroid function by dose group (and received dose subgroup for cohort 5 if needed) and overall, at baseline (P1D-1) and the end of the study (P2D14). Change between the value at baseline and the post-dose values will be described for each parameter by dose group (and received dose subgroup for cohort 5 if needed) and overall. All quantitative and qualitative urinary test results will be listed, sorted by dose group (and received dose subgroup for cohort 5 if needed). – Study Parts III and IV: Values, position according to laboratory range and clinical assessment will be described for each parameter by dose group (and received dose subgroup if needed) and overall, at screening, baseline (D-1), D4, D7, D8 (CRP only) and at the end of the study (D14). Values, position according to laboratory range and clinical assessment will be described for each parameter of thyroid function by dose group (and received dose subgroup if needed) and overall, at baseline (D-1) and the end of the study (D14), separately for parts III, IVa and IVb. Change between the value at baseline and post-dose values will be described for each parameter by dose group (and received dose subgroup if needed) and overall, separately for parts III, IVa and IVb. All quantitative and qualitative urinary test results will be listed, sorted by dose group (and received dose subgroup if needed), separately for parts III, IVa and IVb. <u>Anti-bLF Ab (blood and sputum)</u> - Study Part I: *Blood:* Value will be described by dose group and overall, at baseline and at the end of the study. Change between the value at baseline and the value at end of study visit will be described by dose group and overall. *Sputum:* Value will be described by dose group and overall, at baseline (D-1) and at the end of the study. Change between the value at baseline and the value at end of study visit will be described by dose group and overall. - Study Part II: *Blood:* Value will be described by dose group (and received dose subgroup for cohort 5if needed) and overall, at baseline (P1D1 predose), P1D7 and at the end of the study. Change between the value at baseline and the value at P1D7 and end of study visit will be described by dose group (and received dose subgroup for cohort 5 if needed) and overall. *Sputum:* Value will be described by dose group (and received dose subgroup for cohort 5 if needed) and overall, at baseline (P1D1), P1D7, P2D-1 and at the end of the study. Change between the value at baseline and the values at P1D7 and at the end of the study will be described by dose group (and received dose subgroup for cohort 5 if needed) and overall. - Study Parts III and IV:

	Blood: Value will be described by dose group (and received dose subgroup if needed) and overall, at baseline (D1 pre-dose) and at the end of the study, separately for parts III, IVa and IVb. Change between the value at baseline and the value at end of study will be described by dose group (and received dose subgroup if needed) and overall, separately for parts III, IVa and IVb. *Sputum:* Value will be described by dose group (and received dose subgroup if needed) and overall, at baseline (D-1) and at the end of the study, separately for parts III, IVa and IVb. Change between the value at baseline and the value at the end of the study will be described by dose group (and received dose subgroup if needed) and overall, separately for parts III, IVa and IVb. <u>Spirometry</u> - Study Part I: Value will be described by dose group and overall, at baseline (D-1), D1 T2h and T8h, D2 and at the end of the study. Change between the value at baseline and the value at D1 T2h and T8h, D2 and end of study visit will be described by dose group and overall. - Study Part II: Value will be described by dose group (and received dose subgroup for cohort 5 if needed) and overall, at baseline, P2D-1, each scheduled time point and at the end of the study. Change between the value at baseline and the value at each scheduled time point and end of study visit will be described by dose group (and received dose subgroup for cohort 5 if needed) and overall. - Study Parts III and IV: Value will be described by dose group (and received dose subgroup if needed) and overall, baseline (D-1), each scheduled time point and at the end of the study. Change between the value at baseline and the value at each scheduled time point and end of study visit will be described by dose group (and received dose subgroup if needed) and overall, separately for parts III, IVa and IVb. <u>Holter</u> - Study Part I: Holter parameters values will be described by dose group and overall at D-1 and D1. - Study Part II: Holter parameters values will be described by dose group (and received dose subgroup for cohort 5 if needed) and overall at P1D-1, P1D1, P2D1, P2D4 and P2D7. - Study Parts III and IV: Holter parameters values will be described by dose group (and received dose subgroup if needed) and overall at D-1, D1, D4 and D7, separately for parts III, IVa and IVb. <u>Oxygen saturation</u> - Study parts III and IV: Value will be described by dose group (and received dose subgroup if needed) and overall, at baseline (D-1), each scheduled time point and at the end of the study, separately for parts III, IVa and IVb. Change between the value at baseline and the value at each scheduled time point and end of study visit will be described by dose group (and received dose subgroup if needed) and overall, separately for parts III, IVa and IVb. **Pharmacokinetics:** Pharmacokinetic analysis will be performed using Kinetica (Version 4.3 - Thermo Electron Corporation - Philadelphia - USA).

	Pharmacokinetic parameters of bLF and SCN^- will be summarized by mean, standard deviation, coefficient of variation, minimum and maximum for each dose level. The pharmacokinetic parameters normalized by the dose will be calculated after each dose (C_{max}/Dose, AUC_t/Dose, AUC_{inf}/Dose, Ae_t/Dose and Ae_{inf}/Dose), mean, standard deviation, coefficient of variation, minimum and maximum for each dose level will be presented. A linear regression analysis versus doses will be also performed for C_{max}, AUC_t, AUC_{inf}, Ae_t and Ae_{inf}. **Pharmacodynamics** <u>Inflammatory markers (blood)</u> - Study Part I: Inflammatory markers values will be described at baseline (D1 predose) D1-T1h, D1-T2h and D2-T24h by dose group and overall for each parameter. Inflammatory markers changes will be described from baseline to D1-T1h, D1-T2h and D2-T24h by dose group and overall for each parameter. - Study Part II: Inflammatory markers values will be described at baseline (P1D1 predose) P1D1-T1h, P1D1-T2h, P1D2-T24h, P2D4 pre-dose, P2D7 (pre-dose, T1h, T2h) and P2D8-T24h by dose group (and received dose subgroup for cohort 5 if needed) and overall for each parameter. Inflammatory markers changes will be described from baseline (P1D1 predose) to P1D1-T1h, P1D1-T2h, P1D2-T24h, P2D4 pre-dose, P2D7 (pre-dose, T1h, T2h) and P2D8-T24h by dose group (and received dose subgroup for cohort 5 if needed) and overall for each parameter - Study Parts III and IV: Inflammatory markers (IL-1β, IL-6, IL-8, IL-10 and TNF-α) values will be described at baseline (D1 pre-dose), D1-T1h, D1-T2h, D4-pre-dose, D7 (pre-dose, T1h, T2h) and D8-T24h by dose group (and received dose subgroup if needed) and overall for each parameter, separately for parts III, IVa and IVb. Inflammatory markers (IL-1β, IL-6, IL-8, IL-10 and TNF-α) changes will be described from baseline (D1 pre-dose) to D1-T1h, D1-T2h, D4- pre-dose, D7 (pre-dose, T1h, T2h) and D8-T24h by dose group (and received dose subgroup if needed) and overall for each parameter, separately for parts III, IVa and IVb. <u>Inflammatory markers (sputum)</u> - Study Part I: Inflammatory markers values will be described at baseline (D-1) and D1-T2h and D2-T24h by dose group and overall for each parameter. Inflammatory markers changes will be described from baseline (D-1) to D1-T2h and D2-T24h by dose group and overall for each parameter. - Study Part II: Inflammatory markers values will be described at baseline (P1D-1), P1D1-T2h, P1D2-T24h, P2D4-pre-dose, P2D7 (pre-dose) and P2D8-T24h by dose group (and received dose subgroup for cohort 5 if needed) and overall for each parameter. Inflammatory markers changes will be described from baseline (P1D-1) to P1D1-T2h, P1D2-T24h, P2D4-pre-dose, P2D7 (pre-dose) and P2D8-T24h by dose group (and received dose subgroup for cohort 5if needed) and overall for each parameter. - Study Parts III and IV: Inflammatory markers (IL-1β, IL-6, IL-8, IL-10 and TNF-α) values will be described at baseline (D-1), D1-T2h, D4-pre-dose, D7 (pre-dose, T2h), D8-T24h by dose group (and received dose subgroup if needed) and overall for each parameter, separately for parts III, IVa and IVb. Inflammatory markers (IL-1β, IL-6, IL-8, IL-10 and TNF-α) changes will be described from baseline (D-1) to D1-T2h, D4-pre-dose, D7 (pre-dose, T2h), D8-T24h by dose group (and received dose subgroup if needed) and overall for each parameter, separately for parts III, IVa and IVb.

	Ig E - Study Part I: Ig E value will be described at baseline (D1 predose) and end of the study (D7) by dose group and overall. Ig E change will be described from baseline (D1 predose) to end of the study (D7) by dose group and overall. - Study Part II: Ig E value will be described at baseline (D1 predose), P1D7, P2D8-T24h and end of the study (P2D14) by dose group (and received dose subgroup for cohort 5 if needed) and overall. Ig E change will be described from baseline (P1D1 predose) to P1D7, P2D8-T24h and end of the study (P2D14) by dose group (and received dose subgroup for cohort 5 if needed) and overall. - Study Parts III and IV: IgE value will be described at baseline (D1 pre-dose), D8-T24h and end of the study (D14) by dose group (and received dose subgroup if needed) and overall, separately for parts III, IVa and IVb. IgE change will be described from baseline (D1 pre-dose), to P2D8-T24h and end of the study (D14) by dose group (and received dose subgroup if needed) and overall, separately for parts III, IVa and IVb. Complement test - Study Part I: Complement test parameters values will be described at baseline (D1 predose), D1 (T25min, T40min, T1h and T2h) by dose group and overall for each parameter. Complement test parameters changes will be described from baseline (D1 predose) to D1 (T25min, T40min, T1h and T2h) by dose group and overall for each parameter. - Study Part II: Complement test parameters values will be described at baseline, P1D1 (T25min, T40min, T1h and T2h) and P2D7 (pre-dose, T25min, T40min, T1h and T2h) by dose group (and received dose subgroup for cohort 5 if needed) and overall for each parameter. Complement test parameters changes will be described from baseline (P1D1 predose) to P1D1 (T25min, T40min, T1h and T2h) and P2D7 (pre-dose, T25min, T40min, T1h and T2h) by dose group (and received dose subgroup for cohort 5 if needed) and overall for each parameter. - Study Parts III and IV: Complement test parameters values will be described at baseline (D1 pre-dose), D1 (T25min, T40min, T1h and T2h) and D7 (pre-dose, T25min, T40min, T1h and T2h) by dose group (and received dose subgroup if needed) and overall for each parameter, separately for parts III, IVa and IVb. Complement test parameters changes will be described from baseline (D1 pre-dose) to D1 (T25min, T40min, T1h and T2h) and D7 (pre-dose, T25min, T40min, T1h and T2h) by dose group (and received dose subgroup if needed) and overall for each parameter, separately for parts III, IVa and IVb. Microbiology analysis (for patients only) A total count and a quantitative assessment of the following species will be performed: *Staphylococcus aureus*, *Staphylococcus aureus* MRSA, *Pseudomonas aeruginosa*, *Pseudomonas aeruginosa* MDR, *Haemophilus influenzae*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex, *Aspergillus fumigatus* and *Aspergillus terreus*. Quantitative values will be described at D-1 and D7T10h by dose group (and received dose subgroup for if needed) and overall for species. Quantitative changes will be described between D-1 and D7T10h by dose group (and received dose subgroup if needed) and overall for each parameter. Volume of sputum (for patients only) Quantitative values will be described at baseline (D-1), D1, D2, D3, D4, D5, D6 and D7 by dose group (and received dose subgroup if needed) and overall. Quantitative changes will be described between baseline and D1, D2, D3, D4,

	D5, D6 and D7 by dose group (and received dose subgroup if needed) and overall. **Sample size**: was based upon empirical considerations corresponding to usual practices in this type of studies. No formal calculation was performed.