Clinical Trial Protocol Synopsis

Protocol Title:

A single-center, double-blind, randomized, placebo-controlled, 3-Part, parallel group, single- and multiple escalating dose, Phase 1 study to investigate safety, tolerability, and pharmacokinetics of inhaled murepavadin in healthy subjects.

Protocol Number: [POL7080-201-01]

Amendment Number: [N/A]

Compound Number: POL7080

Study Phase: Phase 1

Short Title:

Safety, tolerability, and pharmacokinetic of ascending doses of murepavadin inhalation solution in healthy subjects.

Sponsor Name:
Polyphor Ltd
Hegenheimermattweg 125
CH-4123 Allschwil

Legal Registered Address:
Polyphor Deutschland GmbH
Marie-Curie-Str. 8
D-79539 Lörrach

Regulatory Agency Identifier Number(s)
[IND:
EudraCT:
NCT:
WHO:
Other:]

Approval Date:

1. Synopsis

Trial title	A single-center, double-blind, randomized, placebo-controlled, 3-Part, parallel group, single- and multiple escalating dose, Phase 1 study to investigate safety, tolerability, and pharmacokinetics of inhaled murepavadin in healthy subjects.
Trial number	POL7080-201-01
EudraCT number	
Sponsor	Polyphor Ltd Hegenheimermattweg 125 CH-4123 Allschwil
Phase	Phase 1
Trial under IND	☐ yes IND No: ☒ no
FDA "covered trial"	☐ yes ☒ no
No of Trial center(s)/country(ies)§	1 / United Kingdom
Planned trial period **(first enrollment-last subject out)**	FSFV: LSLV:
Trial objectives	Primary: • To investigate the safety, overall and local tolerability of single- (SAD) and multiple (MAD) ascending doses of murepavadin by inhalation in healthy adults. Secondary: • To characterize the systemic and pulmonary pharmacokinetics of murepavadin and its metabolites following inhalation of single- and multiple ascending doses in healthy subjects (plasma, urine, and epithelial lining fluid (ELF). Exploratory: • To explore the possible impact of single- and multiple ascending doses of inhaled murepavadin on the pulmonary microbiome in healthy subjects

	• To assess signs of inflammation in bronchoalveolar lavage fluid (BALF).
Trial design and plan	**Trial design** This study includes three parts: <u>Part A: run-in phase</u> Part A consists in an open-label, non-comparative, 3 sequential, single-ascending MIS dose run-in phase. Two (2) healthy subjects per dose level will be administered 12.5 mg, 25 mg, or 50 mg of MIS. The safety, tolerability (local and overall), and pharmacokinetics (PK) (plasma and urine) will be assessed. After each of the first two dose levels, safety data will be reviewed by the Principal Investigator and the Sponsor. A Safety Monitoring Group (SMG) will review aggregate safety data (no PK data) at the end of Part A. <u>Part B: single ascending dose</u> Part B consists in a double-blind, randomized, placebo-controlled, 3 sequential, single-ascending dose study. Single ascending dose of MIS will be investigated in 3 sequential cohorts of 9 healthy subjects each (7 on MIS and 2 on placebo).Each subject will be randomized to undergo a bronchoalveolar lavage (BAL) at one (1) of the three (3) planned time points. PK of murepavadin and its metabolites will be determined in plasma, urine, and ELF. Sentinel dosing will be used for each Cohort. The first two (2) subjects (1 active:1placebo) in each Cohort will receive either MIS or placebo in parallel, followed by a gap to ensure adequate evaluation of safety and tolerability (and pharmacokinetic data after end of Cohort B2) prior to administering the same dose of MIS/placebo to the remaining subjects within the Cohort. The first two (2) cohorts will be administered 75 mg (B1) and 150 mg (B2) of MIS (or placebo), respectively. After completion of the second cohort (*i.e.*, B2), PK data collected that far (Part A, B1, and B2) will be used to determine the MIS dose (i) expected to result in a systemic exposure (C_{max} and

	AUC_{24h}) not exceeding 25% of the systemic exposure achieved following the intravenous administration of 2.5 mg/kg murepavadin, (ii) and without exceeding 400 mg of MIS. The last dose level tested will be between 150 and 400 mg. The Safety Monitoring Group (SMG) will review blinded safety data after completion of each of the three (3) dose levels. Blinded plasma/ELF PK data will be reviewed by the SMG after completion of B2 (for determination of the dose to be investigated in Cohort B3), and after completion of Cohort B3 (to inform the doses to be evaluated in Part C). <u>Part C: multiple ascending doses</u> Part C will be a double-blind, randomized, placebo-controlled, 2 sequential dose levels, repeated, ascending dose study. Similarly to Part B, sentinel dosing will be used for both cohorts in Part C, *i.e.*, the first two (2) subjects (1:active:1 placebo) in each Cohort will be dosed in parallel, followed by the remaining subjects in the Cohort. Repeated doses of MIS will be investigated in 2 sequential cohorts of 9 healthy subjects each (7 on MIS and 2 on placebo). The two (2) doses evaluated in Part C will be determined after completion of Part A and B. The total treatment duration in these two (2) cohorts will be 7 days, split as follows: • First three (3) days: q.d. administration, followed by 3 days b.i.d. dosing, with the last administration in the morning of Day 7. The MIS dose to be administered to subjects in Cohort C1 will be determined after completion of Part B. The MIS dose to be administered to subjects in Cohort C2 will be determined after the results of Cohort C1 are available. The total daily dose will not exceed 400 mg MIS. Each subject will undergo a BAL at one (1) of the three (3) time points (*i.e.*, 2, 24, or 48 hours after start of the last inhalation in the morning of Day 7. PK profiles of murepavadin and its metabolites in plasma will be obtained after the last dose of study drug (*i.e.*, Day 7); in addition, urine and BALF will be collected for PK.

	Sparse blood sampling will be performed during the course of treatment. The Safety Monitoring Group (SMG) will review blinded safety and plasma/ELF PK data after completion of cohort C1. **Trial plan** The decision to progress to the next dose level will be taken by the SMG: after completion of Part A, following completion of each dose levels in Part B and C. The study will consist of a Screening Visit within 28 to 3 days before first dosing, in which eligibility of the subjects will be assessed. Subjects in Part A will be confined in the clinic from Day -1 to Day 2. Subjects in Part B will be admitted in the clinic on Day -1, and discharged either on Day 2 or Day 3 (the latter for those subjects undergoing a bronchoalveolar lavage (BAL) at 48 hours post-dose. Subjects in Part C will be admitted on Day -1, and discharged either on Day 8 or Day 9, depending on the timing of the BAL the subject is randomized to. All subjects will return to clinic 6 to 9 days after the last dose for a follow-up visit. After the follow-up visit, the subjects enrolled in Part A and B will be discharged from the study. Subjects enrolled in Part C will have an End-of-Study visit 30-35 days after last dosing. Any ongoing adverse event (AE) or conspicuous clinical finding will be followed-up in suitable time intervals, if applicable.
Planned number of subjects	Part A: 2 subjects per dose levels (total n=6): 6 on MIS Part B: 9 subjects per dose level (total n=27): 7 on MIS and 2 on placebo Part C: 9 subjects per dose level (total n=18): 7 on MIS and 2 on placebo In total, 51 healthy subjects in eight (8) dose groups will be enrolled.

Schedule of visits and assessments	See below.
Diagnosis and main inclusion and exclusion criteria	**Diagnosis**: healthy subjects **Inclusion Criteria**: 1. Subject has been informed both verbally and in writing about the objectives of the clinical trial, the methods, the anticipated benefits and potential risks and the discomfort to which he/she may be exposed, and has given written consent to participation in the trial prior to trial start and any trial-related procedure; 2. Healthy male or female volunteer aged between 18 and 60, inclusive; Women of childbearing potential are eligible only if the following applies: • Negative quantitative serum pregnancy test at screening and negative qualitative serum pregnancy test on Day -1 • Agreement to undertake a quantitative serum pregnancy test at the Follow-up visit (Part A, B, and C); • Agreement to use one of the methods of birth control described in the protocol from screening up to at least 30 days after the end of treatment Non-vasectomized men are eligible only if they are willing to practice contraception by using a condom from start of the study and for at least 7 days after end of study treatment; 3. Subject assessed as healthy based on a screening examination including medical history without clinically relevant pathologies, physical examination, vital signs, ECG assessment, pulmonary function testing (FEV_1 must be > 80% of predicted), and clinical laboratory results; 4. Body weight according to a body mass index (BMI) between 18 and 32 kg/m^2 (inclusive), and a body weight between 60 and 95 kg; 5. Glomerular filtration rate estimated by the Chronic Kidney Disease – Epidemiology Collaboration (CKP-EPI) creatinine equation:

	> 80 mL/min/1.73 m^2, and < 160 for males or < 150 mL/min/1.73 m^2 for females; 6. Non-smokers or ex-smokers (including e-cigarette smokers or any other nicotine patches, nicotine chewing gum, inhalers) who had stopped smoking for at least sixty (60) days prior to screening; 7. Ability to inhale in an appropriate manner (Subjects will be trained to inhale from the eFlow® nebulizer device). **Exclusion Criteria**: 1. ECG abnormalities of clinical relevance (*e.g.*, QTcF (QTc corrected using Fridericia's formula) ≥ 450 msec for males or ≥ 460 msec for females; 2. Screening ECG evidence of atrial fibrillation, atrial flutter, complete right or left bundle branch block, Wolff-Parkinson-White syndrome, cardiac pacemaker, or subjects with current or previous history of second or third degree heart block and/or clinically-relevant prolongation of the PR interval as determined by the Investigator; 3. Clinically-significant abnormal ECG: QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement (*e.g.*, indistinct QRS onset, low amplitude T-wave, merged T and U waves, prominebt U waves); 4. Subjects with a resting heart rate < 50 bpm or greater than 90 bpm, systolic blood pressure < 90 mmHg or > 140 mmHg, diastolic blood pressure < 60 mmHg or > 90 mmHg. Measurements are taken after 10 minutes in supine position and repeated after 3 minutes in standing position; 5. Abnormalities in clinical chemical or haematological variables considered medically relevant by the investigator. Values for gamma-glutamyltranspeptidase [gamma-GT], alanine aminotransferase [ALT], aspartate aminotransferase [AST], and serum creatinine should be within normal ranges for inclusion; 6. Proteinuria greater than trace, or hematuria greater than trace, or presence of urinary casts, or epithelial cells outside the reference range;

	7. Positive results in any of the following virology tests: human immunodeficiency virus (HIV) antibodies 1 and 2, hepatitis B surface antigen (HbsAg), and anti-hepatitis C virus antibody; 8. Known local or systemic hypersensitivity to any aerosol, medication or food; 9. Subjects who have a regular alcohol consumption of more than twenty-one (21) units per week for males or more than fourteen (14) units per week for females, with one unit = ½ pint [285 mL) beer or lager, a sixth gill [25 mL] of 40% spirit or one (1) glass [125 mL] of wine, depending on type, or subjects with a significant history of drug or alcohol abuse within the past two (2) years; 10. Positive urine drug screen for cannabinoids, amphetamines (including ecstasy [MDMA]), methamphetamines, opiates, cocaine, benzodiazepines, barbiturates, as well as urinary alcohol and cotinine test; 11. Women who are pregnant or nursing; 12. Participation in another study with any investigational drug or device within ninety (90) days prior to first IMP administration; 13. Blood donation of more than 500 mL within sixty (60) days prior to first IMP, or plasma within thirty (30) days prior to first IMP administration; 14. History of any clinically-relevant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrine, hematologic, neuromuscular (*e.g.*, manifestation of muscle weakness, myasthenia gravis) or allergic disease(s), metabolic disorder, cancer (may have had basal or squamous cell carcinoma of skin or cervix so long as surgically removed or deemed cured by cryotherapy, laser therapy, conization, etc., with stability for the past two (2) years), cirrhosis; 15. Unlikely to comply with clinical study protocol such as uncooperative attitude, inability to return to follow-up visits, and improbability of completing the study, as per investigator judgement; 16. Physical activity within four (4) days prior to the first IMP administration;

	17. Treatment with any known enzyme inducing or inhibiting agents (*e.g.*, grapefruit, St. John's Wort, glucocorticoids, barbiturates, phenothiazines, cimetidine, ketoconazole etc.) within 30 days before administration of IMP or during the trial; 18. Any medication that inhibits active tubular secretion, *e.g.*, probenecid, H2-receptor antagonists, trimethoprim, within 4 weeks prior to first inhalation; 19. Use of any medication (including over-the-counter medication such as herbal products) except allowed concomitant medication, within two (2) weeks before administration of IMP or within < ten (10) times the elimination half-life of the respective drug, or the duration of the pharmacodynamic effect, whatever is longer; 20. Regular consumption of large amounts of xanthine-containing substances (*e.g.*, ≥ 5 cups of coffee per day, tea, cola, chocolate, diet pills, "energy drinks*) and alcohol, or unable to refrain from consumption of xanthine-containing substances and alcohol from 48 hours prior to each entry in the clinic and during the in-house period, or unable to limit consumption of xanthine-containing substances and alcohol during the remainder of the study (while not in the clinic) (*i.e.*, not to exceed 5 cups of coffee per day, tea, cola, chocolate, diet pills, "energy drinks" and not o exceed an average of 2 units of alcohol per day; 21. Vegetarian diet or other peculiar dietary habits, which would preclude the subject's acceptance of standardized meals; 22. Planned donation of germ cells, blood, organs, bone marrow during the course of the trial or within four (4) weeks thereafter; 23. Contraindications to bronchoalveolar lavage or suspected intolerability to medications necessary for bronchoscopy; 24. Subject has history of lung transplantation; 25. Subject has history of any upper or lower pulmonary infection within four (4) weeks prior to first IMP administration; 26. Insufficient venous access for PK sampling;

	27. Vulnerable subjects (*e.g.*, subjects who are imprisoned or lawfully kept in a corrective institution); 28. Subjects who are employees at study site, or spouse / partner or relative of the investigator or sub-investigator. 29. Subjects testing positive for active Covid-19.
Investigational Medicinal Product (s): dose/mode of administration/ dosing schedule	The investigational medicinal product (IMP) will consist of two solutions: • sterile solution of murepavadin at pH4 (50 mg/L net peptide) • Sterile solution of phosphate buffer and NaCl for the neutralization of the acidic murepavadin solution. The 2 solutions will be mixed (1:1). The resulting solution (8 mL, 25 mg/mL net peptide), will have a pH 6.5-7.5 with an osmolality of 300-500 mOsm. Further dilutions (NaCl 0.9%) will be used to obtain the different doses to be delivered. The final solution will be delivered through a nebulizer handset based on eFlow® technology (PARI Pharma GmbH). **Table 1. Final concentration** Dose Level / Murepavadin (mg) / Solution (mL) / Concentration (mg/mL) 1 / 12.5 / 8 / 1.56 2 / 25 / 8 / 3.12 3 / 50 / 8 / 6.25 4 / 75 / 8 / 9.38 5 / 150 / 8 / 18.75 6 / 400 / 2 x 8 / 25 Mode of administration: oral inhalation Batch No.: Refer to pharmaceutical documentation
Reference therapy(ies): dose/mode of administration/dosing schedule	The placebo nebulizer solution will be provided as 2 solutions to be mixed; the resulting solution will then be diluted in 0.9% NaCl to match the frequency and volume of one of the MIS dosing regimen.

	Administration will be using a nebulizer handset based on eFlow® technology (PARI Pharma GmbH).
Planned treatment duration per subject	Part A and B: one (1) day (single dose) Part C: seven (7) days (repeated doses) The duration of inhalation is estimated to be between 15 and 20 min (up to 40 min for doses > 200 mg).
Primary endpoint (s)	<u>Safety:</u> • Occurrence, seriousness, and severity of adverse events (AEs) • Physical examination (PE) • Vital signs (blood pressure, pulse, respiration rate, body temperature) • Clinical laboratory investigation (clinical chemistry [incl. creatinine, cystatin C], haematology, urinalysis (semi-quantitative dipstick, α-1 microglobulin, β-2 microglobulin, albumin-to-creatinine ratio, urine microscopy on all samples, urinary biomarkers indicative of kidney function injury [KIM-1, and NAG]) • Spirometry at pre-dose, 10, 30, and 60 minutes, and 2, 4, and 8 hours after end of inhalation to evaluate for provoked bronchospasm (after each dosing) • Pulse oximetry • Local tolerability: evaluation of local irritation of the nose or pharynx (visual inspection) and evaluation of bronchospasm by symptoms such as dyspnea, wheezing, chest tightness, cough by auscultation • Electrocardiograms (ECGs).
Secondary / exploratory endpoint(s)	• microbiota (expectorated sputum) • BALF cell count for assessing inflammation.
Pharmacokinetics	<u>Plasma (parent and metabolites):</u> Part A and B: Day 1: blood samples will be collected before dosing, at the end of the inhalation (1 to 8 min), at 0.167 (10 min), 0.25 (15 min), 0.5 (30 min), 1, 2, 4, 6, 8, 12, 15, and 24 hours after start of inhalation, (in Part B, 48 hours after start of inhalation in subjects having a BAL sampling at that timepoint). Part C: last dosing on Day 7 (same timepoints as above).

	• Day 1 (Part A and Part B): C_{max}, C_{max}/D, t_{max}, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}inf}/D$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}tau}/D$, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}24h}/D$, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}48h}/D$ [Part B], $AUC_{0\text{-}last}$, $AUC_{0\text{-}last}/D$, AUC_{ext}, $t_{½}$, t_{last}, CL, V_z. • Part C (Day 7): C_{max}, C_{max}/D, $C_{ss,av}$, $C_{ss,av}/D$, $AUC_{0\text{-}tau,}$ $AUC_{0\text{-}tau}/D$, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}24h}/D$, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}48h}/D$, $t_{½}$, CL, V_{ss}. The plasma PK parameters of murepavadin and its metabolites will be derived by non-compartmental analysis of the plasma concentration-time profiles. Part C: A trough sample will be collected prior to dosing on Day 1, Day 2, Day 3; on Day 4, Day 5, and Day 6, prior to each dosing. <u>Urine (parent only):</u> Day 1 on Part A, B, and last dosing on Day 7 in Part C: • $A_{e(t1\text{-}t2)}$, A_e, CL_R, f_e. Amount of murepavadin excreted in urine during the following urine sampling intervals: [0-4h], [4-8h], [8-12 h], [12-24] hours after start of dosing, and [24-48] hours after start of dosing for subjects having a BAL procedure at that timepoint. The amount of murepavadin excreted in the urine during a particular sampling interval will be calculated from the drug concentration in the urine sample and the volume of the respective collection interval. <u>BALF (parent and metabolites):</u> Day 1 (Part B), and last dosing on Day 7 in (Part C): 2 hours, 24 hours, 48 hours after the start of dosing. Urea-matched ELF concentrations will be used to determine the ratio of murepavadin and metabolites concentrations ELF/plasma (free and total). Additional PK parameters may be calculated, if deemed appropriate.
Committees & Stopping rules	A Safety Monitoring Group (SMG), which will consist of specialists of the study site, representatives of the sponsor, and an independent expert, will be appointed. The tasks, procedures, and responsibilities of the SMG will be described in a separate SMG Charter. The decision to progress to the next Study Part or to the next dose level, respectively, will be taken by the

	SMG after all subjects on the previous dose level completed the follow-up visit. A double quality-checked summary of the key safety and tolerability results will be issued by the study site after each dose group. The key results listings of the safety, tolerability, and pharmacokinetic data will be thoroughly evaluated by the SMG. The decision to proceed to the next dose level will be taken unanimously by the SMG. The decision will be documented. The SMG will receive and evaluate blinded data. The SMG Chair may request unblinding of a particular subject's treatment assignment or of an entire cohort. The SMG will review safety data at the end of Part A and after each cohort of Part B and C. Plasma PK data will be reviewed after completion of Cohort B2, B3, and C1. ELF PK data will be reviewed after completion of Cohort B2, B3, and C1. Safety data will include 9 days of follow-up after the dose administered for SAD cohort subjects (*i.e*., Part A and B), and 7 days after the last dose administered for MAD (*i.e*., Part C) cohort subjects. Initiation of the first MAD dose cohort (*i.e*., C1) will be based on the determination by the SMG that an adequate safety and pharmacokinetic profile has been demonstrated in the Part A and B cohorts. Similarly, the progress from the first MAD cohort to the second one (*i.e*., C1 to C2) will be initiated based on the determination by the SMG that an adequate safety and pharmacokinetic profile is demonstrated in the first MAD cohort. Lastly, the SMG may review safety data on an *ad hoc* basis. The type of adverse event (AE) that would trigger such an *ad hoc* SMG review would be documented in the data safety monitoring plan. There will be an estimated 8--day window between dose levels when safety data only will be reviewed by the SMG. Interim PK parameters (Part B and C) reviewed by the SMG during the course of the study will be generated by the Sponsor's designated pharmacokineticist. **Study withdrawal** • A subject will have the right to withdraw from the study at any time for any reason

	• A subject will be discontinued from the study by the Investigator if unacceptable toxicity or withdrawal of consent occurs • Subjects withdrawn from the Part A and B (SAD) cohorts should have all assessments conducted at the Follow-up visit at the time of withdrawal • Subjects withdrawn from Part C (MAD) cohorts should have all assessments conducted at the Follow-up, as well as at the End-of-Study visit. **Stopping rules for individual subjects** <u>Part A and B (SAD):</u> • Any SAE suspected of being related to study drug • Any Grade ≥ 2 AE suspected of being related to study drug • Any possibly drug-related significant non-serious adverse event, which in the opinion of the investigator warrants discontinuation of the inhalation procedure for that subject, *e.g.*, a decrease in absolute FEV_1 volume of ≥ 15% from pre-dose value following study drug administration • Unacceptable toxicity considered by the Investigator to be related to study drug treatment • If at any time the subject fails to follow the requirements of the protocol • The subject withdraws consent. Subjects may withdraw from the study at any time without repercussion to their treatment or affiliation with their healthcare providers Further safety-related stopping criteria on the individual subject level are not applicable to Part A and B, as each subject will receive one (1) dose only. The serial safety measurements and pharmacokinetic assessments should always be completed according to protocol, if the subject did not withdraw consent. <u>Part C (MAD):</u> • Any SAE suspected of being related to study drug • Any Grade ≥ 2 AE suspected of being related to study drug • Any possibly drug-related significant non-serious adverse event, which in the opinion of the investigator warrants discontinuation of the inhalation procedure for that subject, *e.g.*, a cumulative decrease in absolute FEV_1 volume of

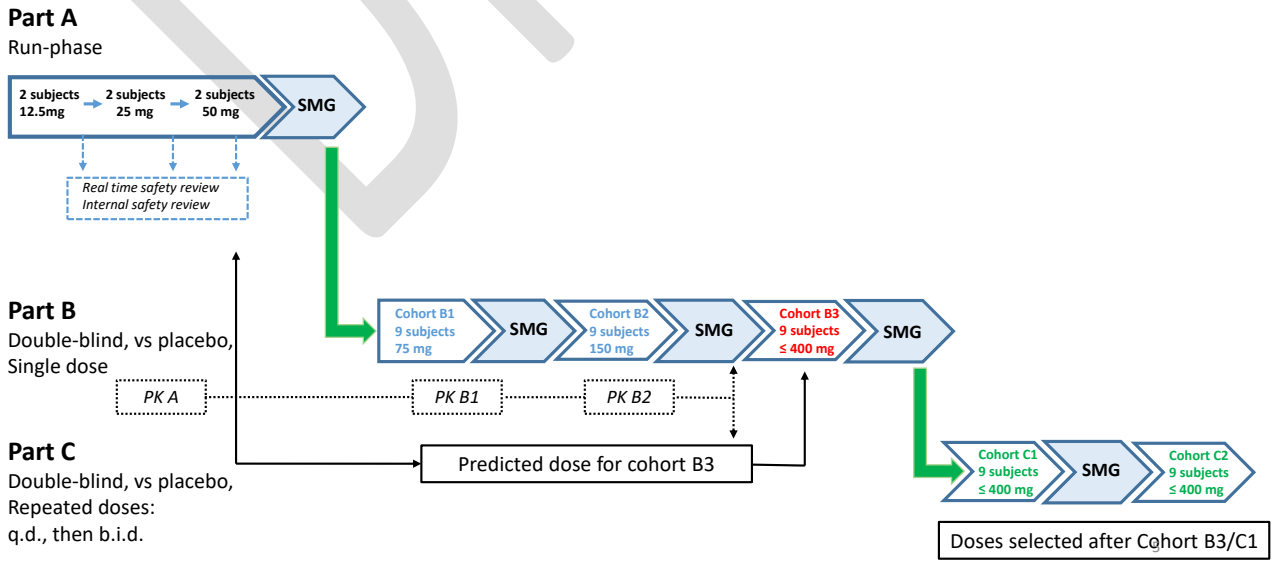
	≥ 20% from pre-dose value following study drug administration • Unacceptable toxicity considered by the Investigator to be related to study drug treatment • Further treatment is deemed to be unsafe in the Investigator's clinical judgment. The decision to discontinue a subject may also result from any clinically significant alteration in any clinical or laboratory finding • If at any time the subject fails to follow the requirements of the protocol • The subject withdraws consent. Subjects may withdraw from the study at any time without repercussion to their treatment or affiliation with their healthcare providers The serial safety measurements and pharmacokinetic assessments should always be completed according to protocol, if the subject did not withdraw consent **Cohort Stopping Criteria** • An intolerable AE is experienced, or • ≥ 2 subjects on active compound and no placebo subject in the same cohort experience a related clinically-significant alteration in any of the parameters monitored to assess safety and tolerability (e.g., ≥Grade 2 event in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0). **Termination of the study** • New information or other evaluation regarding the safety of the study drug that indicates a significant change in the known risk/benefit profile of MIS, such that the risk is no longer acceptable for subjects participating in the study • Significant violation of Good Clinical Practicwe (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety • Subjects in > one (1) cohort have met Cohort Stopping Criteria. **Subject Replacements** Subjects who discontinue the study after having inhaled the IMP are considered dropouts. Drop-outs

	will be replaced after consultation with the Sponsor. Replacement subjects will receive the same treatment as the subjects they replace.
Blinding	In Part B and C, study drug will be administered in a double-blind fashion. Study drug and placebo are both clear, colorless, and odorless aqueous solutions. Subjects, Investigators and study site staff will be blinded to treatment assignment.
Randomization	Part B and C: subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for randomization. Eligible subjects will be randomized on Day -1, utilizing the randomization schedule generated by the designated unblinded statistician. In addition, each subject will be randomized to one (1) of the three (3) timepoints scheduled for a BAL procedure.
Analysis of populations	Safety analysis set: all subjects who receive any amount of study drug. All summaries of safety data will be conducted in the Safety analysis set. Subjects will be analyzed according to the actual treatment received. Pharmacokinetic (PK) analysis set: all subjects who received at least one (1 dose of MIS/placebo and who have at least one (1) valid PK parameter determined. All summaries of PK data as well as PK data from the ELF compartment will be conducted in the PK analysis set. Subjects will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data is unavailable or incomplete, which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion; all decisions on exclusions from the analysis will be made prior to database closure. Demographic data will be summarized in the safety and PK analysis sets.
Statistical methods (includes sample size calculation)	The sample size of this study is based on empirical considerations. No formal statistical hypothesis has been set for this study. No inferential testing will be performed.

	Baseline safety and exploratory endpoints will be summarized descriptively for each dose level separately. Placebo subjects data will be pooled across dose levels within the same Part. In general, categorical data will be summarized with number of missing values, frequencies and percentages, while continuous data will be reported using number of subjects, number of missing values, mean, standard deviation (SD), minimum, median, and maximum. Minimum and maximum values will be provided with the same level of accuracy as raw data. **Safety and tolerability parameters:** Adverse events will be tabulated and summarized according to the current version of Medical Dictionary for Regulatory Activities (MedDRA Version 22.0 or later). Subjects with at least one (1) AE (adverse event) / one TEAE (treatment-emergent adverse event) will be listed.The number of subjects and the number of TEAEs will be tabulated by system organ class (SOC) and by preferred term. TEAEs will also be tabulated versus worst severity and worst relationship to treatment. Subjects with serious adverse events (SAEs) including those leading to death will be likewise summarized. Listings of subjects with SAEs, deaths, AEs leading to discontinuation, and individual narrative summaries for these cases will be produced. Adverse Events of Special Interest (AESI) will be recorded and tabulated as described in the protocol. All vital signs, hematology, blood chemistry, spirometry, urinalysis, pulse oximetry, physical examination, and ECG data will be listed by subject. All values outside the normal reference ranges and clinically significant abnormal values will be flagged in this listing. In addition, all subjects with clinically significant abnormal values will be listed in a separate listing. The number of subjects with at least one (1) clinically significant abnormal value will be tabulated. For ECG data, qualitative results will also be listed by time windows. Number of subjects who showed local irritation of the nose or pharynx or bronchospasm by clinical symptoms such as dyspnoea, wheezing, chest tightness, hypoxia, cough, as well as lung function

	tests (FVC, FEV_1, FEF_{25-75}) and respiratory inflammation biomarkers post dosing will be computed and analyzed with descriptive statistics. **Pharmacokinetic parameters:** Plasma concentrations of murepavadin (and metabolites) will be summarized by dose level and time point. Summary statistics for AUC, C_{max}, t_{max}, $t_{1/2}$, and dose-normalized AUC and C_{max} will be presented by dose level; they will consist of descriptive statistics, *e.g.*, arithmetic mean, median, SD, minimum and maximum, geometric mean and coefficient of variation of geometric mean. Also, plasma concentration graphs showing individual as well as arithmetic mean concentration curves for all doses will be included for AUC and C_{max}. Summaries will be grouped by cohort or dose or treatment and time of assessment. Dose proportionality may be explored using analysis of variance (ANOVA) on log-transformed and dose-normalized C_{max} and AUC parameters, if there are sufficient data to support the analysis. Additionally, the power approach could be used to investigate for dose proportionality. Any *p* values that will be calculated according to the analysis plan will be interpreted in view of the exploratory nature of the study.

2. Schema



3. Schedule of Activities (SoA)

3.1 Part A

Procedures	**Screening**	**Residential Period**[a]			**Follow-up**[b]
		Check-in		**Discharge**	
Day	**-28 to D-3**	**-1**	**1**	**2**	**6-9**
Written informed consent	X				
Admission		X			X
Demographics, body height / weight, BMI	X				
Medical history	X	X			
Prior & concomitant medications	←==========	==========	==========	==========	==========→
Physical examination	X	X		(X)	X
Clinical laboratory (haematology, chemistry, CPK-EPI)	X	X	X[c]	X	X
Pulse oximetry	X		X[d]	X	X
Inhalation training	X	X			
Hepatitis- & human-immunodeficiency virus serology	X				
Drugs screen[e] and urine alcohol test	X	X			
Pregnancy test, FSH[f]	X	X			X
Eligibility review	X	(X)[g]			
Vital signs[h]	X		X	X	X
12-led resting ECG[i]	X		X	X	X
Spirometry[j]	X		X	X[k]	X
Murepavadin dosing by inhalation			X		
Urinalysis (including microscopy)l	X	X	X	X	X
Urine for renal safety biomarkers[m]			X	X	X
Urine for Pharmacokinetics[n]			←==========	==========→	
Expectorated sputum for microbiota			X[o]		X[o]
Blood for Pharmacokinetics			X[p]	X[q]	
Adverse events	←==========	==========	==========	==========	==========→
Overall tolerability[r]				X	

[a] Subjects are admitted to the Investigational Site on Day -1 (approximately 14 hours prior to study drug administration) for eligibility checks and baseline assessments and are discharged on Day 2 following completion of scheduled assessments.

[b] For subjects who withdraw prematurely from the study, the follow-up visit will occur whenever they leave the study.
[c] Day 1: to be performed 6 hours after start of inhalation.
[d] Pulse oximetry; on Day 1: pre-dose, 10, 30, and 60 minutes, and 2, 4, 8, 12 hours after end of inhalation.
[e] Drug screen tests include: cotinine test, alcohol test cannabinoids, amphetamines (including ecstasy [MDMA]), methamphetamines, opiates, cocaine, benzodiazepines, barbiturates.
[f] All female subjects: serum pregnancy test at screening (quantitative test), Day -1 (qualitative test); quantitative serum test at follow-up visit. FSH: at screening only.
[g]: Re-check of those in-/ex-clusion criteria that can be reasonably evaluated after the subject's admission in the evening of Day -1. More specifically, the investigator will make sure the subject has no acute infectious disease or any other alarming clinical symptoms.
[h] Vital signs: blood pressure, pulse, respiratory rate, body temperature. Blood pressure measurements will first be performed after 10 minutes in supine position, and repeated after 3 minutes in standing position. On Day 1, blood pressure, pulse, and respiratory rate will be measured pre-dose, 1, 2, 4, 8, and 24 hours after end of inhalation.
[i]. 12-lead resting ECG: three consecutive measurements within a 5-minute interval. On day 1: pre-dose, and 6 hours after start of inhalation. Day 2: any time
[j] Spirometry: FEV_1, FVC, and FEF_{25-75}. On Day 1: pre-dose, 10, 30, and 60 minutes, and 2, 4, 8, 12 hours after end of inhalation.
[k] Spirometry: 24 hours post-dose; includes FEV_1, FVC, and FEF_{25-75}.
[l] Urinalysis: dipstick, microscopy. On Day 1: spot sample from the pre-dose [-2h to 0h] urine collection, and spot urine sample from the [8-12h] after start of inhalation PK urine collection, and spot urine sample from the void closest to the 24 hour post start of inhalation, as part of the [12-24h] urine PK collection. Screening, Day -1, and Follow-up: random sample, preferably first morning void.
[m] Renal safety biomarkers: α-1 microglobulin, β-2 microglobulin, albumin-to-creatinine ratio. KIM-1, and NAG: on Day 1: spot sample from the pre-dose [-2h to 0h] urine collection, then spot urine sample from the [8-12h], and from the void closest to the 24-hour post start of inhalation, as part of the [12-24h] urine PK urine collection. Screening, and Follow-up visits: random sample, preferably first morning void.
[n] Urine for Pharmacokinetics (parent drug only): on Day 1: pre-dose [-2 to 0h], [0-4h], [4-8h], [8-12h], [12-24h] after start of dosing.
[o] Expectorated sputum for microbiota: on Day 1: pre-dose and Follow-up visit.
[p] Blood sample for pharmacokinetics (parent drug & metabolites): within 30 minutes prior to inhalation, 1 to 8 minutes after end of inhalation, 10, 30, 60 minutes, and 2, 4, 6, 8, 12, and 15 hours after start of inhalation.
[q] Blood sample for pharmacokinetics (parent drug and metabolites): 24 hours after start of inhalation.
[r] Overall tolerability: question subject whether dosing was well accepted.

3.2 Part B

Procedures	**Screening**	**Residential Period[a]**				**Follow-up[b]**
		Check-in		**Discharge[b]**		
Day	**-21 to D-3**	**-1**	**1**	**2**	**3**	**6-9**
Written informed consent	X					
Admission		X				X
Demographics, body height /weight, BMI	X					
Medical history	X	X				
Prior & concomitant medications	←==========→					
Physical examination	X	X		X	(X)	X
Clinical laboratory (haematology, chemistry, CPK-EPI)	X	X	X[dc]	X[d]	(X)	X
Pulse oximetry	X		X[d]	X	(X)	X
Inhalation training	X	X				
Hepatitis- & human-immunodeficiency virus serology	X					
Drugs screen[e] and urine alcohol test	X	X				
Pregnancy test, FSH[f]	X	X				X
Eligibility review	X	(X)[g]				
Randomization		X				
Vital signs[h]	X		X	X	(X)	X
12-led resting ECG[i]	X		X	X	(X)	X
Spirometry[j]	X		X	X[k]	(X)	X
Murepavadin / placebo dosing by inhalation	X		X			
Urinalysis (including microscopy)[l]	X	X	X	X	(X)	X
Urine for renal safety biomarkers[m]			X	X	(X)	X
Urine for Pharmacokinetics[n]			←==========→		(X)	
Expectorated sputum for microbiota			X[o]			X[o]
BAL for Pharmacokinetics and differential cell count[p]			X	X	(X)	
Blood for Pharmacokinetics			X[q]	X[q]	(X)	
Adverse events	←==========→					

Procedures	Screening	Residential Period[a]				Follow-up[b]
		Check-in		Discharge[b]		
Day	-21 to D-3	-1	1	2	3	6-9
Overall tolerability[r]				X	(X)	

[a] Subjects are admitted to the Investigational Site on Day -1 (approximately 14 hours prior to study drug administration) for eligibility checks and baseline assessments and are discharged either on Day 2 (or Day 3 for those with BAL performed 48 hours after start of inhalation) following completion of scheduled assessments.
[b] For subjects who withdraw prematurely from the study, the follow-up visit will occur whenever they leave the study.
[c] Day 1: to be performed 2 hours after start of inhalation (only for those subjects undergoing their BAL procedure at the 2-hour timepoint), 6 hours after start of inhalation in all subjects. On Day 2: 24 hours after start of inhalation in all subjects (must be done concomitantly to BAL procedure for those subjects randomized the the 24-hour BAL procedure). Day 3 (only for subjects randomized to the 48-hour BAL procedure):48 hours after start of inhalation, concomitantly to the BAL procedure. Urea to be determined in all blood samples.
[d] Pulse oximetry; on Day 1: pre-dose, 10, 30, 60 minutes, and 2, 4, 8, 12 hours after end of inhalation. To be performed prior to BAL if BAL is to be performed at the same timepoint.
[e] Drug screen tests include: cotinine test, cannabinoids, amphetamines (including ecstasy [MDMA]), methamphetamines, opiates, cocaine, benzodiazepines, barbiturates.
[f] All female subjects: quantitative serum pregnancy test at screening; qualitative serum pregnancy test on Day -1; quantitative serum pregnancy test at Follow-up visit. FSH: at screening only.
[g] Re-check of those in-/ex-clusion criteria that can be reasonably evaluated after the subject's admission in the evening of Day -1. More specifically, the investigator will make sure the subject has no acute infectious disease or any other alarming clinical symptoms.
[h] Vital signs: blood pressure, pulse, respiratory rate, body temperature. Blood pressure measurements will first be performed after 10 minutes in supine position, and repeated after 3 minutes in standing position. On Day 1, blood pressure, pulse, and respiratory rate will be measured pre-dose, 1, 2, 4, 8, and 24 hours after end of inhalation.
[i] 12-lead resting ECG: three consecutive measurements within a 5-minute interval. On day 1: pre-dose, and 6 hours after start of inhalation. On Day 2, any time.
[j] Spirometry: FEV_1, FVC, and FEF_{25-75}. On Day 1: pre-dose, 10, 30, and 60 minutes, and 2, 4, 8, 12 hours after end of inhalation. To be performed prior to BAL if the BAL assessment falls on the same timepoint.
[k] Spirometry: 24 hours post-dose; includes FEV_1, FVC, and FEF_{25-75}.
[l] Urinalysis: dipstick, microscopy: on Day 1: on Day 1: spot sample from the pre-dose [-2h to 0h] urine collection, and spot urine sample from the [8-12h] after start of inhalation pooled urine PK collection, and void closest to 24-hour void collected as part of the [12-24h] urine PK collection (Day 2). Subjects with 48-hour BAL procedure: spot urine sample from the [24-48h] post start of inhalation urine PK collection. Screening (urinalysis only), Day -1 (urinalysis only), and Follow-up (urinalysis and renal safety biomarkers) : spot urine sample, preferably first morning void.
[m] Urine safety biomarkers: α-1 microglobulin, β-2 microglobulin, albumin-to-creatinine ratio. KIM-1, and NAG: spot sample from the pre-dose [-2h to 0h] urine collection, then spot urine sample from the [8-12h] after start of inhalation pooled urine PK collection, and void closest to 24-hour void collected as part of the [12-24h] urine PK collection (Day 2). Subjects with the 48-hour BAL procedure: spot urine sample from the [24-48h] post start of inhalation urine PK collection. Follow-up: spot urine sample, preferably first morning void.
[n] Urine for Pharmacokinetics (parent drug only): on Day 1: pre-dose [-2 to 0h], [0-4h], [4-8h], [8-12h], [12-24h] after start of inhalation. Subjects with 48-hour BAL procedure: [24-48h] after start of inhalation.
[o] Expectorated sputum: on Day 1: pre-dose, and Follow-up visit.

[p] BAL for Pharmacokinetics (parent drug & metabolites) and differential cell count: either 2, 24, or 48 hours after start of inhalation. One BAL per subject. BAL sampling process to be started after completion of other assessments scheduled for the same timepoint. Urea will be determined on the BAL sample. Differential cell count includes macrophage, lymphocyte, neutrophil, and eosinophil cell counts. Subjects will be fasted for > 4 hours for solid food and > 2 hours for clear fluids.

[q] Blood sample for pharmacokinetics (parent drug & metabolites): within 30 minutes prior to inhalation, 1 to 8 minutes after end of inhalation, 10, 30, 60 minutes, and 2, 4, 6, 8, 12, 15, and 24 hours after start of inhalation. For subjects with 48-hour BAL procedure: sample at 48 hours after start of inhalation.

[r] Overall tolerability: question subject whether dosing was well accepted.

3.3 Part C

Procedure	**Screening**	**Residential Period**[a]							**Follow-up**[c]	**End-of-Study**[b]
							Discharge[b]			
Study day	**D-21 to D-3**	**D-1**	**D1**	**D2-3**	**D4-6**	**D7**	**D8**	**D9**	**D13-16**	**D37-42**[c]
Written informed consent obtained	X									
Admission		X							X	
Demographics / Body height / weight, BMI	X									
Medical history	X	X								
Prior and concomitant medication	←==========→									
Physical examination[c]	X	X			X		X	(X)	X	
Clinical laboratory (haematology, clinical chemistry, CPK-EPI)[d]	X	X		X	X	X[e]	X	(X)	X	(X)
Pulse oximetry[e]	X		X	X	X	X	X	(X)	X	
Inhalation training	X	X								
Reinforcement of correct inhalation procedure			X[f]		X[f]					
Hepatitis-/ human immunodeficiency virus serology	X									
Drugs screen[g] and urine alcohol test	X	X								
Pregnancy test, FSH[h]	X	X							X	
Eligibility review	X	(X)[i]	X							
Randomization		X								
Vital signs (blood pressure, pulse, respiratory rate, body temperature)[j]	X		X	X	X	X	X	(X)	X	
12-lead resting ECG[k]	X		X	X	X	X	X	(X)	X	
Spirometry[l]	X		X	X	X	X	X	(X)	X	

Procedure	Screening	Residential Period[a]							Follow-up[c]	End-of-Study[b]
							Discharge[b]			
Study day	**D-21 to D-3**	**D-1**	**D1**	**D2-3**	**D4-6**	**D7**	**D8**	**D9**	**D13-16**	**D37-42[c]**
Murepavadin / placebo by inhalation[m]			←==========→							
Urinalysis (including microscopy)[n]	X	X	X	X	X	X	X	(X)	X	
Urine for renal safety biomarkers[o]			X	X	X	X	X	(X)	X	
Urine for pharmacokinetics[p]			X			←====→		(X)		
Expectorated sputum for microbiota[q]			X		X	X	X	(X)	X	
BAL for pharmacokinetics and differential cell count[r]						←=====→		(X)		
Blood for pharmacokinetics[s]			X	X	X	X	←======→			
Adverse events	←==========→									
Overall tolerability[t]							X	(X)		X

[a] Subjects are admitted to the Investigational Site on Day -1 (approximately 14 hours prior to study drug administration) for eligibility checks and baseline assessments and are discharged either on Day 8 or Day 9 (for those with BAL performed 48 hours after start of the last dosing) following completion of scheduled assessments. End-of-Study visit can be conducted by phone.

[b] For subjects who withdraw prematurely from the study, the Follow-up and End-of-Study visit will occur whenever they leave the study.

[c] Physical examination: pre-dose on Day 1, 4, 8 (or 9).

[d] Safety lab: Day 2 to 7: prior to the 1st daily inhalation. A blood sample will be taken concomitantly to the BAL procedures (2, or 24, or 48 hours after start of the last inhalation on Day 7) for determination of plasma urea. Day 8 (for those subjects undergoing the 24-hour BAL procedure, the blood sample will be taken concomitantly to the BAL procedure) or 9 (subjects with the 48-hour BAL procedure).

[e] Pulse oximetry; on Day 1: prior to start of inhalation, 10, 30, and 60 minutes, and 2, 4, 8, 12 hours after end of inhalation. Day 2 and 3: pre-dose, 10, 30, and 60 minutes after end of inhalation. Day 4 to 7: pre-dose and 10, 30, 60 minutes after end of each inhalation. On Day 7, oximetry is to be performed prior to BAL if BAL is to be performed at the same timepoint.

[f] Reinforcement of correct inhalation procedure: pre-dose

[g] Drug screen tests include: cotinine test, cannabinoids, amphetamines (including ecstasy [MDMA]), methamphetamines, opiates, cocaine, benzodiazepines, barbiturates.

[h] All female subjects: quantitative serum pregnancy test at screening; qualitative serum pregnancy test on Day -1; quantitative serum pregnancy at Follow-up visit. FSH: at screening only

[i]: Re-check of those in-/ex-clusion criteria that can be reasonably evaluated after the subject's admission in the evening of Day -1. More specifically, the investigator will make sure the subject has no acute infectious disease or any other alarming clinical symptoms.

[j] Vital signs: blood pressure, pulse, respiratory rate, body temperature. Blood pressure measurements will first be performed after 10 minutes in supine position, and then repeated after 3 minutes in standing position. On Day 1 to 3, blood pressure, pulse rate, and respiratory rate will be performed pre-dose, 1, 2 4, 8, and 12 hours after end of inhalation. On Day 4 to 7: blood pressure, pulse rate, and respiratory rate: pre-dose and 1 hour after the end of the 1st daily inhalation.

[k] 12-lead resting ECG (three consecutive measurements within a 5-minute interval); on Day 1: prior to 1st inhalation and 6 hours after start of inhalation; Day 2, 3, 4, 6, 7, 8 (9): 6 hours after start of 1st daily inhalation. On Day 5: pre-dose and 6 hours after start of the 1st daily inhalation.

[l] Spirometry: FEV_1, FVC, and FEF_{25-75}. On Day 1: pre-dose, 10, 30, 60 minutes, and 3, 8 hours after end of the inhalation. All other days: prior to dosing, and 30 and 60 minutes after end of inhalation.

[m] Murepavadin administration: q.d. on Day 1 to 3; b.i.d. from Day 4 to Day 6, and last dosing is in the morning on Day 7.

[n] Urinalysis: dipstick, microscopy: On Day 1: spot sample from the pre-dose [-2h to 0h] urine collection, and spot urine [8-12h] after start of inhalation.. Day 7: spot urine sample pre-dose, spot urine sample from the [8-12h] urine PK collection sample, and void closest to the 24 hour void collected as part of the [12-24h] urine PK collection (Day 8). For subjects with the 48-hour BAL procedure: spot urine closest to the 48-hour void collected as part of the [24-48h] urine PK collection (Day 9). Other days: random sample, preferably first morning void.

[o] Urine safety biomarkers: α-1 microglobulin, β-2 microglobulin, albumin-to-creatinine ratio. KIM-1, and NAG: on Day 1: spot sample from the pre-dose [-2h to 0h] urine collection, and spot urine [8-12h] after start of inhalation. Day 7: spot urine sample pre-dose, spot urine sample from the [8-12h] urine PK collection sample, and void closest to the 24 hour void collected as part of the [12-24h] urine PK collection (Day 8). For subjects with the 48-hour BAL procedure: spot urine closest to the 48-hour void collected as part of the [24-48h] urine PK collection (Day 9). Other days: random sample, preferably first morning void.

[p] Urine for Pharmacokinetics (parent drug only): On Day 1: pre-dose [-2h to 0h] urine collection. On Day 7: prior to last inhalation [-2 to 0h], [0-4h], [4-8h], [8-12h], [12-24h] after start of dosing. For subjects having BAL at the 48-hour timepoint: [12-24h] after start of dosing.

[q] Sputum for microbiology: pre-dosing on Day 1, 4, 7, and Follow-up visit.

[r] BAL for Pharmacokinetics (parent drug & metabolites) and differential cell count: On Day 7 after 2nd dosing: 2, 24, or 48 hours after start of inhalation. BAL sampling process to be started after completion of other assessments scheduled for the same timepoint. Differential cell count includes macrophage, lymphocyte, neutrophil, and eosinophil cell counts. Subjects will be fasted for > 4 hours for solid food and > 2 hours for clear fluids.

[s] Blood for pharmacokinetics (parent drug % metabolites): on Day 1: within 30 minutes prior to start of 1st inhalation. On Day 7: pre-dose, 1 to 8 minutes after end of inhalation, 10, 30, 60 minutes, and 2, 4, 6, 8, 12, 15, 24 hours after start of inhalation. For subjects with 48-hour BAL procedure: sample at 48 hours after start of inhalation. On other days: prior to any of the daily inhalation.

[t] Overall tolerability: question subject whether dosing was well accepted.