STUDY PROTOCOL

STUDY TITLE:	A randomised, double-blind, multi centre, placebo-controlled dose escalation study in healthy subjects investigating the safety, tolerability and pharmacokinetic properties of TD139, a galectin-3 inhibitor, followed by an expansion cohort treating subjects with idiopathic pulmonary fibrosis (IPF)
STUDY NUMBER:	RD 676/25641
SPONSOR NUMBER:	GB-HV-01
EudraCT NUMBER:	2014-001187-35
INVESTIGATIONAL MEDICINAL PRODUCT:	TD139 and matching placebo administered via dry powder inhaler
PLANNED STUDY DOSES:	Part 1 (Single dose): 0.15mg, 1.5mg, 3mg, 10mg, 20mg and 50mg Part 2 (Multiple doses): starting dose = 3mg
CHIEF INVESTIGATOR:	[redacted]
STUDY SPONSOR:	Galecto Biotech AB Cobis Science Park Ole Maaloes Vej 3 DK-2200 Copenhagen Denmark

PROTOCOL FINALIZATION STATEMENT

This protocol is not considered final unless accompanied by an approval letter from the Research Ethics Committees and Notice of Acceptance from the relevant Competent Authority.

Protocol Prepared by: DF/OK

1 SIGNATURE PAGES

1.1 Sponsor Signature Page

I declare that I have read and understood this Study Protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Chief Investigator). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the subjects.

STUDY SPONSOR:

[redacted] Galecto Biotech AB Cobis Science Park, Ole Maaloes Vej 3 DK-2200, Copenhagen Denmark ☎ [redacted]	Signature: [redacted] Date: [redacted]

1.2 Investigator Signature Page

I declare that I have read and understood this Study Protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Chief Investigator). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the subjects.

CHIEF INVESTIGATOR

[redacted] Royal Brompton Hospital Sydney Street London, SW3 6NP UK ☎ [redacted]	Signature: [redacted] Date: [redacted]

PRINCIPAL INVESTIGATOR:

[redacted] Edinburgh University Hospital 47 Little France Crescent Edinburgh, EH16 4TJ UK ☎ [redacted]	Signature: [redacted] Date: [redacted]

PRINCIPAL INVESTIGATOR:

[redacted] Royal Victoria Infirmary Queen Victoria Road Newcastle upon Tyne NE1 4LP UK ☎ [redacted]	Signature: [redacted] Date: [redacted]

PRINCIPAL INVESTIGATOR:

[redacted] Royal Devon & Exeter Hospital Barrack Road, Exeter, Devon EX2 5DW, UK ☎ [redacted]	Signature: [redacted] Date: [redacted]

PRINCIPAL INVESTIGATOR:

[redacted] Simbec Research Limited Merthyr Tydfil CF48 4DR UK ☎ [redacted]	Signature:* [redacted] Date:* [redacted]

* Part 1 of the study (healthy volunteers) has finished and a CSR has been finalised, so the PI at Simbec is no longer required to have any involvement in the study. The PI at Simbec has no responsibilities in terms of Part 2 of the study and will therefore not be required to sign off any protocol amendments that relate to this part of the study.

2 SYNOPSIS

NAME OF COMPANY: Galecto Biotech AB

NAME OF INVESTIGATIONAL MEDICINAL PRODUCT:
TD139 and matching placebo via dry powder inhaler (DPI)

NAME OF ACTIVE INGREDIENT:
TD139 (galectin-3 inhibitor)

TITLE OF STUDY:
A randomised, double-blind, multi centre, placebo-controlled dose escalation study in healthy subjects investigating the safety, tolerability and pharmacokinetic properties of TD139, a galectin-3 inhibitor, followed by an expansion cohort treating subjects with idiopathic pulmonary fibrosis (IPF).

CHIEF INVESTIGATOR: [redacted]

PART 1 STUDY CENTRE: Simbec Research Ltd (Simbec)
Merthyr Tydfil, UK

PART 2 STUDY CENTRES: Royal Brompton Hospital, London, UK
Edinburgh University Hospital, Edinburgh, UK
Royal Victoria Infirmary, Newcastle, UK
Royal Devon and Exeter Hospital, UK

CLINICAL PHASE: I/IIa

OBJECTIVES:

Primary objective

- To evaluate the safety and tolerability of single ascending doses of TD139 in healthy male subjects.
- To evaluate the safety and tolerability of multiple doses of TD139 in male and female subjects of non child-bearing potential with IPF.

Secondary objective

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of TD139 when administered as a single dose to healthy male subjects.
- To evaluate the PK and PD of TD139 when administered in multiple doses to male and female subjects of non child-bearing potential with IPF.

METHODOLOGY:

This study will be divided into 2 parts. Part 1 is a randomised, double-blind, single centre, placebo-controlled, single ascending dose (SAD) phase I study designed to assess the safety, tolerability, PK and PD of TD139 in up to 36 healthy male subjects. Part 2 will be a randomised, double-blind, multi-centre, placebo-controlled, multiple dose expansion cohort, designed to assess the safety, tolerability, PK and PD of TD139 in up to 24 male subjects and female subjects of non child-bearing potential with IPF.

Part 1 of the study will take place in healthy male volunteers and will consist of up to 6 cohorts of 6 subjects. Within each cohort, 4 subjects will receive a single dose of TD139 and 2 subjects will receive a single dose of placebo. Each cohort will include a dose leader group of 2 volunteers (1 TD139 and 1 placebo) to be dosed a day before the rest of the cohort, followed by the remaining 4 subjects who will be dosed approximately 24 hours later. The remaining 4 subjects will be randomised such that one further volunteer receives placebo.

The lowest dose of TD139 will be evaluated first (0.15 mg). Dose administration in the subsequent cohorts will only proceed after blinded safety and PK data for 3 days (48 hours post-dose) after dose administration from a minimum of 5 subjects in the preceding cohort have been reviewed by the Sponsor and Chief Investigator and are found to be satisfactory. The study will be discontinued at any time if any unacceptable safety findings are identified. The maximum dose of TD139 will be 50 mg.

Part 2 of the study will take place in male subjects and female subjects of non child-bearing potential with IPF.

This part of the study will include up to 24 IPF subjects, who will receive a single dose of TD139 or placebo via DPI once daily for 14 days (subjects will receive TD139 and placebo as per **Table S1,** page 12). Subjects will be studied in up to 3 multiple ascending dose cohorts. Based on the safety and PK data from single doses up to 10mg in Part 1, a starting dose of 3 mg has been selected for the first Cohort in Part 2 (8 subjects, 5 TD139 and 3 placebo). The dose escalation design of Part 2 is presented in **Table S1**. At each interim safety review meeting, the available blinded safety, BAL and PK data would be reviewed by the Sponsor and the Chief/Principal Investigator.

There will be an interim review after Cohort 1 has been dosed to review the available data. Following a review of this data, if it is decided that it meets the dose escalation requirements then Cohort 2 (8 subjects, 5 TD139 and 3 placebo) will receive the next dose level. An interim review would then take place after Cohort 2 has been dose to review the available data. Following a review of this data, if it is decided that it meets the dose escalation requirements then Cohort 3 (8 subjects, 5 TD139 and 3 placebo) will receive a third dose level (Outcome 1). If it is decided that the data in Cohort 2 does not meet the dose escalation requirements, a 4 further subjects would be dosed in Cohort 2 with the same dose level (3 TD139 and 1 placebo) (Outcome 2).

After the interim review of Cohort 1 data, if it is decided that the dose escalation requirements have not been met, 4 further subjects would be dosed in Cohort 1 with 3mg (3 TD139 and 1 placebo). After the extra subjects have been dosed an interim review would then take place to review the data, before moving on to the next dose level in Cohort 2 (8 subjects, 5 TD139 and 3 placebo). An interim review would then take place after Cohort 2 has been completed to review the available data. Following a review of this data, if it is decided that it meets the dose escalation requirements then no further subjects would be dosed (Outcome 3). If it is decided that the data in Cohort 2 does not meet the dose escalation requirements, a 4 further subjects would be dosed in Cohort 2 with the same dose level (3 TD139 and 1 placebo) (Outcome 4).

The highest acceptable dose level in Part 1 of the study will not be exceeded in Part 2. Part 2 will be discontinued at any time if any unacceptable safety findings are identified (see Study Stopping Criteria). At the interim review meetings it may be decided it is not appropriate to escalate the dose. In this event the same dose, an intermediate dose or a lower dose may be given following discussion between the Sponsor and the Chief/Principal Investigator. The dose and PK sampling times may also be modified following a review of the data.

Part 1

Pre-study assessments

Pre-study assessments will be carried out in the 28 day period before dosing in order to assess the volunteer for suitability to take part in the study. Potential volunteers will be required to provide written Informed Consent prior to undertaking any screening procedures. Pre-study assessments will include medical history, vital signs (blood pressure, pulse, O_2 saturation, oral temperature, and respiratory rate), physical examination (including body weight, height and BMI), 12-lead ECG, lung function testing, (FEV1 & FVC) and laboratory safety screen (haematology, biochemistry, urinalysis, urine drugs of abuse screen).

Volunteers who fulfil all screening requirements will be invited to return for the Study Period.

Study Period

Each cohort of subjects will undergo 1 Study Period and each cohort will be separated by a data review period. Each Study Period will be approximately 15 days in duration and subjects will be dosed and monitored on a combined inpatient and outpatient basis.

Volunteers will be admitted to the Clinical Centre in the morning of Day -1 where final confirmation of eligibility will be made after baseline assessments have been performed.

Two subjects (dose leaders) will receive either a single dose of TD139 or placebo via DPI (1 treatment/volunteer) following an overnight fast a day before the remaining subjects in the cohort. The remaining 4 subjects of each cohort will be dosed approximately 24 hours later providing there are no safety concerns for either of the dose leaders. These 4 subjects will be randomised such that one further volunteer receives placebo. The randomisation code will be generated using the PROC PLAN procedure of SAS®.

Each subject will stay at the Clinical Centre until 24 h post-dose (morning of Day 2) where they will be discharged providing the scheduled assessments have been completed and there are no ongoing safety concerns.

Subjects will return to the Clinical Centre on an outpatient basis on Day 3 for PK/safety and then Days 8 and 14 for safety assessments.

During the Study Period, assessments will include:

- Vital signs (supine blood pressure, pulse, O_2 saturation, oral temperature and respiratory rate)
- 12-lead ECG
- Physical examination
- Laboratory safety screen (haematology, biochemistry, urinalysis and urine drugs of abuse screen)
- Blood samples for PK, PG and PD measurements
- Exhaled breath condensate (EBC) collection for PD measurements

All Adverse Events (AE) and concomitant medications will be recorded from the time of the screening visit until the post-study follow-up visit.

Post-study assessments will be carried out 12 - 16 days after the last day of the Study Period.

Part 2

Part 2 of the study will include up to 24 male and female subjects of non child-bearing potential with IPF. Four NHS centres (Royal Brompton Hospital, Edinburgh University Hospital, Royal Victoria Infirmary and Royal Devon and Exeter Hospital) will serve as Clinical Centres for Part 2 of the study and will identify eligible patients who present with IPF. Patients who agree to take part in the study will be selected based upon the study inclusion and exclusion criteria.

During Part 2, patients will receive a single dose of TD139 or placebo once daily for 14 days (dosing with TD139 or placebo as per **Table S1**). Patients will undergo study specific assessments throughout and post-study assessments will be carried out (26-30) days after the last day of the Study Period.

Pre-study assessments

Pre-study assessments will be carried out in the 28 day period before dosing in order to assess the volunteer for suitability to take part in the study. Potential volunteers will be required to provide written Informed Consent prior to undertaking any screening procedures. Pre-study assessments will include medical history, vital signs (blood pressure, pulse, O_2 saturation, oral temperature, and respiratory rate), physical examination (including body weight, height and BMI), 12-lead ECG, detailed lung function testing including Carbon Monoxide Diffusing Capacity (DLCO), and laboratory safety screen (haematology, biochemistry, urinalysis, urine drugs of abuse screen).

Volunteers who fulfil all screening requirements will be invited to return for the Study Period.

Study Period

The Study Period will be approximately 43 days in duration and subjects will be dosed and monitored on an outpatient basis.

Volunteers will attend the Clinical Centre in the morning of Day -1 where final confirmation of eligibility will be made after baseline assessments have been performed. Volunteers will then be allowed to leave the unit and return in time for pre-dose procedures on the morning of Day 1.

Each subject will receive either a single dose of TD139 or placebo via DPI once daily for 14 days, following an overnight fast on day -1. The randomisation code will be generated using the PROC PLAN procedure of SAS®. Subjects will remain in the unit until 12 hrs post-dose on Day 1, providing the scheduled assessments have been completed and there are no ongoing safety concerns. Subjects will then return to the Clinical Centre on Days 2, 3, 7, 14 and 15 for scheduled assessments and to receive the IMP. On Days when subjects are not required to attend the Clinical Centre, they will self administer the IMP at home.

During the Study Period, assessments will include:

- Vital signs (supine blood pressure, pulse, O_2 saturation, oral temperature and respiratory rate)

- Lung function testing
- 12-lead ECG
- Physical examination
- Laboratory safety screen (haematology, biochemistry, urinalysis and urine drugs of abuse screen)
- Blood samples for PK and PD measurements
- BAL fluid sampling for PK, PG and PD measurements.
- Exhaled breath condensate (EBC) collection for PD measurements

All Adverse Events (AE) and concomitant medications will be recorded from the time of the screening visit until the post-study follow-up visit.

Post-study assessments will be carried out 26 - 30 days after the last day of the Study Period.

NUMBER OF SUBJECTS:

Part 1

Up to 36 healthy male subjects (studied as up to 6 groups of 6 subjects).

Part 2

Up to 24 male and female subjects of non child-bearing potential with IPF.

INCLUSION CRITERIA:

Part 1

- Healthy male subjects aged between 18 and 55 years of age.
- Male subject willing to use a condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from Day 1 until 3 months afterwards.
- Subject with a body weight of at least 50 kg and a Body Mass Index (BMI) within the range of 18-35 kg/m^2. BMI = Body weight (kg) / $[Height (m)]^2$.
- Subject with no clinically significant abnormal serum biochemistry, haematology and urine examination values within 28 days of the first dose.
- Subject with a negative urinary drugs of abuse screen, determined within 28 days of the first dose (N.B. a positive alcohol result may be repeated at the discretion of the Investigator).
- Subject with negative human immunodeficiency virus (HIV) and hepatitis B surface antigen (Hep B) and hepatitis C virus antibody (Hep C) results.
- Subject with no clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days of the first dose.
- Subjects must be a non-smoker or a former smoker (having ceased smoking for at least 6 months).
- Subjects with no clinically significant impairment in oxygen saturation.
- Subject must satisfy a medical examiner about their fitness to participate in the study.
- Subject must provide written informed consent to participate in the study.
- Subject must be available to complete the study (including all follow up visits).

Part 2

- Male subject or female subject of non child-bearing potential with IPF.

- *For the purposes of this study, a female subject of non child-bearing potential is defined as the subject being amenorrheic for at least 12 consecutive months or at least 4 months post-surgical sterilisation (including bilateral fallopian tube ligation or bilateral oophorectomy with or without hysterectomy).*
- Male subject willing to use a condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from Day 1 until 3 months afterwards.
- Subject aged between 45 and 85 years of age.
- Subjects with an FVC ≥ 45% predicted and an FEV1/FVC ratio ≥ 0.7.
- Subjects with oxygen saturation >90% by pulse oximetry while breathing ambient air at rest.
- Subjects with a diffusing capacity (DLCO) >25%.
- Subjects must have adequate organ function and a clinical diagnosis consistent with IPF prior to screening (based on the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Association (ATS/ERS/JRS/ALAT) consensus criteria. The diagnosis would ordinarily have been confirmed at a multidisciplinary team meeting where the HRCT findings in particular will have been discussed with a radiologist with Respiratory expertise.
- Subjects who are able to undergo bronchoalveolar lavage (BAL).
- Subject must provide written informed consent to participate in the study.
- Subject must be available to complete the study (including all follow up visits).
- Subject with negative human immunodeficiency virus (HIV) and hepatitis B surface antigen (Hep B) and hepatitis C virus antibody (Hep C) results.
- Subject with no clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days of the first dose.
- Subject with a negative urinary drugs of abuse screen, determined within 28 days of the first dose (N.B. a positive alcohol result may be repeated at the discretion of the Investigator).

EXCLUSION CRITERIA:

Part 1

- A clinically significant illness or surgery within 8 weeks prior to first administration of the study medication.
- Significant medical history that, in the Investigator's opinion, may adversely affect participation.
- History of allergy or significant adverse reaction to drugs similar to the investigational drug, to nicotine, or to cholinergic drugs or to any drugs with a similar chemical structure.
- History of hypersensitivity (anaphylaxis, angioedema) to any drug.
- Use of any drug known to induce or inhibit hepatic drug metabolism, within 30 days prior to first administration of the study medication.
- Use of medications known to prolong QT/QTc interval within 14 days prior to the first administration of the study medication.
- Any clinically significant findings of physical examination or laboratory findings at Screening Visit.
- A clinically significant history of drug or alcohol abuse.
- Receipt of regular/over the counter medication within 14 days of the first dose that may have an impact on the safety and objectives of the study (at the Investigator's discretion).
- Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular or metabolic

dysfunction.

- Inability to communicate well with the Investigator (i.e., language problem, poor mental development or impaired cerebral function).
- Participation in a New Chemical Entity clinical study within the previous 4 months or a marketed drug clinical study within the previous 3 months. *(N.B. washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study)*.
- Donation of 450 mL or more blood within the previous 3 months.

Part 2

- Any condition that makes the patient at unacceptable risk for bronchoscopy.
- Active cigarette smoking (defined as smoking more than 3 cigarettes daily within the last 6 months).
- Presence of a significant co-morbidity felt to limit life expectancy to less than 12 months.
- HRCT pattern showing emphysema more than the extent of fibrosis of the lung area conducted within 12 months of Day 1.
- Evidence of renal, hepatic, central nervous system, or metabolic dysfunction
- Evidence of poorly controlled diabetes mellitus (defined as a HbA1c of > 59 mmol/mol [7.5%]).
- Use of systemic immunosuppressants within 30 days of dosing.
- Subjects currently receiving oral corticosteroids, cytotoxic drugs (e.g. chlorambucil, azathioprine, cyclophosphamide, methotrexate), antifibrotic drugs (e.g. pirfenidone), vasodilator therapies for pulmonary hypertension (e.g bosentan), unapproved (e.g. INF-γ, penicillamine, cyclosporine, mycophenolate) and/or investigational therapies for IPF or administration of such therapies within 4 weeks of initial screening. A current inhaled steroid dose of ≤1000 micrograms beclomethasone dipropionate (BDP) equivalent per day is acceptable if the dose is anticipated to remain stable during the study.
- History of malignancy, including carcinoma during the preceding five years.
- History of, or current asthma.
- Participation in a clinical study of an unlicensed drug in the previous 4 months, or a marketed drug study within the previous 3 months. *(N.B. washout period between trials defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study)*.
- Females of child-bearing potential and/or with a positive pregnancy test at Screening Visit.

STUDY DRUG ADMINISTRATION:

All doses will be administered using the Plastiape DPI.

Part 1

Up to 6 cohorts of 6 subjects will be randomly assigned in a blinded fashion to receive either a single dose of TD139 or matching placebo via DPI in an ascending dose fashion. Dose levels may be changed at the discretion of the safety committee based on PK and safety findings. The 6 currently planned ascending doses will be:

Cohort 1: 0.15mg TD139 or matching placebo

Cohort 2: 1.5mg TD139 or matching placebo

Cohort 3: 3mg TD139 or matching placebo

Cohort 4: 10mg TD139 or matching placebo

Cohort 5: 20mg TD139 or matching placebo

Cohort 6: 50mg TD139 or matching placebo

Within each cohort, 4 subjects will receive TD139 and 2 subjects will receive placebo. One subject of the dose

leader group (total of 2 subjects) will receive TD139 and 1 subject will receive placebo. The remaining 4 subjects will be randomised such that one further volunteer receives placebo.

TD139 capsules will be available in 0.15mg, 1.5mg, 5mg and 50mg strengths.

Part 2

Up to 24 patients will be randomly assigned in a blinded fashion to receive a single dose of TD139 or placebo via DPI once daily for 14 days as per **Table S1**. Based on the safety and PK data from single doses up to 10mg in Part 1 and on pre-clinical efficacy and safety data, a starting dose of 3 mg has been selected for the first Cohort in Part 2 (8 subjects, 5 TD139 and 3 placebo).

Subsequent patients will be dosed according to the dose escalation design presented in **Table S1**.

CRITERIA FOR EVALUATION:

Part 1

Safety Assessments:

- Adverse events and concomitant medication, 12-lead ECG, vital signs (blood pressure, pulse, O_2 saturation, oral temperature, respiratory rate), routine laboratory assessments (haematology, biochemistry and urinalysis) and urine drugs of abuse test.

Pharmacokinetic Assessments:

- Plasma concentrations of TD139.

Pharmacodynamic Assessments:

- Exhaled breath condensate analysis.
- Peripheral blood flow cytometry.
- Galectin-3 plasma levels.

Pharmacogenetic Assessments:

- mRNA expression levels from blood leucocytes.

Part 2

Safety Assessments:

- Adverse events and concomitant medication, 12-lead ECG, vital signs (blood pressure, pulse, O_2 saturation, oral temperature, respiratory rate), routine laboratory assessments (haematology, biochemistry and urinalysis) and urine drugs of abuse test.

Pharmacokinetic Assessments:

- Plasma, alveolar macrophage and BAL fluid (saline) concentrations of TD139.

Pharmacodynamic Assessments:

- Macrophage morphology, *ex-vivo* macrophage function and analysis of soluble markers from BAL.
- Exhaled breath condensate analysis.
- Peripheral blood flow cytometry.
- Galectin-3 plasma levels.

Pharmacogenetic Assessments:

- Macrophage phenotypic and mRNA pattern expression analysis from BAL.
- mRNA expression levels from blood leucocytes and analysis of peripheral blood mononuclear cells for

IPF gene signatures.

STATISTICAL METHODS:

Part 1

Pharmacokinetics: ***Non-compartmental analysis***: C_{max} is calculated as the experimental value with the highest plasma concentration. The time of t_{max} is the experimental data point when C_{max} is measured. The $t_{1/2}$ is the time over which plasma concentration falls by one half. The AUC_{0-t} and $AUC_{0-\infty}$ will be calculated using the trapezoidal rule.

Pharmacokinetic parameters of the studied population will be derived using standard non-compartmental methods with Phoenix WinNonlin®.

Safety analysis: Descriptive statistics including number of observations, mean, SD and associated CV, minimum and maximum for numerical data, and counts and frequency for categorical data, will be tabulated for safety parameters by treatment group.

Part 2

Pharmacokinetics: ***Non-compartmental analysis***: C_{max} is calculated as the experimental value with the highest plasma concentration. The time of t_{max} is the experimental data point when C_{max} is measured. The $t_{1/2}$ is the time over which plasma concentration falls by one half. The AUC_{0-t} and $AUC_{0-\infty}$ will be calculated using the trapezoidal rule.

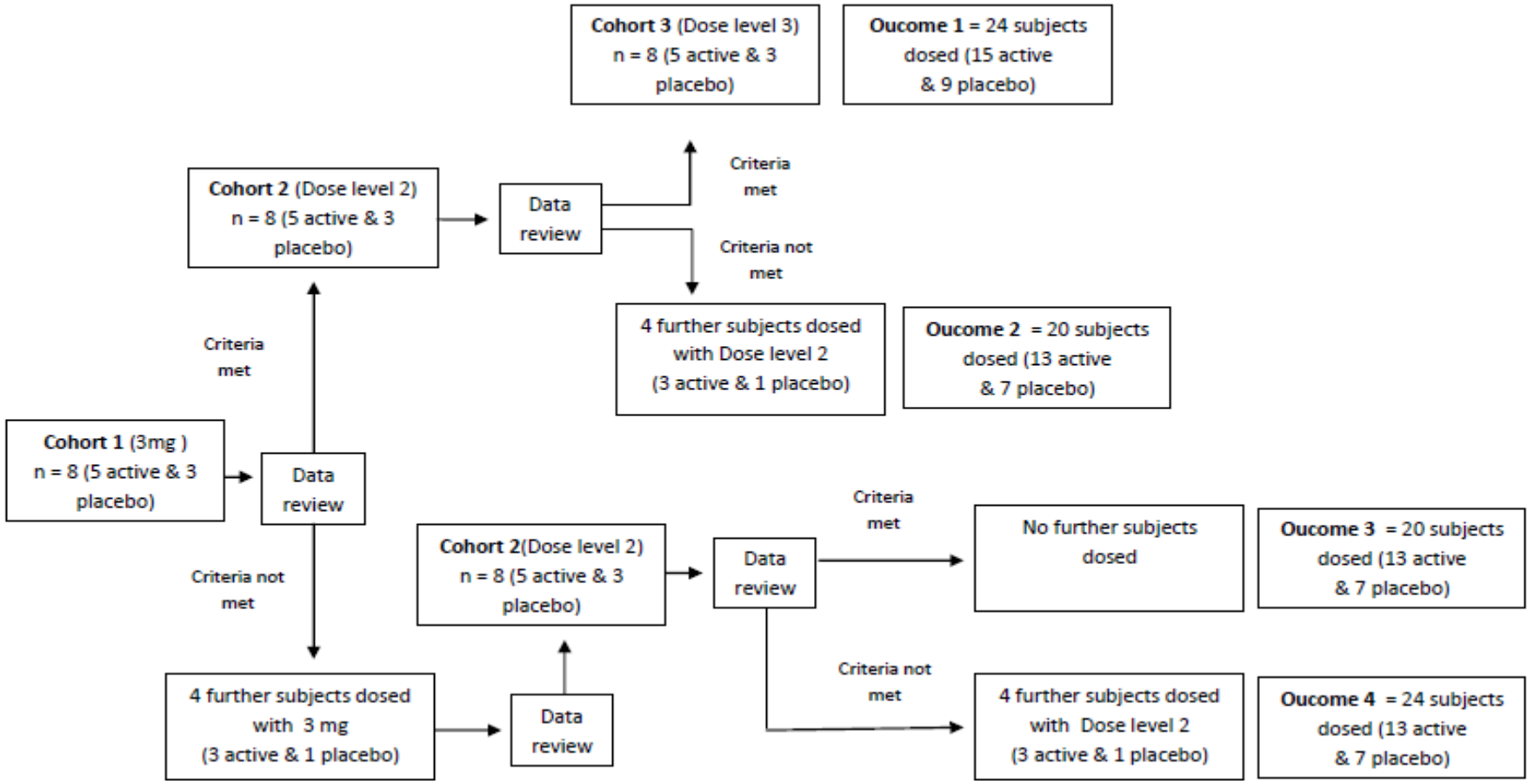
Pharmacokinetic parameters of the studied population will be derived using standard non-compartmental methods with Phoenix WinNonlin®.

Drug compartment measurements in BAL and AM as per the method set out in the study by Naderer *et al*[1] (e.g. $TD139_{AM} = TD139_{pellet}/V_{AC}$ [where the volume of alveolar cells - $V_{AC,}$ is estimated at $2.42\mu l/10^6$ cells])[1].

Safety analysis: Descriptive statistics including number of observations, mean, SD and associated CV, minimum and maximum for numerical data, and counts and frequency for categorical data, will be tabulated for safety parameters by treatment group.

DURATION OF STUDY:	**Part 1:** Approximately 8 weeks for each individual (from the Screening Visit to Post-Study Visit) **Part 2:** Approximately 11 weeks for each individual (from the Screening Visit to Post-Study Visit)

Table S1: Part 2 Dose Escalation Flow Chart



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4 ABBREVIATIONS USED IN THE TEXT

- λ_z elimination rate constant
- ABPI Association of the British Pharmaceutical Industry
- AE(s) adverse event(s)
- ALB albumin
- ALT alanine transaminase
- AST aspartate transaminase
- AUC area under the plasma concentration versus time curve
- AUC_{0-t} AUC from the time of dosing to the time of the last observed concentration
- AUC_{0-inf} AUC extrapolated to infinity from dosing time, based on the last observed concentration
- BAL bronchoalveolar lavage
- BASO basophils
- BIA BioIndustry Association
- BIL-T total bilirubin
- BMI body mass index
- CCRA Clinical Contract Research Association
- C_{max} maximum plasma concentration
- CL/F clearance
- CREA creatinine
- CRF case report form
- CTA Clinical Trial Authorisation
- CV% coefficient of variation
- DLCO Carbon Monoxide Diffusing Capacity
- DPI Dry Powder Inhaler
- EBC Exhaled breath condensate
- EC European Commission
- ECG electrocardiogram
- EOS eosinophils
- FEV1 Forced Expired Volume in 1 second
- FVC Forced Vital Capacity
- g gram
- GCP Good Clinical Practice
- GGT gamma glutamyl transferase
- GLP Good Laboratory Practice
- GLU glucose
- GMP Good Manufacturing Practice
- hr(s) hour(s)
- Hep B hepatitis B surface antigen
- Hep C hepatitis C virus antibody
- HCO_3 bicarbonate
- HCT haematocrit
- HGB haemoglobin
- HIV human immunodeficiency virus
- ICH International Conference on Harmonisation
- IMP investigational medicinal product
- ISF Investigator Site File
- K potassium
- Ltd Limited
- LYMP lymphocytes
- MCV mean cell volume
- MCH mean cell haemoglobin
- MCHC mean cell haemoglobin concentration
- MedDRA Medical Dictionary for Regulatory Activities
- MHRA Medicines and Healthcare products Regulatory Agency
- min(s) minute(s)
- MoA mechanism of action
- MONO monocytes
- N number dosed
- n number of observations
- NA sodium
- NEUT neutrophils
- PD pharmacodynamic
- PK pharmacokinetic
- PLT platelets

- PR interval — time the electrical impulse takes to travel from the sinus node through the AV node and entering the ventricles; measured from the beginning of the P wave to the beginning of the QRS complex
- QP — qualified person
- QRS — QRS complex represents ventricular depolarization
- QT interval — the time for both ventricular depolarization and repolarization to occur, and therefore roughly estimates the duration of an average ventricular action potential.
- QTc — corrected QT interval
- QTcB — corrected QT interval using Bazett's formula
- RBC — red blood cells
- REC — Research Ethics Committee
- SAE — serious adverse event
- SAP — statistical analysis plan
- SAS — statistical analysis software by SAS Institute Inc., USA
- SD — standard deviation
- SOC — system organ class
- SOP — standard operating procedure
- SUSAR — suspected unexpected serious adverse reaction
- tds — ter die sumendum, three times a day
- $t_{½}$ — terminal half-life
- t_{max} — the time to C_{max} during a dosing interval
- TP — total protein
- UK — United Kingdom
- WBC — white blood cells

5 ETHICS

5.1 Research Ethics Committee or Institutional Review Board

This Study Protocol will be submitted to the Research Ethics Committee (REC) for review and approval. The approval of the REC must be obtained before commencement of any study procedures.

All substantial protocol amendments must be approved by the REC responsible for the study. Non-substantial amendments will not require prior approval by the REC.

If the study is stopped due to adverse events (AEs) it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 days of completion of the last subject's final study procedures. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 days.

A summary of the Clinical Study Report will be submitted to the REC responsible for the study within 1 year of completion of the last subject's final study procedures.

The REC will be informed that Simbec is a commercial organisation and that the study is funded by Galecto Biotech AB. The subjects who take part in the clinical study will be paid for their inconvenience and have been informed that there will be no benefits gained by their participation. All potential conflicts of interest will be declared by the Investigators.

5.2 Ethical Conduct of the Study

The Chief Investigator shall be responsible for ensuring that the clinical study is performed in accordance with the following:

- Declaration of Helsinki (Brazil 2013)[2].
- Association of the British Pharmaceutical Industry (ABPI) Guidelines for Phase 1 Trials (2012)[3].
- International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP)[4].
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031) and subsequent amendments[5].

This clinical study has been registered in the EudraCT database and a Clinical Trials Authorisation (CTA) will be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA) prior to the start of the study in accordance with Part 3, Regulation 12 of the United Kingdom (UK) Statutory Instrument.

5.3 Subject Information and Consent

Prior to undergoing any study-specific procedure, each potential study subject will be asked to provide signed acknowledgement of their freely given informed consent. Either the Chief Investigator or a designated person, qualified to meet any applicable local regulations, who is equally knowledgeable about the study will explain the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. A corresponding written explanation (Subject Information Sheet) will also be provided and the subject will be allowed sufficient time to consider the study information.

Prior to signing the Informed Consent Form, the subject will be given an opportunity to discuss any issues concerning the study with a physician who has suitable knowledge of the study and will have all questions answered openly and honestly.

If the subject is willing to participate in the study, the Informed Consent Form will be signed and personally dated by the subject, the physician taking the consent and, if applicable, the designated person who explained the nature of the study. The subject will receive a copy of the Informed Consent Form together with the Subject Information Sheet, and the original signed Informed Consent Form will be retained with the study records at the Investigator site.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Part 1 of the study will be performed at a single site, Simbec Research Limited (Ltd.) and Part 2 of the study will be performed at 4 NHS Centres (Royal Brompton Hospital, Edinburgh University Hospital, Royal Victoria Infirmary and Royal Devon and Exeter Hospital). The trial manager will act on behalf of the Chief Investigator to ensure the smooth and efficient running of all aspects of the study.

6.1 Study Personnel

Galecto Biotech AB (Sponsor)

Project Manager (Main Contact): [redacted]

Sponsor's Responsible Physician: [redacted]

Monitor: [redacted]

Simbec Research Ltd (Contract Research Organisation)

Principal Investigator: [redacted]

Trial Manager: [redacted]

Co-Investigators: [redacted]

Pharmacokinetics (PK): [redacted]

Statistics: [redacted]

Principal Scientist, Bioanalytical Unit: The Principal Scientist will be assigned prior to study start and documented in the Bioanalytical Phase Plan.

Manager, Simbec Central Laboratories: [redacted]

Edinburgh University Hospital

Principal Investigator: [redacted]

Royal Brompton Hospital

Chief Investigator: [redacted]

Royal Victoria Infirmary

Principal Investigator: [redacted]

Royal Devon and Exeter Hospital

Principal Investigator: [redacted]

Pharmacovigilance (PV): Diamond PV Services Ltd

The Chief Investigator will delegate study related activities according to staff responsibilities and job descriptions. This will be documented in a study specific Delegation of Responsibilities form.

6.2 Indemnity Arrangements

Each study site carries insurance to pay compensation for injury, accident, ill health or death caused by participation in this study without regard to proof of negligence and without delay. Provision for arbitration in the case of disagreement must be agreed with the insured. It is suggested that a Barrister of at least 10 years standing appointed by the Royal College of Physicians be arbiter.

Where there is any doubt about causation, the benefit of the doubt must be given to the subject.

Where ill health, injury or death is due to negligence by the Sponsor party, the study site should promptly compensate the subject but reserve the right to take action against the Sponsor in order to recoup such compensation.

It is hoped that insurance companies will honour life and sickness policies of subjects participating in research that has been approved by an appropriately constituted REC and involves no more than minimal risk.

The above section accords with Insurance and compensation in the event of injury in phase I clinical trials 2012[6], guidance developed by the ABPI, the BioIndustry Association (BIA) and the Clinical Contract Research Association (CCRA) in consultation with the Department of Health and the National Research Ethics Service.

7 INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and invariably fatal disease characterized by progressive scarring of the lung. IPF is thought to occur after recurrent injury to the alveolar epithelium followed by abnormal repair; this abnormal repair is characterized by the formation of fibroblast and myofibroblast foci and excessive deposition of extracellular matrix[7][8].

IPF occurs more commonly in men than women and typically presents in individuals of between 40 and 70 years of age. Recently published estimates from the USA suggest the prevalence of IPF is between 14 and 42.7 per 100 000 with an annual incidence of 6.8–16.3 per 100 000. In the UK the incidence of IPF has been estimated at 4.6 per 100 000 and accounts for 5000 deaths per year, a figure greater than many malignancies, including myeloma, lymphoma, and stomach cancer[7][8].

Individuals with IPF typically present with breathlessness and cough, which becomes progressively debilitating over time. The overwhelming majority of patients with IPF eventually die from respiratory failure, with a median survival from diagnosis of 2.9–5.0 years[7][8]. More effective treatments for IPF represent a very important unmet clinical need. It is a debilitating disease, which results in progressive lung scarring with a rapid decline in lung function and a high mortality rate. There are approximately 5,000 cases of IPF diagnosed in the UK each year[9] and the incidence is rising. In the US and Canada the overall prevalence is estimated at 150,000[10]. The outlook for patients with IPF is poor - 50% of patients with IPF in the UK die within 3 years of diagnosis. Though Esbriet (pirfenidone), a drug with anti-inflammatory and anti-fibrotic effects has recently been approved by the FDA for the treatment of IPF, the lack of a clearly defined mechanism of action (MoA), high price, frequent incidence of upper gastrointestinal side effects and moderate therapeutic effect impede its clinical use whilst drug developmental issues surrounding its MoA make drug class specific improvements extremely difficult. Ofev (Nintedanib) has also been approved but is similarly priced and whilst its MOA is established (tyrosine kinase inhibitor) the incidence of side effects with this drug is even higher than that of Esbriet. Therefore a novel, targeted therapy with a clear MoA and limited side effect profile that could halt and potentially reverse disease progression is urgently required. In addition, the inhaled delivery route could offer further benefits in targeting the site of disease whilst limiting systemic toxicity.

Galecto Biotech has developed a novel IPF treatment (TD139) that acts as a Galectin-3 (Gal-3) inhibitor. TD139 has been inhibitor developed as a dry powder for inhalation (DPI) for the indication “Treatment of adults with Idiopathic Pulmonary Fibrosis” (IPF). The chemical name is Bis-(3-deoxy-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-ß-D-galactopyranosyl) sulfane. Galectin-3 is a member of the lectin family of carbohydrate-binding proteins and it is implicated in a number of cellular processes, including cell adhesion, cell activation, chemo-attraction, cell growth, differentiation and apoptosis. Galectin-3 binds to itself and to TGFβ receptors, forming lattices that hold the receptors at the cell surface thus altering TGFβ signal transduction. TGFβ signalling is thought to drive many of the processes associated with fibrosis and inhibiting this pathway should reduce IPF disease progression.

In this trial, TD139 will be studied to explore its safety and tolerability in healthy volunteers and subsequently safety and tolerability in patients with IPF whilst pharmacodynamic measurements from samples taken from the lung in these patients before and after 14 days of treatment with TD139 may help to establish a proof of mechanism for TD139.

Further details regarding the mechanism of action of TD139, including safety data and a summary of the known and potential risks and benefits can be found in the IB[11] . A separate interim report (Interim Report Part 1, v1.0 28 Nov 2014), summarising safety and PK up to the 10mg doses of TD139 in healthy volunteers has been written. All adverse events were mild and self-limiting and there were no significant changes from baseline in any of the following parameters; ECG, vital signs, biochemistry, haematology and urinalysis.

8 STUDY OBJECTIVES

8.1 Primary Study Objective

- To evaluate the safety and tolerability of single ascending doses of TD139 in healthy male subjects.
- To evaluate the safety and tolerability of multiple doses of TD139 in male and female subjects of non child-bearing potential with IPF.

8.2 Secondary Study Objective

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of TD139 when administered as a single dose to healthy male subjects.
- To evaluate the PK and PD of TD139 when administered in multiple doses to male and female subjects of non child-bearing potential with IPF.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study will be divided into 2 parts**. Part 1** is a randomised, double-blind, single centre, placebo-controlled, single ascending dose (SAD), phase I study designed to assess the safety, tolerability, PK and PD of TD139 in up to 36 healthy male subjects. **Part 2** will be a randomised, double-blind, multi-centre, placebo-controlled, multiple dose expansion cohort, designed to assess the safety, tolerability, PK and PD of TD139 in up to 24 male subjects and female subjects of non child-bearing potential with IPF.

Part 1 of the study will take place in healthy male volunteers and will consist of up to 6 cohorts of 6 subjects. Within each cohort, 4 subjects will receive a single dose of TD139 and 2 subjects will receive a single dose of placebo. Each cohort will include a dose leader group of 2 volunteers (1 TD139 and 1 placebo) to be dosed a day before the rest of the cohort, followed by the remaining 4 subjects who will be dosed approximately 24 hours later. The remaining 4 subjects will be randomised such that one further volunteer receives placebo.

The lowest dose (0.15 mg) of TD139 will be evaluated first. Dose administration in the subsequent cohorts will only proceed after blinded safety and PK data for 3 days after dose administration from a minimum of 5 subjects in the preceding cohort have been reviewed by the Sponsor and Chief Investigator and are found to be satisfactory. The study will be discontinued at any time if any unacceptable safety findings are identified. The maximum dose of TD139 will be 50 mg.

Part 2 of the study will take place in male subjects and female subjects of non child-bearing potential with IPF. This part of the study will include up to 24 IPF subjects, who will receive a single dose of TD139 or placebo via DPI once daily for 14 days (subjects will receive TD139 and placebo as per Table S1). Subjects will be studied in up to 3 multiple ascending dose cohorts. Based on the safety and PK data from single doses up to 10mg in Part 1, a starting dose of 3 mg has been selected for the first Cohort in Part 2 (8 subjects, 5 TD139 and 3 placebo). The dose escalation design of Part 2 is presented in Table S1. At each interim safety review meeting, the available blinded safety, BAL and PK data would be reviewed by the Sponsor and the Chief/Principal Investigator.

There will be an interim review after Cohort 1 has been dosed to review the available data. Following a review of this data, if it is decided that it meets the dose escalation requirements then Cohort 2 (8 subjects, 5 TD139 and 3 placebo) will receive the next dose level. An interim review would then take place after Cohort 2 has been dose to review the available data. Following a review of this data, if it is decided that it meets the dose escalation requirements then Cohort 3 (8 subjects, 5 TD139 and 3 placebo) will receive a third dose level (Outcome 1). If it is decided that the data in Cohort 2 does not meet the dose escalation requirements, a 4 further subjects would be dosed in Cohort 2 with the same dose level (3 TD139 and 1 placebo) (Outcome 2).

After the interim review of Cohort 1 data, if it is decided that the dose escalation requirements have not been met, 4 further subjects would be dosed in Cohort 1 with 3mg (3 TD139 and 1 placebo). After the extra subjects have been dosed an interim review would then take place to review the data, before moving on to the next dose level in Cohort 2 (8

subjects, 5 TD139 and 3 placebo). An interim review would then take place after Cohort 2 has been completed to review the available data. Following a review of this data, if it is decided that it meets the dose escalation requirements then no further subjects would be dosed (Outcome 3). If it is decided that the data in Cohort 2 does not meet the dose escalation requirements, a 4 further subjects would be dosed in Cohort 2 with the same dose level (3 TD139 and 1 placebo) (Outcome 4).

The highest acceptable dose level in Part 1 of the study will not be exceeded in Part 2. Part 2 will be discontinued at any time if any unacceptable safety findings are identified (see Study Stopping Criteria). At the interim review meetings it may be decided it is not appropriate to escalate the dose. In this event the same dose, an intermediate dose or a lower dose may be given following discussion between the Sponsor and the Chief/Principal Investigators. The dose and PK sampling times may also be modified following a review of the data.

Part 1

Pre-study assessments

Pre-study assessments will be carried out in the 28 day period before dosing in order to assess the volunteer for suitability to take part in the study. Potential volunteers will be required to provide written Informed Consent prior to undertaking any screening procedures. Pre-study assessments will include medical history, vital signs (blood pressure, pulse, O_2 saturation, oral temperature, and respiratory rate), physical examination (including body weight, height and BMI), 12-lead ECG, lung function testing, (FEV1 & FVC) and laboratory safety screen (haematology, biochemistry, urinalysis, urine drugs of abuse screen).

Volunteers who fulfil all screening requirements will be invited to return for the Study Period.

Study Period

Each cohort of subjects will undergo 1 Study Period and each cohort will be separated by a data review period. Each Study Period will be approximately 15 days in duration and subjects will be dosed and monitored on a combined inpatient and outpatient basis.

Volunteers will be admitted to the Clinical Centre in the morning of Day -1 where final confirmation of eligibility will be made after baseline assessments have been performed.

Two subjects (dose leaders) will receive either a single dose of TD139 or placebo via DPI (1 treatment/volunteer) following an overnight fast a day before the remaining subjects in the cohort. The remaining 4 subjects of each cohort will be dosed approximately 24 hours later providing there are no safety concerns for either of the dose leaders. These 4 subjects will be randomised such that one further volunteer receives placebo. The randomisation code will be generated using the PROC PLAN procedure of SAS®.

Each subject will stay at the Clinical Centre until 24 h post-dose (morning of Day 2) where they will be discharged providing the scheduled assessments have been completed and there are no ongoing safety concerns. Subjects will return to the Clinical Centre on an outpatient basis on Days 3 for PK/safety and then Day 8 and 14 for assessments.

During the Study Period, assessments will include:

- Vital signs (supine blood pressure, pulse, O_2 saturation, oral temperature and respiratory rate)
- 12-lead ECG
- Physical examination
- Laboratory safety screen (haematology, biochemistry, urinalysis and urine drugs of abuse screen)
- Blood samples for PK, PG and PD measurements
- Exhaled breath condensate (EBC) collection for PD measurements

All Adverse Events (AE) and concomitant medications will be recorded from the time of the screening visit until the post-study follow-up visit.

Post-study assessments will be carried out 12 - 16 days after the last day of the Study Period (See Table 9.7.1).

Part 2

Part 2 of the study will include up to 24 male subjects and female subjects of non child-bearing potential with IPF. Four NHS centres (Royal Brompton Hospital, Edinburgh University Hospital, Royal Victoria Infirmary and Royal Devon and Exeter Hospital) will serve as Clinical Centres for **Part 2** of the study and will identify eligible patients who present with IPF. Patients who agree to take part in the study will be selected based upon the study inclusion and exclusion criteria.

During **Part 2**, patients will receive a single dose of TD139 or placebo once daily for 14 days (TD139 and placebo dosed according to **Table S1**). Patients will undergo study specific assessments throughout and post-study assessments will be carried out (26-30) days after the last day of the Study Period (See Table 9.7.12).

Pre-study assessments

Pre-study assessments will be carried out in the 28 day period before dosing in order to assess the volunteer for suitability to take part in the study. Potential volunteers will be required to provide written Informed Consent prior to undertaking any screening procedures. Pre-study assessments will include medical history, vital signs (blood pressure, pulse, O_2 saturation, oral temperature, and respiratory rate), physical examination (including body weight, height and BMI), 12-lead ECG, detailed lung function testing including Carbon Monoxide Diffusing Capacity (DLCO), and laboratory safety screen (haematology, biochemistry, urinalysis, urine drugs of abuse screen).

Volunteers who fulfil all screening requirements will be invited to return for the Study Period.

Study Period

The Study Period will be approximately 43 days in duration and subjects will be dosed and monitored on an outpatient basis.

Volunteers will attend the Clinical Centre in the morning of Day -1 where final confirmation of eligibility will be made after baseline assessments have been performed. Volunteers will

then be allowed to leave the unit and return in time for pre-dose procedures on the morning of Day 1.

Each subject will receive either a single dose of TD139 or placebo via DPI once daily for 14 days, following an overnight fast on day-1. The randomisation code will be generated using the PROC PLAN procedure of SAS®. Subjects will remain in the unit until 12 hrs post-dose on Day 1, providing the scheduled assessments have been completed and there are no ongoing safety concerns. Subjects will then return to the Clinical Centre on Days 2, 3, 7, 14 and 15 for scheduled assessments and to receive the IMP. On Days when subjects are not required to attend the Clinical Centre, they will self administer the IMP at home.

During the Study Period, assessments will include:

- Vital signs (supine blood pressure, pulse, O_2 saturation, oral temperature and respiratory rate)
- Lung function testing
- 12-lead ECG
- Physical examination
- Laboratory safety screen (haematology, biochemistry, urinalysis and urine drugs of abuse screen)
- Blood samples for PK, PG and PD measurements
- BAL fluid sampling for PK, PG and PD measurements.
- Exhaled breath condensate (EBC) collection for PD measurements

All Adverse Events (AE) and concomitant medications will be recorded from the time of the screening visit until the post-study follow-up visit.

Post-study assessments will be carried out 26 - 30 days after the last day of the Study Period (See Table 9.7.1).

The conclusion of the study is defined as the last visit of the last subject.

9.2 Dose Escalation Procedures and Stopping Criteria

9.2.1 Dose Escalation Procedures (Part 1)

Following completion of each cohort, a summary of all relevant safety data (AEs, vital signs, 12-Lead ECG and laboratory safety tests) and PK data (Cmax, Tmax, AUC0-24, AUC0-t, AUC0-∞ and t½) up to Day 3 (48 hours post dose) will be produced on behalf of the Chief Investigator. Planned doses may be modified following a review of emerging data. Progression to the next dose level and dose selection will be based on the available safety and PK data from at least 5 subjects from the preceding dose level. If fewer than 5 evaluable subjects are obtained then additional subjects must be dosed for that cohort prior to considering dose escalation. If it is not appropriate to escalate the dose according to the proposed dose escalation schedule, then the same dose, an intermediate dose or a lower dose may be given following discussion between the Sponsor and the Investigator. If the dose escalation stopping criteria in section 9.2.3 are met, then the dose level that was tested will

not be repeated or exceeded, however a lower dose may be given following discussion between the Sponsor and the Investigator.

The members of the dose escalation review committee will consist of [redacted] (chair and voting member), [redacted] (voting member) and [redacted] (PK, non voting member). Both voting safety committee members must participate in all meetings or provide an acceptable designee if unavailable.

There will be a Telephone Conference at a pre-appointed time to involve the Simbec Trial manager and Investigator (or their deputies) and the Sponsor's representative(s). After discussion of all the data, the decision will be made to dose escalate and a written document signed by the Investigator (or deputy) and Sponsor will be produced ratifying that decision. Recommendations to continue the study will require unanimous consent from the 2 voting members. In the event that unexpected safety issues are observed that are beyond the expertise of committee members, additional committee members or ad hoc committee members may be added to the safety committee. In the event that there is not a unanimous decision among the 2 voting members, an independent arbiter will be appointed to resolve the disagreement. Full minutes, to be agreed by all parties, will be produced for each discussion regarding dose escalation and filed in the Investigator Site File (ISF). A copy will be provided to the Simbec Pharmacist and this will allow the Investigational Medicinal Product (IMP) to be assembled for the next dose level prior to the performance of the next stage of the protocol.

The continuation of the study will be dependent upon the accrual of acceptable safety data following each cohort as indicated by the signature of each safety summary by the Chief Investigator or delegate and by the Sponsor.

Please see Section 9.2.3 for dose escalation stopping criteria.

9.2.2 Dose Decision and Review Procedures (Part 2)

Dose Selection for Part 2:

The dose of TD139 to be administered in Part 2 will be 3mg, based on data from Part 1 (single doses up to 10mg) and on pre-clinical efficacy and safety data. The highest acceptable dose level in Part 1 of the study will not be exceeded in Part 2.

Ongoing Safety Review:

Part 2 will be discontinued at any time if any unacceptable safety findings are identified (see Study Stopping Criteria in section 9.2.3).

Formal Interim Review:

During **Part 2** there will be an interim review by a safety committee after 8 subjects have been dosed to review the available blinded safety and PK data. The initial 8 subjects will be randomised in such a way that 5 will receive TD139 and 3 will receive placebo. Following a review of this data a decision will made as to whether to randomise up to 4 further subjects (where 3 subjects will receive TD139 and 1 will receive placebo). The dose and PK sampling times may also be modified following a review of the data.

The following will be reviewed at the interim review meeting:

- A summary of all relevant safety data from at least 7 out of 8 subjects (AEs, vital signs, 12-Lead ECG, spirometry and laboratory safety tests),
- PK data from at least 7 out of 8 subjects (Cmax, Tmax, $AUC_{0-\tau}$, AUC0-t, AUC0-∞ and t½)
- BAL data: At least 7 out of 8 subjects will have completed both of the following:
    - paired BAL samples
    - adequate BAL macrophage cell yields (absolute minimum macrophage numbers = 4 million)

The data will be compiled by Simbec on behalf of the Chief Investigator once the first 8 subjects have been dosed. Subsequent interim review meetings will take place as detailed in **Table S1**. Each site will be required to scan the applicable CRF pages and transfer the required safety data needed to Simbec data management in order for the data to be consolidated from each site. PK samples will be shipped to Simbec for assaying and subsequent PK analysis. A summary of all of the available data will be provided to all the safety committee for review.

The members of the safety committee will consist of [redacted] (joint chair and voting member), [redacted] (joint chair and voting member), [redacted] (joint chair and voting member), [redacted] (joint chair and voting member) and [redacted] (voting member). All 5 voting safety committee members must participate in all meetings or provide an acceptable designee if unavailable.

There will be a Telephone Conference at a pre-appointed time to involve all of the safety committee members. After discussion of all the data, the decision will be made as to whether to randomise up to 4 further subjects in Cohort 1 or move on to a second dose level in Cohort 2 (see Table S1). It will also be decided whether the dose and PK sampling times will also be modified. Recommendations to continue/discontinue/amend the study will require unanimous consent from the 5 voting members. In the event that unexpected safety issues are observed that are beyond the expertise of committee members, additional committee members or ad hoc committee members may be added to the safety committee. In the event that there is not a unanimous decision among the 5 voting members, an independent arbiter will be appointed to resolve the disagreement.

A written document signed by each site Investigator (or deputy) and Sponsor will be produced ratifying that decision. Full minutes, to be agreed by all parties, will be produced for each discussion regarding dose escalation and filed in the Investigator Site File (ISF). A copy will be provided to the Simbec Pharmacist and this will allow the Investigational Medicinal Product (IMP) to be assembled accordingly for each site. The procedure for the ongoing and interim data review in Part 2 will be fully documented to a dose review manual. The manual will be approved by the sponsor and all clinical site Investigators prior to the start of the trial.

Please see Section 9.2.3 for study stopping criteria.

9.2.3 Study Stopping Criteria

Part 1:

- Dose Escalation will stop if 3 or more subjects in a cohort experience the same moderate adverse event that is deemed possibly, probably or definitely related to IMP treatment.
- Dose Escalation will stop if 1 or more subjects in a cohort experience severe adverse event that is deemed possibly, probably or definitely related to IMP treatment.
- Dose escalation would stop if 1 or more than 1 subject in the cohort experience a drug related SAE or a clinically significant drug-related non-SAE.
- Dose escalation will stop if the C_{max} and/or AUC values in each cohort reach or exceed those observed in the dog following 9.1 mg/kg/day 14 day repeat dosing, equating to a gender-averaged AUC(0-t) of 2450 ng*hr/mL and Cmax of 558 ng/mL on Day 14.

Part 2:

- The study will be stopped if 3 or more subjects experience the same moderate adverse event.
- The study will be stopped if 2 or more subjects experience a severe adverse event.
- The study will be stopped if 1 subject experiences a drug related SAE or a clinically significant drug-related non-SAE.
- The study will be stopped if the Cmax and/or AUC values reach or exceed those observed in the dog following 9.1 mg/kg/day 14 day dosing, equating to gender-averaged AUC(0-t) of 2450 ng*hr/mL and Cmax of 558 ng/mL on Day 14.

During the clinical conduct of the study, all Investigators will be required to immediately inform the Chief Investigator, the sponsor and Simbec of any moderate, severe, SAE or clinically significant non-SAE. This notification is required in order to allow coordination of information and assessment on whether the stopping criteria has been met.

The procedure for the ongoing and interim data review in Part 2 will be fully documented to a dose review manual, approved by all parties.

The study will be discontinued if any unacceptable safety findings are identified. The Chief Investigator, Principal Investigators and the Sponsor will make this decision jointly. A written document signed by the Investigator (or deputy) and Sponsor will be produced ratifying the decision.

Please see Section 9.4.3 for possible reasons for discontinuation of an individual subject.

9.3 Discussion of Study Design, including the choice of Control Groups and Dose Leaders

This study will be divided into 2 parts. **Part 1** is a randomised, double-blind, single centre, placebo-controlled, SAD, phase I study designed to assess the safety, tolerability, PK and PD of TD139 in up to 36 healthy male subjects.

Part 1 of this study employs a single ascending dose design; corresponding placebo control will be administered in order to evaluate treatment-related effects.

The design of **Part 1** of this study is typical of that used for FIM studies with a “dose leader” design for built-in safety. A dose leader design will be implemented in which 2 subjects (1

TD139 and 1 placebo) in each cohort will be dosed approximately 24 hours before the rest of the Cohort. Providing there have been no safety concerns in the dose leader group up to the 24 hour time point, the remainder of the cohort (4 subjects) will be dosed a day later and will be randomised in such a way that one further subject receives placebo. This design allows maintenance of the "blind".

Safety and PK data from a minimum of 5 subjects of each cohort will be required for data review prior to dose escalation.

Part 2 will be a randomised, double-blind, multi-centre, placebo-controlled, multiple dose expansion cohort study designed to assess the safety, tolerability, PK and PD of TD139 in up to 24 male and female subjects of non child-bearing potential with IPF.

This part of the study will consist of 1 cohort of up to 24 IPF subjects, who will receive a single dose of TD139 or placebo via DPI once daily for 14 days (TD139 and placebo dosed according to **Table S1**). The initial dose level used will be 3mg based on PK and safety data from **Part 1** and on pre-clinical efficacy and safety data.

During **Part 2** there will be an interim review by the safety committee after 8 subjects have been dosed to review the available blinded safety and PK data. The initial 8 subjects will be randomised in such a way that 5 will receive TD139 and 3 will receive placebo. Following a review of this data a decision will made as to whether to randomise up to 4 further subjects (where 3 subjects will receive TD139 and 1 will receive placebo) in Cohort 1 or move on to a second dose level in Cohort 2 (see Table S1). The dose and PK sampling times may also be modified following a review of the data.

9.4 Selection of Study Population

Up to 36 healthy male subjects will be required to complete **Part 1** of the study. The subjects will be selected from a large panel who have offered their services as volunteers to Simbec for the purpose of undertaking REC and Regulatory Authority-approved studies on drug safety, absorption and disposition.

Part 1 of the study is to be conducted in healthy subjects and therefore participants are not expected to derive any therapeutic benefit from taking part. TD139 has not been previously administered to humans; therefore its effects in humans are as yet unknown. A healthy subject population with carefully considered inclusion/exclusion criteria will avoid the potential for interaction of TD139 with any underlying disease state or concomitant medication that it may be necessary for patients to take, while ensuring that subjects are fit and well enough for participation in the study.

Up to 24 male and female subjects of non child-bearing potential with a confirmed diagnosis of IPF will participate in **Part 2** of this study. Eligible subjects will be identified at 4 NHS centres (Royal Brompton Hospital, Edinburgh University Hospital, Royal Victoria Infirmary and Royal Devon and Exeter Hospital).

This clinical study can fulfil its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment and procedures are considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

9.4.1 Inclusion Criteria

Part 1

To be confirmed at Screening Visit:

- Healthy male subjects aged between 18 and 55 years of age.
- Male subject willing to use a condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from Day 1 until 3 months afterwards.
- Subject with a body weight of at least 50 kg and a Body Mass Index (BMI) within the range of 18-35 kg/m^2. BMI = Body weight (kg) / $[Height (m)]^2$.
- Subject with no clinically significant abnormal serum biochemistry, haematology and urine examination values within 28 days of the first dose.
- Subject with a negative urinary drugs of abuse screen, determined within 28 days of the first dose (N.B. a positive alcohol result may be repeated at the discretion of the Investigator).
- Subject with negative human immunodeficiency virus (HIV) and hepatitis B surface antigen (Hep B) and hepatitis C virus antibody (Hep C) results.
- Subject with no clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days of the first dose.
- Subjects must be a non-smoker or a former smoker (having ceased smoking for at least 6 months).
- Subjects with no clinically significant impairment in oxygen saturation.
- Subject must satisfy a medical examiner about their fitness to participate in the study.
- Subject must provide written informed consent to participate in the study.
- Subject must be available to complete the study (including all follow up visits).

To be confirmed at Baseline / Prior to First Dose:

- Subject continues to meet all screening inclusion criteria.
- Subject with a negative urinary drugs of abuse screen (including alcohol) prior to dosing.

Part 2

To be confirmed at Screening Visit:

- Male subject or female subject of non child-bearing potential with IPF.
- *For the purposes of this study, a female subject of non child-bearing potential is defined as the subject being amenorrheic for at least 12 consecutive months or at least 4 months post-surgical sterilisation (including bilateral fallopian tube ligation or bilateral oophorectomy with or without hysterectomy).*
- Male subject willing to use a condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from the first IMP administration until at least 3 months after receiving the last dose of the IMP.
- Subject aged between 45 and 85 years of age.
- Subjects with an FVC $\geq$ 45% predicted and an FEV1/FVC ratio $\geq$ 0.7.
- Subjects with oxygen saturation >90% by pulse oximetry while breathing ambient air at rest.
- Subjects with a diffusing capacity (DLCO) >25%.
- Subjects must have adequate organ function and a clinical diagnosis consistent with IPF prior to screening (based on the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Association (ATS/ERS/JRS/ALAT) consensus criteria. The diagnosis would ordinarily have been confirmed at a multidisciplinary team meeting where the HRCT findings in particular will have been discussed with a radiologist with Respiratory expertise.
- Subjects who are able to undergo bronchoalveolar lavage (BAL).
- Subject must provide written informed consent to participate in the study.
- Subject must be available to complete the study (including all follow up visits).
- Subject with a negative urinary drugs of abuse screen, determined within 28 days of the first dose (N.B. a positive alcohol result may be repeated at the discretion of the Investigator).
- Subject with negative human immunodeficiency virus (HIV) and hepatitis B surface antigen (Hep B) and hepatitis C virus antibody (Hep C) results.
- Subject with no clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days of the first dose.

To be confirmed at Baseline / Prior to First Dose:

- Subject continues to meet all screening inclusion criteria.

9.4.2 Exclusion Criteria

Part 1

To be confirmed at Screening Visit:

- A clinically significant illness or surgery within 8 weeks prior to first administration of the study medication.
- Significant medical history that, in the Investigator's opinion, may adversely affect participation.
- History of allergy or significant adverse reaction to drugs similar to the investigational drug, to nicotine, or to cholinergic drugs or to any drugs with a similar chemical structure.
- History of hypersensitivity (anaphylaxis, angioedema) to any drug.
- Use of any drug known to induce or inhibit hepatic drug metabolism, within 30 days prior to first administration of the study medication.
- Use of medications known to prolong QT/QTc interval within 14 days prior to the first administration of the study medication.
- Any clinically significant findings of physical examination or laboratory findings at Screening Visit.
- A clinically significant history of drug or alcohol abuse.
- Receipt of regular/OTC medication within 14 days of the first dose that may have an impact on the safety and objectives of the study (at the Investigator's discretion).
- Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular or metabolic dysfunction.
- Inability to communicate well with the Investigator (i.e., language problem, poor mental development or impaired cerebral function).
- Participation in a New Chemical Entity clinical study within the previous 4 months or a marketed drug clinical study within the previous 3 months. *(N.B. washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study)*.
- Donation of 450 mL or more blood within the previous 3 months.

To be confirmed at Baseline / Prior to First Dose:

- Development of any exclusion criteria since the Screening Visit
- Receipt of any medication since the Screening Visit that may have an impact on the safety and objectives of the study (at the Investigator's discretion).

Part 2

- Any condition that makes the patient at unacceptable risk for bronchoscopy.

- Active cigarette smoking (defined as smoking more than 3 cigarettes daily within the last 6 months).
- Presence of a significant co-morbidity felt to limit life expectancy to less than 12 months.
- HRCT pattern showing emphysema more than the extent of fibrosis of the lung area conducted within 12 months of Day 1.
- Evidence of renal, hepatic, central nervous system, or metabolic dysfunction
- Evidence of poorly controlled diabetes mellitus (defined as a HbA1c of > 59 mmol/mol (7.5%).
- Use of systemic immunosuppressants within 30 days of dosing.
- Subjects currently receiving oral steroids, cytotoxic drugs (e.g. chlorambucil, azathioprine, cyclophosphamide, methotrexate), antifibrotic drugs (e.g. pirfenidone), vasodilator therapies for pulmonary hypertension (e.g bosentan), unapproved (e.g. INF-γ, penicillamine, cyclosporine, mycophenolate) and/or investigational therapies for IPF or administration of such therapies within 4 weeks of initial screening. A current inhaled steroid dose of ≤1000 micrograms Beclomethasone dipropionate (BDP) equivalent per day is acceptable if the dose is anticipated to remain stable during the study.
- History of malignancy, including carcinoma during the preceding five years.
- History of, or current asthma.
- Participation in a clinical study of an unlicensed drug in the previous 4 months, or a marketed drug study within the previous 3 months. *(N.B. washout period between trials defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study)*.
- Females of child-bearing potential and/or with a positive pregnancy test at Screening Visit.

To be confirmed at Screening Visit:

- Development of any exclusion criteria since the Screening Visit

9.4.3 Removal of Subjects from Therapy or Assessment

Each subject will be informed of their right to withdraw from the study at any time and for any reason.

The Investigator may withdraw a subject from the study at any time for any of the following reasons:

- If a subject experiences a serious or intolerable AE, that prevents them from continuing. As there have been no significant clinical or pre-clinical toxicology flags in studies with TD139 there are no drug specific side effects anticipated.
- If a subject incurs a significant protocol violation.

- At the request of the Sponsor.
- If the Investigator considers that remaining in the study compromises the subject's health or the subject is not sufficiently cooperative.
- If a subject is lost to follow-up.

The reasons for any subject withdrawal will be recorded on the study completion form of the Case Report Form (CRF).

If a subject is withdrawn, chooses to withdraw from the study for any reason or prematurely discontinues the IMP, the Chief Investigator will make every possible effort to perform the evaluations described for the Post Study Visit. At the discretion of the Chief Investigator, the subject could continue with study assessments after discontinuation of IMP until the Post-Study Visit is performed. Once a subject prematurely discontinues the IMP or is withdrawn the subject cannot re-enter the study. The data collected from withdrawn subjects will be included in the study report.

In the event of any abnormalities considered to be clinically significant by the investigating physician, subjects will be followed up with appropriate medical management until values are considered to be clinically acceptable. Referral or collaborative care will be organized if considered necessary.

In **Part 1** up to 36 subjects and in **Part 2** up to 24 subjects are required to complete the study. Subjects who withdraw from the study before receiving any study medication will be replaced. Subjects who are withdrawn from the study due to significant drug-related AEs will not be replaced. Replacement of all other subjects withdrawn from the study after receiving study medication will be decided on a case by case basis by the Chief Investigator and Sponsor.

9.5 Additional Advice for Study Population

9.5.1 Contraception

To prevent pregnancy male subjects (**Part 1** and **Part 2**) with female partners of child bearing potential must take adequate contraceptive precautions for the entire duration of study participation. Adequate contraceptive precautions for male subjects include:

- Condom
- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The chosen contraception method(s) must be followed from the first IMP administration until at least 3 months after receiving the last dose of the IMP.

9.5.2 Sperm Donation

Subjects must not donate sperm throughout the study and for a safety period of at least 3 months after the final dose of IMP.

9.5.3 Diet and Fluid Restrictions

9.5.3.1 Meal Times/Fasts

Part 1

Subjects will fast overnight for at least 10 hours (hrs) then -

Lunch will be served: 4 hrs post-dose

Dinner will be served: 8 hrs post-dose

Snack will be served: 12 hrs post-dose

On all non-dosing study days, whilst resident at the Clinical Unit, meals will be served at standard times.

Part 2

In Part 2 there will be no restrictions on volunteer meal times.

9.5.3.2 Fluid Intake

Water is allowed *ad libitum* during the study.

In **Part 1**, decaffeinated tea and coffee as well as squash/cordial are allowed from 4 hrs post-dose.

9.5.3.3 Alcohol Intake

The consumption of alcohol will be limited to a maximum of 2 units per day from 7 days prior to the administration of the first dose. Alcohol will be avoided completely for a period of not less than 48 hrs prior to the first dose and throughout the study period.

N.B. Any deviation outside this alcohol intake restriction will be assessed on a case by case basis at the Investigator's discretion (provided the subject's alcohol intake will not impact in the safety aspects and objectives of the study and the subject has a negative alcohol screen prior to dosing).

9.5.3.4 Caffeine

Food or drink containing caffeine, including coffee, tea, cola, energy drinks or chocolates will be avoided completely whilst the subjects are resident in the Clinical Unit (during the dosing period).

9.5.3.5 Poppy Seeds

Subjects will be advised that they must not eat food containing poppy seeds for 3 days before each visit to the Clinical Unit as consumption of poppy seeds can lead to a positive opiate result in the drugs of abuse test.

9.5.3.6 Grapefruit Juice and Other Restrictions

No food or drink containing grapefruit, cranberry, or Seville oranges (including marmalade and fruit juices), and/or food or drink, sweets, candies or other confectionary containing liquorice will be allowed from 7 days before dosing until the end of the study.

9.5.4 Other Life-Style Restrictions

9.5.4.1 Strenuous Exercise

Subjects should not engage in any strenuous exercise from 3 days before the first dose until the end of the study (i.e. completion of follow up visit).

9.5.4.2 Blood Donation

Subjects will be advised that they should not donate blood for at least 3 months after the final study visit.

9.6 Investigational Medicinal Product

9.6.1 Identity

The identity of each treatment is detailed in Table 9.6.1.

Table 9.6.1 Identity of Investigational Medicinal Products

IMP Name	Strength	Presentation/Form	Route
TD139	0.15mg	Capsule	Inhalation via DPI
TD139	1.5mg	Capsule	Inhalation via DPI
TD139	5mg	Capsule	Inhalation via DPI
TD139	50mg	Capsule	Inhalation via DPI
Placebo for TD-139	N/A	Capsule	Inhalation via DPI

The documentation supplied with the bulk IMP will make it possible to retrace the composition and pharmaceutical quality of the product.

9.6.2 Receipt and Storage

The IMPs will be prepared by the sponsor and supplied to the Investigator as open labeled bulk medication. The Sponsor must notify the Investigator prior to dispatch of IMP supplies, and of the anticipated date of their arrival. The IMP should arrive at each study site at least 7 days before the first dosing day.

The IMPs must be received at each Investigational site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. After a review of the temperature monitors included with shipments the Sponsor will confirm that the transportation conditions were acceptable.

The IMPs will be stored under quarantine in a segregated, study-specific area, at room temperature in a secure, temperature-controlled pharmacy.

9.6.3 Assembly and Release

The IMP will be assembled by suitably trained staff according to local pharmacy SOPs at each Investigational site.

The IMP will be labelled as specified in Annex 13 (manufacture of investigational medicinal products) of the European Commission (EC) guide to Good Manufacturing Practice (GMP) [10].

In **Part 1** the finished IMP will be certified by Simbec's QP according to the Simbec SOP BD/324/13/29.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

9.6.4 Administration

All doses will be administered using the Plastiape DPI (a CE marked device). Study centre personnel will dispense the IMPs, and site personnel will facilitate administration when the subject is in the clinic, however subjects themselves will hold the DPI device during inhalation.

Capsules will be loaded into the DPI as per the instructions provided with the device. A single device will be used per capsule actuation throughout **Part 1** of the study (to avoid any potential carry over). This means that in **Part 1**, each time a subject/patient is dosed with a capsule they will use a new device (e.g. if the dose requires 2 capsules, then 2 devices are used). For **Part 2**, subjects will use a new device per week (7 days) for the 14 day dosing period.

Two inhalations will be performed on each capsule. Any problems with drug administration will be noted in the CRF. All empty capsules should be retained for accountability purposes.

In **Part 2** where some of the doses will be administered at home, site staff will instruct the patient on how to take the drug, including the number of capsules to be inhaled each day and the timing of dose administration. For daily doses taken at home, patients should be advised to administer the study drug at approximately the same time of day. Subjects will be given a DPI device and enough supplies to cover the number of home doses required. Subjects will be asked to make a note in their diary if they have an issue whilst using the inhaler. The subjects will also be instructed to bring back used and unused medication at selected time-points for drug accountability checking.

All subjects must be trained in the use of the inhaler device on Day -1, according to the instructions provided with the device. Placebo capsules and inhaler devices will be provided for training and demonstration purposes. The same DPI devices can be used for training throughout the study but must not be used for dosing.

Part 1

A dose leader design will be implemented in which 2 subjects in each cohort will be dosed approximately 24 hours before the rest of the Cohort. Of these 2 subjects, 1 will receive TD139 and 1 will receive placebo. Providing there have been no safety concerns in the dose leader group up to the 24 hour time point, the remainder of the cohort (4 subjects) will be dosed. Of these 4 subjects, 3 will receive TD139 and 1 will receive placebo.

Dose escalation will only proceed in the subsequent cohorts if blinded safety and PK data (up to Day 3) from the subjects in the preceding cohort have been reviewed by the Sponsor and Chief Investigator and have been found to be satisfactory.

Planned dose levels are as follows:

Up to 6 cohorts (Cohorts 1-6) of 6 subjects will be randomly assigned to receive either a single oral dose of TD139 in an ascending dose fashion or a single dose of placebo. Within each cohort, 4 subjects will receive TD139 and 2 subjects will receive placebo.

The 6 planned ascending doses to be studied are:

- Cohort 1: 0.15mg TD139 or matching placebo
- Cohort 2: 1.5mg TD139 or matching placebo
- Cohort 3: 3mg TD139 or matching placebo
- Cohort 4: 10mg TD139 or matching placebo
- Cohort 5: 20mg TD139 or matching placebo
- Cohort 6: 50mg TD139 or matching placebo

Dose escalation will stop at any time or dose levels may be modified downwards if unacceptable safety findings are identified. If there is any indication that it is not possible to maintain an ample safety margin with higher doses in subsequent cohorts, the dose escalation will be stopped or modified accordingly. Subsequent doses may vary from those planned depending on safety and pharmacokinetic results. The maximum dose of TD139 (50 mg) will not be exceeded.

IMP administration will be documented in the Case Report Forms (CRFs).

There will be at least 14 days between cohorts.

Part 2

Part 2 will include up to 24 subjects with IPF. Randomisation of the 24 subjects will take place according to the schedule outlined in **Table S1** with TD139 and placebo via DPI once daily for 14 days. The randomisation code will be designed so that the first 8 subjects will be randomised in a 5:3 TD139 to placebo ratio..

The starting dose of TD139 to be administered in Part 2 is 3mg based on interim data from Part 1 and on pre-clinical efficacy and safety data. The highest acceptable dose level in Part 1 of the study will not be exceeded in Part 2. Dose escalation will not take place or dose levels may be modified downwards if unacceptable safety findings are identified.

IMP administration will be documented in the Case Report Forms (CRFs) whilst the subject is in house or in a subject diary whilst they are at home.

9.6.5 Return/Destruction

Following the Sponsor's approval, all remaining IMP will either be returned to the Sponsor or sent for destruction within 8 weeks of completion of the study-dosing period.

All used IMP containers and unused IMP will be held under quarantine in the investigator site pharmacy pending return/destruction.

9.6.6 Method of Assigning Subjects to Treatment Groups

Part 1

Subjects will be allocated to treatment cohorts according to a randomisation code produced by Simbec Research using the PROC PLAN procedure of SAS® version 9.1.3.

A dose leader design will be implemented for each Cohort, with 2 subjects being dosed on the first dosing day (of these, 1 will receive TD139 and 1 will receive placebo) and the remainder of the cohort dosed 24 hours later (4, including 1 further subject receiving placebo). Thus the remainder of the volunteers should be randomly allocated 3:1 to receive TD139 or placebo.

Up to 36 subjects will be randomised (6 cohorts of 6 subjects).

Subjects will be numbered sequentially from 001 (i.e. 001, 002 etc). Replacement subjects will be assigned the same number and randomisation as the subject they are replacing, however, the number will be prefixed with 100 (i.e. 101 would replace 001 etc).

Part 2

Subjects will be allocated to treatment according to a randomisation code produced by Simbec Research using the PROC PLAN procedure of SAS® version 9.1.3. Up to 24 subjects will be randomised. The randomisation code will be designed so that the first 8 subjects will be randomised in a 5:3 TD139 to placebo ratio and thereafter according to the schedule in **Table S1**.Following each interim review meeting in Part 2, a new randomisation code will be produced based on the decision of the safety committee.

The randomisation process and subject numbering format will be documented in a Part 2 pharmacy manual.

9.6.7 Selection of Doses in the Study

For Part 1, the planned doses of TD139 to be studied are: 0.15mg, 1.5mg, 3mg, 10mg, 20mg and 50mg. The maximum dose of TD139 (50 mg) will not be exceeded.

The planned dose levels have been selected following review of non-clinical pharmacokinetic, safety pharmacology and toxicology data.

Pharmacokinetic, toxicokinetic and toxicology studies in mice, rats and dogs indicate the drug is readily bioavailable via the inhaled route with little or no accumulation after 14-day dosing and is excreted in the faeces with a $t_{1/2}$ of approximately 6 h. The human starting dose is 0.15mg. Given the NOAEL's in mouse and dog studies, this FIM dose is over 100-fold below the industry accepted safe starting dose. Given the lack of adverse effects seen in the two species, no direct anticipated adverse drug specific side effects are expected in man nor are any drug interactions anticipated given the clear cytochrome profiling. Further details regarding non-clinical pharmacokinetic, safety pharmacology and toxicology data can be found in the IB[11].

If unacceptable safety findings are identified or if there is any indication that it is not possible to maintain an ample safety margin with higher doses in subsequent cohorts the dose escalation will be stopped or modified accordingly. Subsequent doses therefore may vary from those planned depending on safety and pharmacokinetic results. If the dose escalation stopping criteria for Part 1 in section 9.2.3 are met, then the dose level that was tested will not be repeated or exceeded, however a lower dose may be given following discussion between the Sponsor and the Investigator.

The selection of the 3mg starting dose for **Part 2** was determined based upon interim safety and PK data from **Part 1 (in single doses up to 10mg)** and on pre-clinical efficacy and safety data. The highest acceptable dose level in Part 1 of the study will not be exceeded in Part 2.

9.6.8 Timing of Dose for Each Subject

In **Part 1** doses will be administered on day 1 at approximately 9.00 a.m.

In **Part 2** doses will be administered on Day 1 at approximately 9.00 am. For doses taken at home, patients should be advised to administer the study drug at approximately the same time as the first dose, each day it is taken.

9.6.9 Blinding

A designated individual from the Pharmacy Department at Simbec will generate the randomisation code under the guidance of a statistician. All site and Sponsor personnel involved in the study will be blinded with regard to the IMP being administered with the exception of the pharmacist or designee at each site responsible for the preparation of subject doses who will not be blinded. A copy of the original randomisation code will be issued to the pharmacist or designee for this purpose.

The Bioanalytical Scientist (at Simbec) will be provided with a copy of the randomisation code for the purposes of analysing the samples. The Bioanalytical Scientist will provide the drug concentration data in a re-coded subject number format, in order to maintain the blind of study personnel. Re-coded PK data will also be included in an interim data report following completion of the single-dosing periods for each cohort. Analysis of the safety data will also be performed on blinded data.

Subject doses: Once the randomisation code has been authorised as per Simbec SOPs, each subject dose will be packaged and labelled for individual subjects by designated individuals from the Pharmacy Department at each clinical site on behalf of the Sponsor.

Code break envelopes: Once the randomisation code has been authorised as per applicable Simbec SOPs, the pharmacist or designee will produce individual sealed code-break envelopes that contain the treatment allocation(s) for each subject. The pharmacist or designee will provide the Principal Investigator with the applicable set of sealed envelopes. Each site will store the sealed envelopes in the restricted access pharmacy. A set of code break envelopes will also be provided to the person responsible for pharmacovigilance.

If the Investigator believes that knowledge of the IMPs received by a subject is essential for appropriate treatment of an AE, the Investigator should ideally consult the Sponsor before breaking the code. In any event, the Investigator should inform the Sponsor as soon as practical whenever the code has been broken for a subject. In the event that the site requires

emergency access to an individual subject code and personnel from the Sponsor are not available each site may break the blind without prior consultation with the Sponsor. In such an event, the Chief Investigator, Principal Investigator or delegate would notify the Sponsor as soon as possible *via* email or fax. If the Investigator needs to break the blind for an individual subject, the date and reason will be recorded in the subject's CRF. The Investigator will not reveal the unblinded treatment code to any other member of the clinical team involved in the study or to the Study Monitor. If the code is broken for any individual subject, the subject will be withdrawn from the study and the procedures accompanying withdrawal performed. If the code is broken without justification, this will be deemed a serious protocol violation.

9.6.10 Prior and Concomitant Therapy

Part 1: Prescribed drugs should not be taken for 14 days before the first dose and throughout the duration of the study-dosing period. Over the counter drugs and herbal remedies and supplements should not be taken from 14 days prior to the first dose and throughout the duration of the study dosing periods. Prescribed or over the counter drugs and herbal remedies and supplements taken during the 14 days before the first dose, and the reason for taking them, will be noted in the subject's CRF. Inclusion of subjects who have taken prescribed or over the counter medication during this period will be reviewed on a case-by-case basis in relation to the safety aspects and objectives of this study.

Part 2: Prescribed drugs should not be taken for 14 days before the first dose and throughout the duration of the study dosing period, with the exception of those listed in the study inclusion/exclusion section. Over the counter drugs and herbal remedies and supplements should not be taken from 14 days prior to the first dose and throughout the duration of the study dosing periods. Prescribed or over the counter drugs and herbal remedies and supplements taken during the 14 days before the first dose, and the reason for taking them, will be noted in the subject's CRF. Inclusion of subjects who have taken prescribed or over the counter medication during this period will be reviewed on a case-by-case basis in relation to the safety aspects and objectives of this study.

Concomitant medication should be avoided throughout the duration of the study dosing periods, with the exception of paracetamol (which may be taken as an analgesic to a maximum of 2 g in 24 hrs) and ibuprofen (which may be taken as an analgesic to a maximum of 1200 mg in 24 hrs [400 mg tds]), with the agreement of the Investigator.

If intake of concomitant medication becomes necessary for the treatment of an AE during the study, the daily dosage, duration and reasons for administration will be recorded on the subject's CRF. Subjects will inform the Investigator as soon as possible if concomitant medication was necessary during out-patient periods and the daily dosage, duration and reasons for administration will be recorded on the subject's CRF.

All concomitant medication taken during the screening period and between first dose and the Post-Study Visit will be recorded in the subject's CRF.

9.6.11 Treatment Compliance

When in the Clinical Unit, doses will be taken under supervision and the exact dosing time for each subject will be recorded on the subject's CRF. For doses administered by the subject at home, the dosing time will be recorded in a dosing diary.

9.7 Efficacy and Safety Variables

9.7.1 Efficacy and Safety Measurements Assessed and Flow Chart

Pre-study screening assessments will be carried out in the 28 day period before the first dose.

In **Part 1** post-study assessments will be carried out 12-16 days after the final study procedure on day 14.

In **Part 2** post-study assessments will be carried out 26 - 30 days after the last day of the Study Period.

All study personnel who have been appropriately trained will carry out study procedures.

The Study Flow Chart is provided in Table 9.7.1 and Table 9.7.2.

Where more than one procedure is scheduled for the same time-point, the following order of priority will apply:

1. PK and PD blood sampling (a window of ± 2 min in relation to the nominal time-point is allowed)

2. Vital signs and 12-lead ECG (a window of ± 10 min in relation to the nominal time-point is allowed. A window of ± 30 mins will apply to the Day 14, 2h time point in Part 2 to fit around the BAL sampling procedure).

All pre-dose/baseline assessments may be performed within the 30 mins before dosing.

Table 9.7.1 Part 1 Study Flow Chart

Visit	Screening	Treatment Period						Post Study
		In-house			Return Visits			
Day (h)	(Day -28 to -2)	Day -1	Day 1	Day 2 (24h)	Day 3 (48h)	Day 8 (168h)	Day 14 (312h)	(Day 26-30)
Informed consent	X							
Inclusion/Exclusion	X	X						
Demographics	X							
Height / Weight / BMI [1]	X							X
Medical History & Concurrent Conditions	X							
Biochemistry Haematology Urinalysis	X	X	X[2]	X				X
Virology	X							
Drugs of Abuse	X	X						
12-Lead ECG	X	X	X[3]	X		X	X	X
Physical Examination	X							X
Vital Signs[4]	X	X	X[5]	X	X	X	X	X
Spirometry (FEV1 & FVC)	X							
Dose			X					
PK Blood Sampling			X[6]	X	X			
PG & Flow Cytometry sampling		X	X[7]	X				X
Galectin-3 Blood sampling		X	X[8]		X			X
Exhaled Breath Condensate		X	X[9]					X
Adverse Events		←	—	—	—	—	—	→
Concomitant Medication	X	←	—	—	—	—	—	→

Table 9.7.1 Study Flow Chart Footnotes:

1. Height at Screening Visit only.
2. Laboratory safety samples will be taken at 6h post-dose.
3. 12-lead ECG to be measured prior to dosing = 0h and then at 30min and 2h post-dose.
4. Blood pressure, pulse, O_2 saturation, oral temperature, respiratory rate.
5. Vitals signs will be recorded prior to dosing = 0h and then at 5min, 15min, 30min, 2h, and 6h post-dose.
6. PK blood sampling will be taken prior to dosing = 0h and then at 15min, 30min, 45min, 1h, 2h, 3h, 4h, 5h, 6h, 12h and 18h post-dose.
7. Blood sampling for pharmacogenetic analysis (mRNA) and peripheral blood flow cytometry will be taken prior to dosing = 0h and then at 30min, 2h and 18h post-dose.
8. Blood sampling for Galectin-3 analysis will be taken prior to dosing = 0h and then at 5h post-dose.
9. Exhaled Breath Condensate will be taken prior to dosing = 0h and then at 1.5h post-dose.

Table 9.7.2 Part 2 Study Flow Chart

Visit	Screening	Treatment Period						Post Study
Day	(Day -28 to -2)	Day -1	Day 1-3	Day 4-6	Day 7	Day 8-13	Day 14-15	(Day 41-45)
Clinic Visits	X	X	X		X		X	X
Informed consent	X							
Inclusion/Exclusion	X	X						
Demographics	X							
Height / Weight / BMI [1]	X							X
Medical History & Concurrent Conditions	X							
Biochemistry, Haematology, Urinalysis	X	X	X[2]				X[2]	X
Pregnancy Test	X							
Virology	X							
Drugs of Abuse	X	X						
12-Lead ECG	X	X			X[3]		X[3]	X
Physical Examination	X							X
Vital Signs[4]	X	X	X[5]		X[5]		X[5]	X
Spirometry[6]	X						X[7]	X
DLCO	X							
Dose[8]			X	X	X	X	X	
PK Blood Sampling			X[9]		X[9]		X[9]	
PG & Flow Cytometry Sampling			X[10]		X[10]		X[10]	
PBMC analysis			X[11]				X[11]	
Galectin-3 Blood sampling		X	X[12]		X[11]		X[12]	X
Exhaled Breath Condensate		X					X[13]	X
Bronchoalveolar Lavage		X[14]					X[14]	
Adverse Events		←	—	—	—	—	→	
Concomitant Medication	X	←	—	—	—	—	→	

Table 9.7.2 Study Flow Chart Footnotes:

1. Height at Screening Visit only.
2. Laboratory safety samples will be taken on Day 1 at 6h post-dose, on Day 3 (prior to dosing) and Day 14 at 6h post-dose.
3. 12-lead ECG to be measured on Day 7 and Day 15.
4. Blood pressure, pulse, O_2 saturation, oral temperature, respiratory rate.
5. Vitals signs will be recorded on Day 1 prior to dosing = 0h and then at 5min, 15min, 30min, 2h, and 6h post-dose; Day 2, 3 and 7 prior to dosing = 0h; Day 14 prior to dosing = 0h and then at 5min, 15min, 30min, 2h, and 6h and 24h post-dose. (A window of ± 30 mins will apply to the Day 14, 2h timepoint in Part 2 to fit around the BAL sampling procedure)
6. Spirometry measurement to be recorded at equivalent time at each timepoint (± 1h).
7. Spirometry to be performed on Day 14 **prior** to BAL sampling procedure.
8. Subjects will be dosed with the IMP at the Clinical Centre during clinic visits and will self administer the IMP on non clinic visit days.
9. PK blood sampling will be taken on Day 1 prior to dosing = 0h and then at 15min, 30min, 45min, 1h, 2h, 3h, 4h, 5h, 6h and 12h post-dose; Day 2, 3 and 7 prior to dosing = 0h; Day 14 prior to dosing = 0h and then at 15min, 30min, 45min, 1h, 2h, 3h, 4h, 5h, 6h, 12h and 24h post-dose.
10. Blood sampling for pharmacogenetic analysis (mRNA) and peripheral blood flow cytometry will be taken Day 1 prior to dosing = 0h and then at 30 min post-dose, Day 7 at 2h post-dose and Day 14 prior to dosing = 0h and then at 30 min post-dose.
11. Blood sampling for pharmacogenetic analysis of peripheral blood mononuclear cells (PBMCs) will be taken Day 1 prior to dosing = 0h and Day 14 at 30 min post-dose.
12. Blood sampling for Galectin-3 analysis will be taken on Day 1 prior to dosing = 0h and then at 5h post-dose, Day 7 (anytime) and Day 14 prior to dosing = 0h.
13. Exhaled Breath Condensate to be performed on Day 14 between 1h and 2h post-dose.
14. BAL to be performed on Day 14 between 1h and 4h post-dose. (It is essential post treatment bronchoscopy is performed in the morning.)

9.7.1.1 Demographic and Background Assessments

Demographic and background assessments will be performed during the study at the time-points specified in the Study Flow Chart, Table 9.7.1 and Table 9.7.2 and include:

9.7.1.1.1 Demographics

Demographic data to be collected include: age, date of birth, gender, race, ethnicity, height, weight and BMI.

Height in metres (to the nearest cm) and weight in kilograms (to the nearest 0.1 kilogram) in indoor clothing and without shoes will be measured. Body Mass Index = Body weight (kg) / [Height (m)]^2 will be calculated.

9.7.1.1.2 Medical History and Concurrent Conditions

Relevant medical history and current conditions will be recorded in the CRF.

9.7.1.1.3 Physical Examination

A Physician will perform a physical examination. The examination will include: Ear/nose/throat, ophthalmological, dermatological, cardiovascular, respiratory, gastrointestinal, central nervous system, lymph nodes and musculoskeletal systems. Other body systems can be examined if required, at the discretion of the Investigator.

9.7.1.1.4 Virology

Virology screen will include: Hep B, Hep C and HIV.

Virology will be analysed by the local laboratory according to their local procedures.

9.7.1.1.5 Drugs of Abuse and Alcohol

Urine alcohol and drugs of abuse screen will include: Cannabinoids, amphetamines, benzodiazepines, opiates and cotinine.

Drugs of abuse and alcohol samples will be analysed by the local laboratory according to their local procedures.

9.7.1.1.6 Pregnancy Test, Menstrual and Obstetric History

Part 2 only: Pregnancy tests will be performed on all female subjects regardless of post-menopausal or sterilised status. Pregnancy tests will be performed by the local laboratory according to their local procedures.

9.7.1.2 Compliance with Inclusion/Exclusion Criteria

The Investigator will assess all participants against the study inclusion and exclusion criteria at the Screening Visit. Compliance will be re-confirmed at Baseline.

9.7.1.3 Efficacy Assessments

Not applicable to this study

9.7.1.4 Safety Assessments

Safety assessments will be performed during the study at the time-points specified in the Study Flow Charts and include:

9.7.1.4.1 Adverse Events

AEs and serious adverse events (SAEs) that occurred during the study along with their severity and relationship to study drug will be reported.

An AE is defined as:

Any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An unexpected adverse reaction is defined as:

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorized product)

AEs will be monitored throughout the study from the first dose through to the follow-up post study visit. All AEs should be recorded, whether considered minor or serious, drug-related or not.

All abnormal laboratory findings considered to be clinically significant must be recorded as AEs.

Recording of Adverse Events

All of the following details should be recorded in the subject's CRF for each AE:

- Full description of AE.
- Date and time of onset.
- Date and time of resolution.
- Severity of event, to be assessed by the investigating physician in accordance with the definitions below.
- Relationship to IMP to be assessed by the investigating physician in accordance with the definitions below.
- Action taken (if any).
- Outcome and details of any further follow-up.

Grades of Adverse Event Severity

The following grades should be used by the investigating physician to describe the severity of AEs.

The following are the only grades which should be used to describe AE severity. Only 1 severity grade should be used for each AE (e.g. mild - moderate is not acceptable).

SEVERITY OF THE AE	DEFINITION
Mild AE	The AE does not interfere with the subject's daily routines. It causes no more than slight discomfort
Moderate AE	The AE interferes with some aspects of the subject's daily routines.
Severe AE	The AE causes inability to carry out the subject's daily routine.

Definitions of Adverse Event Causality

The following definitions should be used by the investigating physician to describe the relationship between an AE and the IMP.

The following are the only definitions, which should be used to describe the relationship between AEs and the IMP. Only 1 relationship definition should be used for each AE (e.g. possible-probable is not acceptable).

RELATIONSHIP TO IMP	DEFINITION
Almost Definite	• Distinct temporal relationship with drug treatment. • Known reaction to agent or chemical group, or predicted by known pharmacology. • Event cannot be explained by subject's clinical state or other factors.
Probable	• Reasonable temporal relationship with drug treatment. • Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. • Event cannot easily be explained by subject's clinical state or other factors.
Possible	• Reasonable temporal relationship with drug treatment. • Event could be explained by subject's clinical state or other factors.
Unlikely	• Poor temporal relationship with drug treatment and/or • Event easily explained by subject's clinical state or other factors.
Unrelated	• Event occurred before dosing or • Event or intercurrent illness due wholly to factors other than drug treatment.

Serious Adverse Events

"SAE", "serious adverse reaction" or "unexpected serious adverse reaction" is defined in Statutory Instrument 2004 No. 1031 as any AE, adverse reaction or unexpected adverse reaction, respectively, that

a. results in death,
b. is life-threatening,
c. requires hospitalisation or prolongation of existing inpatients' hospitalisation,
d. results in persistent or significant disability or incapacity, or

e. consists of a congenital anomaly or birth defect.

Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (referred to as 'important medical events') should also be considered as 'serious' in accordance with the definition.

SAEs must be notified immediately (and within 24 hrs) by telephone or email to the Sponsor's Responsible Physician, [redacted] (Tel: [redacted] E-mail: [redacted]), Study Monitor, [redacted] (Tel: [redacted] Email: [redacted]) and Diamond Pharma Services by [redacted] This should be followed by a written report within 3 working days.

AEs which meet all of the following criteria

- Serious
- Unexpected (i.e. is not consistent with the investigator's brochure)
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product

will be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs) and should be reported to the REC and to the MHRA in accordance with applicable regulatory requirements for expedited reporting. It is the Sponsor's responsibility to report SUSARs to the REC and MHRA, although this responsibility will be delegated to the Investigator.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Monitoring of Subjects with Adverse Events

In the event of any abnormalities considered to be clinically significant by the investigating physician, subjects will be followed up with appropriate medical management until:

- It has resolved/returned to normal or baseline.
- The event has stabilized at a level acceptable to the Investigator and is not considered to be clinically significant.

Pregnancy

Pregnancies must be reported immediately and should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy outcomes must be collected for females who took the study drug and the female partners of any males who took the study drug. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.7.1.4.2 Laboratory Safety Assessments

9.7.1.4.2.1 Routine Laboratory Safety Screen

Routine laboratory safety screen samples will be analysed by the local laboratory according to their local procedures. Printed laboratory Reports will include normal reference ranges.

A decision regarding whether the result outside the reference range is of clinical significance or not shall be made by the investigator and the report will be annotated accordingly. Clinically significant abnormalities should be recorded on the AE page. The reference ranges for local laboratory parameters will also be filed in the Investigator Site File.

Haematology: Haematology assessments will include: Haemoglobin (HGB), haematocrit (HCT), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), red blood cells (RBC), white blood cells (WBC), neutrophils (NEUT), lymphocytes (LYMP), monocytes (MONO), eosinophils (EOS), basophils (BASO) and platelets (PLT).

Biochemistry: Biochemistry assessments will include: Total protein (TP), albumin (ALB), total bilirubin (BIL-T), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transferase (GGT), glucose (GLU), sodium (NA), potassium (K), bicarbonate (HCO_3), urea and creatinine (CREA).

Urinalysis: Urinalysis assessments will include: protein, GLU, specific gravity, ketones, urobilinogen, bilirubin, pH and blood). In the event that the 'dipstick' was positive, RBCs, WBCs, epithelial cells, crystals, bacteria and casts will be examined microscopically. The microscopy will be performed by the local laboratory according to their local procedures.

Urinalysis will be performed by the local laboratory according to their local procedures.

9.7.1.4.3 Vital signs

Vital signs assessments will include: Systolic and diastolic blood pressure, pulse, O_2 saturation, oral temperature and respiratory rate.

Measurements will be recorded in the supine position after 5 minutes (mins) rest. Blood pressure, pulse, O_2 saturation and temperature will be measured using an automated validated device, with an appropriately sized cuff.

9.7.1.4.4 12-lead ECG

12-lead ECG assessments will include: Heart rate, PR interval, QRS width, QT interval, and QTcB interval.

ECGs will be recorded in the supine position after 5 mins rest.

ECG recordings will be made using a MAC 5500 or equivalent. Each ECG trace should be labelled with the study number, subject initials and subject number. An investigator will

provide an interpretation of each tracing. Clinically significant abnormalities should be recorded on the AE page.

9.7.1.4.5 Concomitant Medication

All concomitant medication taken during the screening period and between first dose and the Post-Study Visit will be recorded in the subject's CRF (see Section 9.6.7).

9.7.1.4.6 Spirometry

All spirometry evaluations should follow the recommendations of the ATS/ERS 2005[13] .

The spirometry equipment used during the trial must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline. Calibration of the spirometry equipment is mandatory and must be performed before the first study measurement. All calibration reports and subject spirometry reports should be stored as source data. All staff conducting the spirometry tests must have received appropriate training that must be documented.

All spirometry manoeuvres should be performed in sitting position whilst wearing nose-clips. At least three acceptable manoeuvres should be performed for each time point, and the results must meet within-test and between-test criteria for acceptability. A maximum of six manoeuvres should be performed at any time point.

Spirometry assessments will include: Forced Expired Volume in 1 second (FEV1), Forced Vital Capacity (FVC) and FEV1/FVC.

9.7.2 Appropriateness of Measurements

All measurements performed in the study are standard measurements.

The total volume of blood to be collected from each subject during the study (approximately 177 mL in Part 1 and 242 mL in Part 2) is considered acceptable.

9.7.3 Primary Efficacy Variable(s)

Not applicable

9.7.4 Drug Concentration Measurements

Plasma samples for drug concentration measurements will be analysed by the Bioanalytical Unit at Simbec according to applicable local SOPs.

9.7.4.1 Pharmacokinetic Blood Sampling

Blood samples (4 mL) for determination of TD139 plasma levels will be taken into K2 EDTA tubes at the times specified in Table 9.7.1 and Table 9.7.2:

Immediately upon sampling the sample will be identified with a bar coded label bearing details of study number, subject number, sampling time point, sample type and a unique 9 digit identification number. The sample will be separated by centrifugation at 1500xg and 4°C for 10 mins. Two (2) equal aliquots of plasma will be transferred to polypropylene tubes labelled identically to the original blood sample and stored at approximately -20°C pending

analysis. The time at which samples are taken, received into the separating room and placed in the freezer will be recorded in the study documentation.

9.7.4.2 Drug concentration measurements in BAL

BAL samples will also be collected for determination of TD139 concentrations in alveolar macrophages and BAL fluid (saline).

See Section 9.7.5.3 for full details of the BAL collection and handling.

9.7.5 Pharmacodynamics

9.7.5.1 Exhaled Breath Condensate Sampling

Exhaled breath condensate samples will be collected using a commercially available device. The subject will be required to breathe into the device for approximately 10 minutes whilst in a seated position.

Samples will be analysed by the University of Rochester, New York. Specific instructions on sample collection, handling, and shipment will be provided in a set of sampling instructions to each site.

9.7.5.2 Galectin-3 Blood Sampling

Blood samples (3 mL) for determination of galectin-3 plasma levels will be taken into K2 EDTA tubes at the times specified in Table 9.7.1 and Table 9.7.2:

Immediately upon sampling the sample will be identified with a bar coded label bearing details of study number, subject number, sampling time point, sample type and a unique 9 digit identification number. The sample will be separated by centrifugation at 1500xg and 4°C for 10 mins. Two (2) equal aliquots of plasma will be transferred to polypropylene tubes labelled identically to the original blood sample and stored at approximately -20°C pending analysis. The time at which samples are taken, received into the separating room and placed in the freezer will be recorded in the study documentation.

9.7.5.3 Peripheral Blood Flow Cytometry Blood Sampling

Peripheral blood flow cytometry will be performed by the University of Edinburgh on the same sample that is collected for pharmacogenetic analysis (mRNA). See Section 9.7.6 for details.

9.7.5.4 Bronchoalveolar Lavage (BAL)

In Part 2 only, BAL fluid samples will be collected for analysis of:

- Macrophage morphology,
- Ex-vivo macrophage function,
- Macrophage phenotypic and mRNA expression pattern,
- BAL analysis of soluble markers.

BAL samples will also be collected for determination of TD139 concentrations in alveolar macrophages and BAL fluid (saline) (see Section 9.7.4.2).

BAL will be performed by flexible bronchoscopy at each centre's local facility. Specific instructions for performing the bronchoscopy and collecting the BAL samples will be provided in a standard operating procedure, to ensure that there is consistency in technique between sites. Where possible, the procedure will be performed by the same site Investigator.

Detailed information on sample handling and shipment requirements will also be contained in the standard operating procedure.

9.7.6 Pharmacogenetics

The study includes a pharmacogenetic component. This is mandatory in order for the subject to participate in the study.

A 10 mL whole blood sample will be collected into an EDTA tube at the times specified in Table 9.7.1 and Table 9.7.2. After collection, the sample will be inverted several times to prevent clotting. These samples will be shipped to the University of Edinburgh for mRNA analysis.

In addition a 20ml blood sample will be collected at the times specified in Table 9.7.1 and Table 9.7.2. After collection PBMCs will be extracted by density centrifugation and frozen pending analysis. These samples will be shipped to the University of Edinburgh for analysis of IPF gene signatures.

Full information on sample collection, handling, and shipment will be contained in a set of study Pharmacogenetic sampling instructions. The sample collection date and exact time must be entered on the sample collection CRF page.

Macrophage phenotypic and mRNA expression pattern analysis will also be performed in BAL fluid samples at the University of Edinburgh. See Section 9.7.5.4 for details.

9.8 Data Quality Assurance

At the time the study is initiated, a representative of the Sponsor will thoroughly review the Final Protocol and CRFs with the Investigator and staff. During the course of the study the Monitor will visit each Clinical site regularly to check the completeness of the subjects records (including the Volunteer (Subject) Master Files (**Part 1**), Patient Hospital Notes (**Part 2**), laboratory and ECG print-outs), the accuracy of entries into the CRFs, the adherence to the Final Protocol and to ICH GCP[3], the progress of enrolment and also to ensure the storage, handling and accountability of the IMP. The Investigator and key study personnel will be available to assist the Monitor during these visits.

The Investigator will give the Monitor, Auditor(s), the REC, and the MHRA direct access to relevant clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the Clinical sites. The Sponsor will maintain the confidentiality of all subject records.

Study data will be fully documented in the CRFs, subject diaries (Part 2) and study log-books. Dated signatures will be given to account for all interventions in the study by research staff.

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

For the purposes of Part 1 the source data will be recorded as detailed in Table 9.8.1.

Table 9.8.1 Summary of Source Documentation Location (Part 1)

Data	Source Document	
	Volunteer Master File	Case Report Form
Evidence of healthy subject status for entry into clinical study	X	
Demographic Data		X
Medical History	X	
Inclusion and Exclusion Criteria		X
Informed consents[1]	X	X
Subject participation in the clinical study		X
Subject number in the clinical study		X
Adverse Events		X
Previous and on-going therapy	X	
Concomitant therapy		X
Results of study examinations (e.g. ECGs, Vital signs and Laboratory Safety Tests)[2]		X
Study Visit dates		X
Administration of study medication		X
Plasma PK sample collection times		X

1. Copies of the Informed Consent Form should be present in the volunteer master file. The original Informed Consent Forms will be maintained in the study officer file during the clinical phase and will then be transferred to the Trial manager for archiving with the Investigator Site File at the end of the study.
2. The 12-lead ECG trace and Laboratory Safety Test print-out will be stored in the case report form.

Table 9.8.1 (**Part 1**) indicates where source data will be recorded but for completeness the following information should also be recorded in the volunteer master file/patient hospital notes:

- Clinical Study code.
- Study visit dates (pre-dose; post-dose).
- IMP administration (date of last dose).
- Results of any key safety and efficacy measures from the clinical study that should be noted in the opinion of the Investigator.
- Any concomitant medications used to treat the subject during the study that should be noted in the opinion of the Investigator.

For **Part 2** a Summary of Source Documentation Location table will be inserted into the study monitoring plan.

The data collected in the CRFs during the study will be subject to quality control checking by clinical staff prior to sign off.

Part 1 of the study will be subject to an independent audit by the Simbec Quality Assurance Unit as outlined in Simbec SOP BD/324/9/01.

Independent clinical quality assurance audits may be performed at any time during or following completion of the Study by the Sponsor, or its authorised agents and Regulatory Authorities and/or the REC.

9.9 Statistical Methods and Determination of Sample Size

9.9.1 Statistical and Analytical Plan

9.9.1.1 Primary and Secondary Variables for Assessment

The primary safety assessment variables will be the vital signs data, ECG data, laboratory data and the adverse events reported.

The secondary pharmacokinetic variables will be the following non-compartmental pharmacokinetic end-points:

- C_{max} Maximum plasma concentration
- t_{max} The time to maximum observed concentration sampled during a dosing interval
- λ_z Elimination rate constant
- $t_{1/2}$ Terminal half-life
- AUC_{0-t} Area under the plasma concentration-time curve (AUC) from the time of dosing to the time of the last observed concentration
- $AUC_{0-\tau}$ Area under the plasma concentration-time curve (AUC) from the time of dosing to time t at steady state
- AUC_{0-inf} The area under the curve (AUC) extrapolated to infinity from dosing time, based on the last observed concentration
- CL/F Plasma clearance, calculated as Dose / AUC_{0-inf}
- $AUC_{\% \text{ extrapolated}}$ Residual area

The secondary pharmacodynamic variables will be the peripheral blood flow cytometry data and galectin-3 plasma concentration data.

9.9.1.2 Definition of Evaluability

All randomised subjects who receive at least one dose of placebo or TD139 will be included in the safety analysis.

All randomised subjects who receive all doses of TD139, have sufficient plasma concentration by time profiles and who do not violate the protocol in such a way that may

invalidate or bias the results (major protocol violators) will be included in the pharmacokinetic analysis.

9.9.1.3 Description of Statistical Methods

Simbec Research Limited will carry out the statistical analysis. Full details of the statistical analyses of the data will be documented in an agreed statistical analysis plan, which will be finalised prior to locking the database and subsequent analysis of the study data.

The pharmacokinetic parameters of TD139 in plasma will be determined from the individual concentration versus time data using WinNonlin Phoenix 32. For the calculation of derived pharmacokinetic parameters, concentrations below the limit of quantification (BLQ) will be assigned a value of zero. In case of a deviation from the theoretical time, the actual time of blood sample will be used in the calculation of the derived pharmacokinetic parameters.

Derived pharmacokinetic parameters of TD139 in plasma will be listed and summarised for each treatment. The descriptive statistics presented will be N, n, arithmetic mean, arithmetic standard deviation (SD), coefficient of variation (CV%), minimum, median, maximum and geometric mean (with the exception of t_{max}). The results for t_{max} will be reverted back to the nominal time.

Mean and individual plasma concentration-time curves of TD139 in plasma will be presented for each dose on both linear and semi-logarithmic scales.

Statistical analysis will be performed using SAS® version 9.1.3 or higher.

Dose-Proportionality/Independence: Dose proportionality will be assessed by performing a regression analysis of the log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} values versus the log-transformed dose using the power model with a fixed effect for dose and a random effect for subject. For each parameter a point estimate and 95% confidence interval will be calculated for the slope of the regression line.

The power model is defined as:

$$\log_e(C_{max}, AUC_{0-t}, AUC_{0-inf}) = \alpha + \beta\log_e(Dose) + \varepsilon,$$

where α is the intercept, β is the slope and ε is the error term.

Dose independence will be assessed for t½ and CL/F by performing a regression analysis of the untransformed parameters versus dose with a fixed effect for dose and a random effect for subject. For each parameter a point estimate and corresponding 95% confidence interval will be calculated for the slope of the regression line.

Derived pharmacokinetic parameters will be presented graphically for mean C_{max}, AUC_{0-t}, AUC_{0-inf}, t½ and CL/F versus dose.

The same analysis will be carried out (for C_{max}, AUC_{τ}, t½ and CL/F) for Part 2 of the study on Days 1, 7 and 14.

Accumulation Assessment: Log-transformed trough levels at pre-dose on Day 2 through to Day 14 will be used to establish any accumulation of TD139. The ratio of trough concentrations on each consecutive day will be presented and summarized along with a 90% confidence interval. The analysis will be done for each dose level.

Assessment of Steady State: Log-transformed trough concentration levels at pre-dose on Days 7, and 14 will be subjected to mixed effects ANOVA with study day as a fixed effect and subject as a random effect in order to establish whether and when steady state has been attained for each dose level. Back-transformed ratios for the Day 14/Day 7, comparisons will be presented along with corresponding 90% CI.

Additional PK Assessments:

Alveolar macrophage and BAL fluid concentrations of TD139 will be presented as a data listing.

Drug compartment measurements in BAL and alveolar macrophages will be analysed as per the method set out in the study by Naderer *et al*[1] (e.g. TD139AM = TD139pellet/VAC [where the volume of alveolar cells - VAC, is estimated at 2.42µl/106 cells])[1].

PD Assessments:

Macrophage morphology parameters (*ex-vivo* macrophage function and BAL soluble markers) will be presented as a data listing.

Exhaled breath condensate data will be presented as a data listing.

Descriptive statistics of absolute and change from baseline for peripheral blood flow cytometry data will be presented at each time point by dose.

Descriptive statistics of absolute and change from baseline for Galectin-3 plasma concentration data will be presented at each time point by dose.

PG Assessments:

Macrophage phenotypic, mRNA pattern expression analysis from BAL and analysis of peripheral blood mononuclear cells for IPF gene signatures will be presented as a data listing.

Descriptive statistics of absolute and change from baseline of mRNA expression levels from blood leucocytes will be presented at each time point by dose.

Safety Assessments:

Vital signs parameters will be listed with any out of normal range values flagged. Descriptive statistics of absolute and change from baseline (pre-dose) supine systolic and diastolic blood pressure, supine pulse rate, respiration rate, oral temperature and O_2 saturation at each time point, up to and including Day 15, will be tabulated by dose.

The mean change from baseline data will also be plotted by dose across time, up to and including Day 15.

12-Lead ECG parameters will be listed with any out of normal range values flagged. Descriptive statistics of absolute and change from baseline (pre-dose) heart rate, PR interval, QRS interval, QT interval and QTcB interval at each time point, up to and including day 15, will be tabulated by dose.

The mean change from baseline data will also be plotted by dose across time, up to and including Day 15.

In addition, frequencies of QTcB data will be calculated according to the following categories:

For absolute values

- QTcB > 450 mSec
- QTcB > 480 mSec
- QTcB > 500 mSec

For change from baseline

- QTcB increase > 30 mSec
- QTcB increase > 60 mSec

All adverse events will be coded using the MedDRA dictionary, version 16.1.

All adverse events, including those that occur prior to the first administration of the study drug, will be listed. Only treatment-emergent adverse events (TEAEs), i.e. existing conditions that worsen or events that occur during the course of the study after administration of study drug, will be included within the summary tables. Adverse event summaries will be presented by treatment and overall (data from all dose groups will be pooled).

An overall summary of adverse events will be produced including the number of TEAEs; the number and percentage of subjects reporting at least one: TEAE, serious TEAE, TEAE leading to withdrawal from the study; the number and percentage of subjects reporting TEAEs by severity and relationship to study drug.

The number of TEAEs and the number and percentage of subjects reporting at least one TEAE will be tabulated by system organ class (SOC) and preferred term (PT). A subject reporting multiple episodes of a particular adverse event within a study period will only contribute one count towards the corresponding system organ class and preferred term within that study period.

In addition, the number and percentage of subjects reporting TEAEs will be tabulated by maximum severity and strongest relationship to study drug. For the summary of TEAEs by severity, if a subject has multiple events occurring within the same SOC or preferred term, the event with the highest severity will be counted. Similarly, for TEAEs by relationship to study drug, if a subject has multiple events occurring within the same SOC or preferred term, the event with the highest association to study drug will be counted.

Biochemistry, haematology and urinalysis parameters will be listed with any out of normal range values flagged. Laboratory test results that are out of normal range will also be presented separately along with normal reference ranges. Descriptive statistics of absolute and change from baseline (pre-dose) values for each biochemistry and haematology parameter at each time point, up to and including day 15, will be tabulated by dose.

Frequencies of the total number of subjects randomised, completed, and prematurely discontinued (including reason for discontinuation) from the study will be summarised by dose. Additionally the frequency of subjects within each analysis population (safety, PK) will be summarised by dose.

Demographic data will be listed and descriptive statistics will be tabulated for the continuous variables age, height, weight and BMI and frequencies for the categorical variable race. These descriptive statistics will be presented by dose and overall.

9.9.2 Sample Size Calculation

No formal sample size calculation has been performed. The number of subjects is considered sufficient to meet the safety objectives of **Part 1** of the study. For **Part 2** all PD measurements are exploratory and will provide information for a clinical Phase 2b study.

10 PRACTICAL CONSIDERATIONS

10.1 Storage of Data

The Investigator Site File (ISF) and associated study documentation will be archived for at least 5 years after the conclusion of the study (last subject last visit) as per The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (No. 1928)[4]. The study documentation may be transferred to an offsite storage facility during this period but will remain under the control of Simbec.

The Sponsor has delegated the set up and maintenance of the Sponsor Trial Master File (TMF) to Simbec. The TMF will be returned to the Sponsor at the end of the study, who will archive it for at least 5 years after the conclusion of the study.

10.2 Protocol Amendments

Changes in the Study Protocol must take the form of written protocol amendments and shall require the approval of all persons responsible for the study (see Section 1).

A protocol amendment is deemed to constitute a substantial protocol amendment if it is considered to be likely to affect to a significant degree either:

a. the safety or physical or mental integrity of the subjects of the study
b. the scientific value of the study
c. the conduct or management of the study
d. the quality or safety of any IMP used in the study.

Such amendments must be submitted to the REC responsible for the study and the MHRA for approval prior to implementation.

Protocol amendments required for urgent safety reasons may be implemented immediately. However, the REC and MHRA must be notified in writing within 3 days of the measures taken and the reasons for implementation.

All other amendments shall be deemed to be non-substantial and as such do not need the prior approval of the REC and the MHRA.

10.3 Confidentiality

The Investigators must agree to maintain the confidentiality of the study at all times and must not reveal any information relating to the study without express permission from the study Sponsor.

10.4 Study Report and Publication Policy

Simbec will investigate and analyse the data generated with all due speed.

A draft study report will be sent to the Sponsor for review. The Sponsor will forward any comments on the draft study report to the trial manager within 30 days of receipt. Upon receipt of these comments a final, QA approved report will be issued with all due speed. A copy of the report will be forwarded to the Sponsor.

The Investigator will obtain the Sponsor's written permission before any information concerning this study is submitted for publication.

11 REFERENCES

[1] Naderer O. et al. Antimicrob. Agents Chemother. 2014, 58(1):419.

[2] World Health Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, and 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, 53rd WMA General Assembly, Washington 2002 (Note of Clarification on Paragraph 29 added), 55th WMA General Assembly, Tokyo 2004 (Note for Clarification on Paragraph 30 added), 59th WMA General Assembly, Seoul, October 2008 and 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

[3] ABPI (The Association of the British Pharmaceutical Industry). Guidelines for Phase 1 Clinical Trials. 2012 edition.

[4] ICH (International Conference on Harmonisation) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (CPMP/ICH/135/95) 1996.

[5] The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031) and subsequent amendments.

[6] Insurance and compensation in the event of injury in Phase I clinical trials 2012. Guidance developed by the ABPI (The Association of the British Pharmaceutical Industry), the BioIndustry Association and the Clinical Contract Research Association in consultation with the Department of Health and the National Research Ethics Service

[7] Mahendran, S. and Sethi, T. (2012). Treatments in idiopathic pulmonary fibrosis: time for a more targeted approach? *Q. J. Med*. 105:929–934

[8] Woodcock, H.V. and Maher, T.M. (2014). The treatment of idiopathic pulmonary fibrosis. *F1000Prime Reports*. 6:16

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[10] Raghu, G. et al. (2006) Incidence and prevalence of idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med*. 174, 810-816

[11] Investigator's Brochure.

[12] European Commission. EudraLex The rules governing medicinal products in the European Union – Volume 4: Good Manufacturing Practice Guidelines

[13] ATS/ERS (2005) Taskforce: Standardization Of Lung Function Testing. Available from http://www.thoracic.org/statements/resources/pfet/pft1.pdf

APPENDIX 1: DECLARATION OF HELSINKI (BRAZIL, 2013)

DECLARATION OF HELSINKI (BRAZIL, 2013)

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent,

preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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