Imperial College London

# Research Protocol

## Investigating the relationship between endothelial cell activation and total pulmonary resistance in pulmonary artery hypertension (PAH)

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| **Protocol Version:** | 1 |
| **Superseding:** | |
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| **R&D Ref.:** | 22HH7807 |
| **IRAS registration:** | 316863 |
| **REC Ref.:** | 22/LO/0657 |

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| **Sponsor:** | Imperial College London, UK |
| **Funding:** | Imperial College London |
| **Chief Investigator:** | Professor Martin Wilkins |

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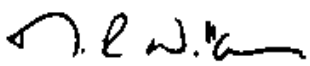
|---|---|---|
| **Developed by:** | Dr David Owen<br>Professor Martin Wilkins | |
| **Authorised by:** | Professor Martin Wilkins | **Name, Role** |
| |  | **Signature** |
| | 05 DEC 2022 | **Date** |

This protocol describes the xxx study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

## ORGANISATION / CONTACTS

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| **Sponsor** | **Imperial College London**<br>Research Governance and Integrity<br>Imperial College London<br><br>Room 221<br>Medical School Building<br>St Marys Campus<br>Norfolk Place<br>London W2 1PG |
| **Chief Investigator** | **Professor Martin Wilkins** |
| **Co-Investigators**<br>(sorted alphabetically) | **David Owen**<br>**Lan Zhao** |

## CLINICAL ENQUIRIES

Urgent clinical enquiries to be addressed to the site Investigator, who will direct the enquiry to the appropriate person.

| Site ID | Site Name | Site Investigator | Emergency Telephone |
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| 1000 | Royal Hallamshire | Dr Alexander Rothman | TBC |
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**PROTOCOL AMENDMENTS**

# Investigating the relationship between endothelial cell activation and total pulmonary resistance in pulmonary artery hypertension (PAH)

| Substantial Amendment | Date |
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**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

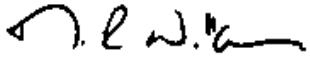
**Clinical Study Protocol Version 1.0, Dated 01-June-2022**

# Investigating the relationship between endothelial cell activation and total pulmonary resistance in pulmonary artery hypertension (PAH)

● I confirm agreement to conduct the study according to the Protocol and in compliance with GCP standards and other applicable requirements.

● I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

● I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

| **Investigator's Approval** | | | |
|---|---|---|---|
| **Name:** | **Research Site:** | **Signature** | **Date** |
| Martin Wilkins | ICL |  | **05 DEC 2022** |

| **Sponsor's Approval** | | | |
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| **Name:** | **Role:** | **Signature** | **Date** |
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## GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| 6MWD | 6-Minute Walk Distance |
| 6MWT | 6-Minute Walk Test |
| AE | Adverse Event |
| AR | Adverse Reaction |
| β-hCG | beta human Chorionic Gonadotropin |
| BP | Blood Pressure |
| CRF | Case Report Form |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| PAH | Pulmonary Arterial Hypertension |
| PCR | Polymerase Chain Reaction |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SNP | Single Nucleotide Polymorphism |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TPR | Total Pulmonary Resistance |
| WHO | World Health Organisation |

**Keywords:** Pulmonary Arterial Hypertension; PAH; XBD173;

## STUDY SUMMARY

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| **TITLE:** | Investigating the relationship between endothelial cell activation and total pulmonary resistance (TPR) in pulmonary artery hypertension (PAH) | | |
| **PHASE:** | IB | | |
| **MEDICINAL PRODUCT:** | XBD173 | | |
| **DESIGN:** | Open-label, single-centre | | |
| **OBJECTIVE(S):** | To determine whether changes in endothelial cell dysfunction are associated with changes in total pulmonary resistance in patients with pulmonary arterial hypertension | | |
| **INTERVENTION:** | XBD173 - oral administration for up to 8 weeks | | |
| **EVALUATION MEASURES:** | 1. Change in plasma sVCAM1, e-selectin, GDF-15 and NT-proBNP<br>2. Change in total pulmonary resistance | | |
| **POPULATION:** | Up to 6 individuals with PAH. | | |
| **STUDY CENTRES:** | **Site ID** | | |
| **STUDY CENTRES:**<br>**STUDY DURATION:** | | **Site Name** | **Academic Affiliation** |
| | 1000 | Royal Hallamshire | University of Sheffield |
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| **ELIGIBILITY** | **Inclusion criteria:**<br>**1.** Subjects aged between 18-75 years old<br>**2.** PAH which is: idiopathic; PAH heritable; PAH associated with connective tissue disease; PAH after ≥ 1 year repair of congenital systemic to pulmonary shunt; or PAH associated with anorexignes or other drugs.<br>**3.** Resting mean pulmonary artery pressure ≥25 mmHg, pulmonary capillary wedge pressure ≤15 mmHg, PVR >5 wood units, and normal or reduced cardiac output, as measured by a previous right heart catheterisation (RHC).<br>**4.** Have an insertable FDA/CE cardiac rhythm monitor and pulmonary artery pressure monitor that captures cardiopulmonary haemodynamics and daily activity.<br>**5.** Six-minute walking distance >50m at entry<br>**6.** Stable on an unchanged PAH therapeutic regime comprising at least 2 therapies licensed for PAH (any combination of endothelin receptor | | |

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| | antagonist, phosphodiesterase inhibitor or prostacyclin analogue) for at least 1 month prior to screening<br>**7.** Subjects willing to be genotyped for genes that influence XBD173 activity<br>**8**. Able to provide written informed consent prior to any study mandated procedures<br>**9.** Contraception: Fertile females (women of childbearing potential) are eligible to participate after a negative highly sensitive pregnancy test, if they are taking a highly effective method of contraception other than the oral contraceptive pill during treatment and until the end of relevant systemic exposure **-see details in section 4.3.1-**<br><br>**Exclusion criteria:**<br>**1.** Unable to provide informed consent and/or are non-fluent speakers of the English language<br>**2.** Hypersensitivity to XBD173 or to any of the excipients<br>**3.** Clinically-significant renal disease (confirmed by creatinine clearance <30 ml/min per 1.73m$^2$)<br>**4.** Clinically-significant liver disease (confirmed by serum transaminases >2 times than upper normal limit)<br>**5.** Anaemia confirmed by haemoglobin concentration <10 g/dl<br>**6.** Individuals known to have haemoglobinopathy sickle cell disease, thalassaemia<br>**7.** Hospital admission related to PAH or change in PAH therapy within 3 months prior to screening<br>**8.** History of left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:<br>a. Aortic or mitral valve disease (stenosis or regurgitation) defined as greater than mild aortic insufficiency, mild aortic stenosis, mild mitral stenosis, moderate mitral regurgitation<br>b. Mechanical or bioprosthetic cardiac valve<br>c. Pericardial constriction, effusion with tamponade physiology, or abnormal left atrial size.<br>d. Restrictive or congestive cardiomyopathy<br>e. Left ventricular ejection fraction ≤50% (measured in echocardiogram at screening)<br>f. Symptomatic coronary disease<br>g. Significant (2+ for regurgitation) valvular disease other than tricuspid or pulmonary regurgitation<br>h. Acutely decompensated left heart failure within 1 month of screening<br>i. History of untreated obstructive sleep apnoea<br>**9.** Evidence of significant lung disease on high-resolution CT (if available) or recent (performed within 12 months) lung function, where FEV1 < 50% predicted and FVC < 70% predicted, and DLCO (or TLCO) < 50% predicted if any CT abnormalities; judged by the |

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| | Site Physician<br>**10.** Patients with a history of uncontrolled systemic hypertension<br>**11.** Acute infection (including eye, dental, and skin infections)<br>**12.** Chronic inflammatory disease including HIV, and Hepatitis B<br>**13.** Women of childbearing potential who are pregnant or breastfeeding (if applicable)<br>**14.** Patients who have received an Investigational Medicinal Product (IMP) within 5 half-lives of the last dose of the IMP or 1 month (which ever is greater) before the baseline visit<br>**15**. Use of the following medications or therapies:<br>• Severe and moderate P450 CY3A4 inhibitors: Boceprevir, Clarithromycin, Cobicistat, Idelalisib, Itraconazole, Ketoconazole, Nelfinavir, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Voriconazoleb, Aprepitant, Conivaptan, Crizotinib, Diltiazem, Dronedarone, Erythromycin, Fluconazole, Imatinib, Isavuconazole, Nefazodone, Netupitant, Nilotinib, Posaconazolee, Tofisopam, Verapamil, Delavirdine.<br>• Severe and moderate P450 CY3A4 inducers: Carbamazepine, Enzalutamide, Fosphenytoin, Mitotane, Phenytoin, Rifampicin, Bosentan, Efavirenz, St John's wort, Barbiturates, Nevirapine, Primidone, Rifabutin, Rifapentine.<br>• Oral contraceptives<br>• Oral anticoagulants or antiplatelet agents other than low dose aspirin<br>• Levothyroxine |
| **PHARMACOLOGICAL CHALLENGE:** | For the first 2 participants, XBD173 will be given orally 90mg once daily for 8 weeks, in addition to their usually medication.<br><br>For the next 4 participants, XBD173 will be given orally 90mg once daily for the first 2 weeks, in addition to their usually medication, and then orally 90mg twice daily for 6 weeks.<br><br>Enrolment will be staggered so that each participant will start dosing at least 2 weeks after the previous participant.<br><br>Patients will be monitored for safety by clinic visit at the end of Weeks 2, 4, and 8. They will be followed for a further 4 weeks off study treatment.<br><br>Blood levels of XBD173 will be measured in each patient at the end of Week 8. |

## 1. BACKGROUND AND RATIONALE

### 1.1 Pulmonary arterial hypertension (PAH)

PAH is an uncommon condition characterised by pre-capillary resistance to pulmonary blood flow in the absence of airway or parenchymal lung diseases, left heart failure or chronic thromboembolism (1,2). The resultant elevation in pulmonary artery pressure places an increased pressure load on the right ventricle, leading to right heart failure and premature death.

In around 50% of patients there is no identifiable underlying cause, and patients are classified as idiopathic PAH or, where there is a family history, heritable PAH. Histological examination of post-mortem or transplantation PAH lung tissue shows marked pulmonary arterial remodelling with vascular cell proliferation narrowing the vascular lumen (3).

The estimated prevalence of PAH is 15 per million (2,4). It affects people in middle age and is an unmet clinical need. Five-year mortality for idiopathic/heritable PAH managed by experienced centres in the UK is around 58% (5). The current licensed treatments [prostanoids, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and soluble guanylate cyclase stimulator] focus on pharmacologically manipulating 3 signaling pathways better known for regulating vascular tone (1,2,4). These treatments have little impact on the underlying vascular remodeling and do not arrest or reverse the course of the condition.

The past few years have seen attempts to target pulmonary vascular remodeling directly with antiproliferative or anti-inflammatory drugs (6). We have shown that pharmacological and gene modulation of the 18kDa Translocator Protein (TSPO) improves endothelial function in primary human endothelial cells treated with PAH-relevant activating stimuli. Furthermore, in rodent models, we have shown that this improvement in endothelial function mediated by TSPO modulation reduces total pulmonary resistance, implying that endothelial dysfunction drives pulmonary vascular resistance. In this study, we wish to test this hypothesis in humans. To do so, we will use the TSPO ligand XBD173 as a tool compound. We have shown that XBD173 reduces activation of endothelial cells in people with multiple sclerosis (MS). Here, we will use it to reduce endothelial cell activation in people with PAH, in order to determine if there are associated changes in total pulmonary resistance (TPR).

### 1.2 XBD173

XBD173 binds the mitochondrial membrane Translocator Protein (TSPO) with high affinity and was developed in a partnership between Novartis and Dainippon Sumitomo Pharma for the treatment of anxiety. Development was ceased at Phase IIa due to lack of efficacy as an anxiolytic. XBD173 has been used in several studies in healthy volunteers and people with multiple sclerosis and has been well tolerated, with a side effect profile similar to placebo (see more details in Section 4 below).

XBD173 in doses of 1 to 2mg/kg improves endothelial function and reduces total pulmonary resistance and vascular remodelling in two animal models of pulmonary hypertension – the monocrotaline and Sugen-hypoxia rat. Genetic knock-out of TSPO in the rat attenuates the development of hypoxia-induced pulmonary hypertension, consistent with XBD173 acting as an antagonist of TSPO.

## 2. STUDY OBJECTIVES

Primary objective: To determine whether changes in endothelial cell dysfunction are associated with changes in total pulmonary resistance in patients with pulmonary arterial hypertension

There are no secondary objectives

## 3. STUDY OUTCOME MEASURES

### 3.1 Primary measures evaluating effect:

1. Change in plasma sVCAM1, e-selectin, GDF-15 and NT-proBNP by week 8
2. Change in total pulmonary resistance by week 8

### 3.2 Secondary outcome measures:

There are no secondary outcome measures

### 3.3 Exploratory outcome measures:

- Change in total pulmonary resistance from baseline according to rs6971 (a genetic variant that regulates XBD173 activity).
- Change in plasma proteome from baseline at 8 weeks.

## 4. Design

### 4.1 Overall study design and plan

Patients will be invited to participate by their local pulmonary hypertension hospital. The first 2 participants will be treated with XBD173 90mg once daily for 8 weeks. The first patient will be followed for at least 2 weeks before the second patient starts the XBD173. Subsequent participants will be treated with XBD173 90mg once daily for 2 weeks at intervals of at least 2 week and if the drug is tolerated (defined as an absence of grade 2 adverse events) the dose will be increased to 90mg twice daily for a further 6 weeks. The total period of treatment for each patient is 8 weeks, followed by 4 weeks follow up off XBD173. If a grade 2 AE occurs during 90mg once daily dosing, the participant will be withdrawn. If a patient does not tolerate 90mg twice daily, the local PI will determine whether to stop XBD173, reduce the dose to 90mg once daily or pause dosing and restart at 90mg once daily.

The starting dose of 90mg OD is based on experience from studies of XBD173 in healthy volunteers and in patients with multiple sclerosis.

Rupprecht et al randomised 71 healthy volunteers to 7 days treatment with placebo, 10, 30, or 90 mg/day XBD173 or 2 mg/day alprazolam (PMID: 19541954). The number of side effects reported with XBD173 was comparable to the incidence in the placebo group. In contrast, a much higher incidence was reported by the alprazolam-treated group.

In addition, 4 studies have been sponsored by Imperial College London using XBD173. In all studies XBD173 was well tolerated with no SAEs:

17/LO/0566. This study recruited healthy volunteers (n=31) and people with MS (n=12) and administered XBD173 90mg for 7 days. (To be submitted for publication September 2022).

14/LO/0343. This study recruited people with MS (n=6) and administered a single dose of XBD173 (90mg) prior to PET scanning with 11C-GE180. (PMID: 30796709).

12/LO/0735. This study recruited healthy volunteers (n=6) and administered a single dose of XBD173 ranging from 10mg-90mg prior to PET scanning with 11C-PBR28. (PMID: 24623083).

13/LO/1916. This study recruited healthy volunteers (n=6) and people with MS (n=6) and administered a single doses of XBD173 (90mg) prior to PET scanning with 11C-PBR28. (PMID: 30796709)

The proposed study will recruit patients with PAH attending specialist clinics that have both an approved implanted cardiopulmonary monitor (CardioMEMS$^{TM}$ Heart Failure system) and an activity monitor (a Fitbit activity monitor) that permits remote sensing. The monitors will have been implanted on clinical grounds; specifically, to aid control of pulmonary hypertension by enabling more personalised dose adjustments to licensed treatments. Despite this, the drugs are not curative and patients live with very high pressures (typically 5 times normal resting pressures in a healthy individual). Patients with stable readings for at least a month will be considered for recruitment. These stable readings provide a good baseline from which to measure the effect of the study drug and relate to changes in blood biomarkers.

Remote sensing offers greater oversight of the patient and closer safety monitoring. Remotely acquired patient data are reviewed twice a week via a central clinical team based in Sheffield. Relevant data will be shared as de-identifiable information, and sent to Imperial College London (upon request) as pseudonymised (coded) data if there are any concerns regarding patients' safety. Follow-up would be scheduled by telephone or video conferencing with hospital visits being optional.

The most common side effects reported with XBD173 include nervous system and gastrointestinal symptoms, but the frequencies of these side effects are no higher than placebo.

If a patient is unable to continue with the prescribed dose of XBD173 to 8 weeks, they will be withdrawn from the study.

The end of the study will be the last visit of the last subject.

**4.2 Discussion of study design**

This is an open label study. The aim of the study is to use XBD713 as a tool to modulate endothelial cell function, and to determine whether this is associated with a change in total pulmonary resistance (TPR). Patients with implanted devices act as their own control. A change in total pulmonary resistance from a stable baseline can be reasonably attributed to the study drug and would be expected to be accompanied by a reduction in plasma pro-NT-BNP. Patients will continue to be monitored at the end of the study, as part of clinical practice as the devices remain implanted, and any change in total pulmonary resistance return to baseline after discontinuing XBD173 will add weight to the interpretation.

No intervention or procedure which would normally be considered a part of routine care will be withheld.

**4.3 Selection of study population**

Patients participating in this study are adult males and females with symptomatic PAH as defined by the eligibility criteria below.

PAH is a rare condition. Patients with PAH attend one of 8 UK specialist centres in the UK for diagnosis and management decisions. The patients attending the specialist clinic in Sheffield are offered CardioMEMS$^{TM}$ Heart Failure system and a Fitbit activity monitors as part of the FIT-PH study (Feasibility of Novel Clinical Trial Infrastructure, Design and Technology for Early Phase Studies in Patients with Pulmonary Hypertension; Ethics approval 19/YH/0354). This is an observational study where in which the devices are used to help stabilise and personalise a patient's treatment. The present cohort have been under follow-up for a mean of 7 months and are stable.

This patient group provide daily data about their health (level of physical activity, day and night cardiac rate and rhythm, heart rate variability, thoracic impedance, respiratory rate, systemic blood pressure, oxygen saturations, body weight, pulmonary artery pressure, cardiac output and stroke volume) to a hospital-based monitoring team and benefit from close contact with the specialist team while reducing travel to the hospital. Remote systemic blood pressure, oxygen saturations and body weight are provided through the FDA/CE approved Cordella Heart Failure System (7). The protocol of the FIT-PH study observational study permits the opportunity to introduce and address additional research questions. This group of patients would be suitable for assessing the effects of XBD173 in this study population and insights into the mechanisms driving the disease.

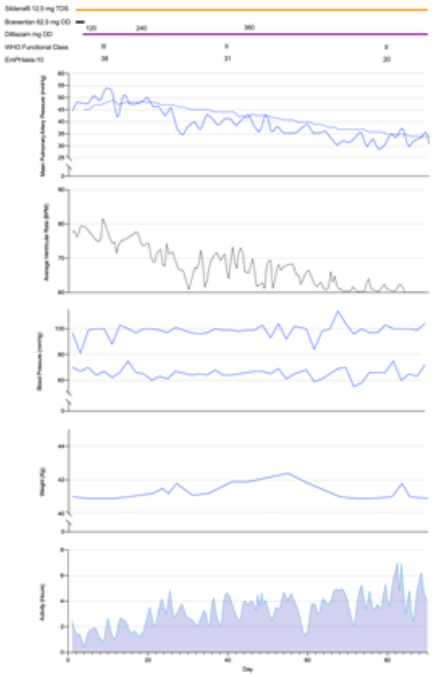

**Figure 1 -** Remote monitoring of a 55-year old patient with PAH over 90 days reporting mean pulmonary artery pressure (mmHg), heart rate (bpm), blood pressure (mmHg), body weight (kg), and physical activity (in hours). Note response to increased dose of Diltiazem (120 to 360 mg).

**4.3.1 Inclusion criteria**

**1.** Subjects aged between 18-75 years old

**2.** PAH which is: idiopathic; PAH heritable; PAH associated with connective tissue disease; PAH after ≥ 1 year repair of congenital systemic to pulmonary shunt; or PAH associated with anorexigens or other drugs.

**3.** Resting mean pulmonary artery pressure ≥25 mmHg, pulmonary capillary wedge pressure ≤15 mmHg, PVR >5 wood units, and normal or reduced cardiac output, as measured by a previous right heart catheterisation (RHC).

**4.** Have an insertable FDA/CE cardiac rhythm monitor and pulmonary artery pressure monitor that captures cardiopulmonary haemodynamics and daily activity.

**5.** Six-minute walking distance >50m at entry

**6.** Stable on an unchanged PAH therapeutic regime comprising at least 2 therapies licensed for PAH (any combination of endothelin receptor antagonist, phosphodiesterase inhibitor or prostacyclin analogue) for at least 1 month prior to screening

**7.** Subjects willing to be genotyped for genes that influence XBD173 activity

**8**. Able to provide written informed consent prior to any study mandated procedures

**9.** Contraception: Women of childbearing potential are eligible to participate after a negative highly sensitive pregnancy test if they are taking a highly effective method of contraception during treatment and until the end of relevant systemic exposure. As the oral contraceptive is an exclusion criterion, the following methods are permitted:

- sexual abstinence
- intrauterine device (also called IUD)
- intrauterine hormone-releasing system (also known as IUS)
- bilateral tubal occlusion
- vasectomised partner

*Definition of fertile females (women of childbearing potential) and of fertile men:
For the purpose of this document, a woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

**4.3.2 Exclusion criteria:**

**1.** Unable to provide informed consent and/or are non-fluent speakers of the English language

**2.** Hypersensitivity to XBD173 or to any of the excipients

**3.** Clinically-significant renal disease (confirmed by creatinine clearance <30 ml/min per 1.73m$^2$)

**4.** Clinically-significant liver disease (confirmed by serum transaminases >2 times than upper normal limit)

**5.** Anaemia confirmed by haemoglobin concentration <10 g/dl

**6.** Individuals known to have haemoglobinopathy sickle cell disease, thalassaemia

**7.** Hospital admission related to PAH or change in PAH therapy within 3 months prior to screening

**8.** History of left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:

b. Aortic or mitral valve disease (stenosis or regurgitation) defined as greater than mild aortic insufficiency, mild aortic stenosis, mild mitral stenosis, moderate mitral regurgitation

b. Mechanical or bioprosthetic cardiac valve

c. Pericardial constriction, effusion with tamponade physiology, or abnormal left atrial size.

d. Restrictive or congestive cardiomyopathy

e. Left ventricular ejection fraction ≤50% (measured in echocardiogram at screening)

f. Symptomatic coronary disease

g. Significant (2+ for regurgitation) valvular disease other than tricuspid or pulmonary regurgitation

h. Acutely decompensated left heart failure within 1 month of screening

i. History of untreated obstructive sleep apnoea

**9.** Evidence of significant lung disease on high-resolution CT (if available) or recent (performed within 12 months) lung function, where FEV1 < 50% predicted and FVC < 70% predicted, and DLCO (or TLCO) < 50% predicted if any CT abnormalities; judged by the Site Physician

**10.** Patients with a history of uncontrolled systemic hypertension

**11.** Acute infection (including eye, dental, and skin infections)

**12.** Chronic inflammatory disease including HIV, and Hepatitis B

**13.** Women of childbearing potential who are pregnant or breastfeeding (if applicable)

**14.** Patients who have received an Investigational Medicinal Product (IMP) within 5 half-lives of the last dose of the IMP or 1 month (whichever is greater) before the baseline visit

**15.** Use of the following medications or therapies:

- P450 CY3A4 inhibitors
  - Potent: Boceprevir, Clarithromycin, Cobicistat, Idelalisib, Itraconazole, Ketoconazole, Nelfinavir, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Voriconazoleb
  - Moderate: Aprepitant, Conivaptan, Crizotinib, Diltiazem, Dronedarone, Erythromycin, Fluconazole, Imatinib, Isavuconazole, Nefazodone, Netupitant, Nilotinib, Posaconazolee, Tofisopam, Verapamil
  - Unclassified: Delavirdine
- P450 CY3A4 inducers
  - Potent: Carbamazepine, Enzalutamide, Fosphenytoin, Mitotane, Phenytoin, Rifampicin
  - Moderate; Bosentan, Efavirenz, St John's wort
  - Unclassified; Barbiturates, Nevirapine, Primidone, Rifabutin, Rifapentine

- oral contraceptives
- oral anticoagulants or antiplatelet agents other than low dose aspirin
- levothyroxine

#### 4.3.3 Subject completion

Subjects will be considered complete for the purpose of this study once they have completed all procedures. The end of the study is defined as the last assessment of the last subject undergoing the study.

#### 4.3.4 Discontinuation criteria

It is possible that the Sponsor, REC or HRArequest termination of the study if there are concerns about conduct or safety, or due to a change in the opinion of the Ethics Committee.

When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the Investigators. Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The site Investigator/Chief Investigator can discontinue subjects from the study for any of the following reasons:

**1**. Occurrence of an unacceptable Adverse Event due to Grade 2 or above defined by the NCI Common Terminology Criteria for Adverse Events (version 5.0, 2017), adapted for this study -see Appendix 2.
**2**. Subject request
**3.** Subject is lost to follow-up
**4.** Administrative reasons
**5.** Development of an intercurrent illness, condition, or procedural complication, which would interfere with the subject's continued participation
**6.** Patient becomes pregnant

The site Investigator/Chief Investigator also reserves the right to discontinue subjects in the interest of subject safety and welfare. Investigators must contact all participants and the hospital pharmacy (where applicable) to notify them of the termination of the study. In cases of an early termination (discontinuation), a follow-up telephone assessment will be performed 4 weeks ± 3 days -see Appendix 1.

#### 4.3.5 Subject identification and replacement policy

After informed consent is obtained, patients who are screened will be assigned a 7-digit permanent identification number (subject ID) such that all patients given consecutive identification numbers in successive order of inclusion. The first 4 digits of the will be the designated research site ID, and the last 3 digits will be assigned at the research study centre (e.g., if the site ID is 4410, the third patient screened at 4410 site, would be given the number of 4410003).

A patient who is screened but fails to proceed into baseline assessment (e.g., because entry criteria were not met or enrolment did not occur within the specified time frame) may be considered for screening again. Re-screening will be permitted by the site Investigator on a case-by-case basis. A new informed consent form will be signed in any case of re-screening. A new subject ID will be assigned to the subject. Patients who are discontinued will be replaced. Each replacement is by a default a new subject, who will be assigned a completely new subject ID.

## 5. PHARMACOLOGICAL CHALLENGE AGENT

Patients who are eligible to participate in the study will receive XBD173.

**5.1 XBD173**

**5.1.1 Preparation**

XBD173 will be formulated by Royal Free Hospital for administration in capsules. XBD173 will be formulated in accordance with regulatory requirements of the Royal Free Hospital pharmacy.

**5.1.2. Administration**

Oral

**5.2 Labelling**

The study drug will be labelled by Royal Free Hospital for administration in capsules in accordance with local regulatory requirements.

**5.3 Study drug accountability**

Accountability for the study drug at the study site is the responsibility of the site Investigator. He/she will ensure that the study drug is used only in accordance with this protocol. Where allowed, the site Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual.

Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and end-of-study destruction and disposal of the drug, will be maintained by each clinical site. These records will adequately document that the subjects were provided the doses as specified in the protocol. Site's accountability pharmacy logs can be used to confirm if sites can destroy/dispose of unused drug in line with their local requirements.

**5.4 Treatment assignment**

All patients will receive XBD173 at 90mg once daily. Patient 3 onwards will escalating to 90mg twice daily after 2 weeks.

**5.5 Concomitant medications**

**5.5.1 Permitted concomitant medications**

Approved endothelin receptor antagonists, phosphodiesterase-5 type inhibitors and/or prostacyclin analogues are permitted for the treatment of PAH. The dose must be stable for at least 1 month prior to entry into the study.

**5.5.2 Patients taking one of the following medications will be excluded:**

- P450 CY3A4 inhibitors
    - Potent: Boceprevir, Clarithromycin, Cobicistat, Idelalisib, Itraconazole, Ketoconazole, Nelfinavir, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Voriconazoleb
    - Moderate: Aprepitant, Conivaptan, Crizotinib, Diltiazem, Dronedarone, Erythromycin, Fluconazole, Imatinib, Isavuconazole, Nefazodone, Netupitant, Nilotinib, Posaconazolee, Tofisopam, Verapamil
    - Unclassified: Delavirdine
- P450 CY3A4 inducers
    - Potent: Carbamazepine, Enzalutamide, Fosphenytoin, Mitotane, Phenytoin, Rifampicin
    - Moderate; Bosentan, Efavirenz, St John's wort
    - Unclassified; Barbiturates, Nevirapine, Primidone, Rifabutin, Rifapentine
- oral contraceptives

- oral anticoagulants or antiplatelet agents other than low dose aspirin
- levothyroxine

## 6. VISIT AND ASSESSMENT SCHEDULE

For a tabulated summary of all visits and assessments see the Schedule of Events, Appendix 1. Screening and baseline assessments can be performed on a single day as long as this is feasible and the patient agrees to a long study visit. On those occasions, procedures which are common among screening and baseline should be performed once, unless deemed clinically necessary to repeat.

### 6.1 Screening assessment (before Week 0)

The screening assessment should be performed no more than 28 days prior to the baseline visit. Participants' eligibility will be determined using data collected during their routine hospital appointment:

- Review of inclusion/exclusion criteria
- Obtain written informed consent
- Demographics
- Medical and medication history (incl. smoking and alcohol history)
- Physical examination
- Concomitant medications
- Vital signs: (i) Resting supine blood pressure (BP), (ii) pulse measurement, (iii) temperature, (iv) pulse oximetry (incl. respiratory rate), (v) height, and (vi) weight
- World Health Organisation (WHO) Functional Class
- Six-minute walk test (6MWT) and Borg dyspnoea index
- Electrocardiogram (ECG)
- Blood samples for haematology, clinical chemistry, TSPO rs6971 genotype and serum pregnancy test whereas indicated (for women of childbearing potential)

### 6.2 Baseline assessment (Week 0)

The patient will undergo the following procedures:

- Review of test results and reports with the Study Physician
- Urinary pregnancy test where indicated
- Concomitant medications
- Record of readings from implanted devices
- Research blood sampling

Following completion of the above procedures, each patient will receive their first dose of XBD173.

### 6.3 Telephone assessment (Week 1 ± 3 days)

Patients will receive a telephone call at the end of Week 1 to check concomitant medications, and for the occurrence of AEs.

### 6.4 Hospital assessment (Week 2 ± 3 days)

Patients will attend for safety, urinary pregnancy test (if indicated) and research blood tests, to check concomitant medications, and for the occurrence of AEs. Following completion of these procedures and review of the blood tests, the physician can increase the dose of XBD173 to 90mg twice daily.

### 6.5 Telephone assessment (Week 3 ± 3 days)

Patients will receive a telephone call at the end of Week 3 to check concomitant medications, and for the occurrence of AEs

**6.6 Assessment on Week 4 (Week 4 ± 3 days)**

The patient will be invited to attend their local hospital or a home assessment will be made at the end of Week 4 in order to undergo the following procedures:

- Physical examination
- Concomitant medications
- Document AEs
- Vital signs: (i) Resting supine BP, (ii) pulse measurement, (iii) temperature, (iv) pulse oximetry (incl. respiratory rate), and (v) weight
- ECG
- Blood samples for haematology and clinical chemistry, and urinary pregnancy test (if indicated)
- Blood sample for XBD173 levels
- Research blood sampling
- XBD173 collection and reconciliation

**6.7 Assessment on Week 8 (Week 8 ± 3 days)**

The patient will be invited to attend their local hospital or a home assessment will be made at the end of Week 8 in order to undergo the following procedures:

- Physical examination
- Concomitant medications
- Document AEs
- Vital signs: (i) Resting supine BP, (ii) pulse measurement, (iii) temperature, (iv) pulse oximetry (incl. respiratory rate), and (v) weight
- ECG
- Blood samples for haematology and clinical chemistry, and urinary pregnancy test (if indicated)
- Blood sample for XBD173 levels
- Research blood sampling
- XBD173 collection and reconciliation

**6.8 Assessment on Week 12 (Week 12 ± 3 days)**

The patient will be invited to attend their local hospital or a home assessment will be made at the end of Week 12 in order to undergo the following procedures:

- Physical examination
- Concomitant medications
- Document AEs
- Vital signs: (i) Resting supine BP, (ii) pulse measurement, (iii) temperature, (iv) pulse oximetry (incl. respiratory rate), and (v) weight
- ECG
- Research blood sampling

**6.9 Unscheduled visit (when needed)**

This type of visit can be performed at any time during the study, when the patient/study physician finds it necessary. For example, an unscheduled visit can be performed if the patient experiences discomfort at home due to ankle swelling that needs further investigation. In every unscheduled visit, the patient will undergo the following procedures:

- Physical examination
- Concomitant medications
- Document AEs
- Vital signs: (i) Resting supine BP, (ii) pulse measurement, (iii) temperature, (iv) pulse oximetry (incl. respiratory rate), and (v) weight

- ECG*
- Echocardiogram*
- Blood samples for haematology and clinical chemistry*
- Urinary pregnancy test (if indicated)

**if clinically required*.

## 7. STUDY ASSESSMENTS

### 7.1 Physical examination, medical and medication history

Physical examinations will be performed to ensure suitability according to the inclusion and exclusion criteria at screening and to document the health status at the time-points specified in the Schedule of Events - see Appendix 1. The physical examination (incl. vital signs) is a routine medical examination. A medical history will be recorded at screening only. The medical history will elicit information concerning existing medical conditions, major illnesses, and related surgical procedures. Any prescribed or over-the-counter medications that the subject received within the past 30 days should be recorded on the case report form (CRF). Medication prescribed for the treatment of PAH for 2 months prior to enrolment should be recorded on the CRF. Subjects will be instructed to notify the study physician before beginning new prescribed or over-the-counter medications.

### 7.2 WHO functional class

Functional assessment of PAH will be made according to the WHO classification system (26).

| | |
|---|---|
| Class I: | Patients with PAH without limitation of physical activity. Ordinary physical activity does not cause increased dyspnoea or fatigue, chest pain, or near syncope. |
| Class II: | Patients with PAH resulting in slight limitation of physical activity. No discomfort at rest. Normal physical activity causes increased dyspnoea or fatigue, chest pain, or near syncope. |
| Class III: | Patients with PAH resulting in marked limitation of physical activity. There is no discomfort at rest. Less than ordinary activity causes increased dyspnoea or fatigue, chest pain, or near syncope. |
| Class IV: | Patients with PAH with inability to carry out any physical activity without discomfort. Indications of manifest right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by the least physical activity. |

### 7.3 Vital signs

Systolic and diastolic systemic BP will be measured by means of either a standard manual or an automatic BP measuring device (cuff method). The same arm will be used for each measurement of BP, and BP will be measured after 5 minutes seated. Heart rate (HR), respiratory rate, and oxygen saturation will be measured by pulse oximetry after the subject has been at rest for at least 5 minutes.

### 7.4 Borg Dyspnoea Index

| | |
|---|---|
| 0 | Nothing at all |
| 0.5 | Very, very slight (just noticeable) |
| 1 | Very slight |
| 2 | Slight |
| 3 | Moderate |
| 4 | Somewhat severe |
| 5 | Severe |
| 6 | |

| | |
|---|---|
| 7 | Very severe |
| 8 | |
| 9 | Very, very severe (almost maximal) |
| 10 | Maximal |

**7.5 Six-minute walk distance (6MWD):**

Distance walked during an unencouraged 6MWT conducted according to American Thoracic Society guidelines (6). This is a standard tool for the study of functional capacity in PAH patients and is primarily determined by cardiac output and hence right ventricular function.

**7.6 Laboratory measurements**

**7.6.1 Routine laboratory measurements**

Routine clinical laboratory parameters (haematology, clinical chemistry) will be analysed by local accredited hospital laboratories. Tests may vary slightly depending on the availability of local hospital assays and so some flexibility with regards to the specific tests will be tolerated.

Routine laboratory tests include the following:

| | |
|---|---|
| **Haematology** | White blood cell count (WBC) and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count (RBC), platelet count, haemoglobin (Hb), haematocrit level (Hct), mean cell volume (MCV), mean cell haemoglobin level (MCH), mean cell haemoglobin concentration (MCHC), and reticulocytes, red cell distribution width (RDW) |
| **Clinical chemistry** | Albumin, total bilirubin, urea, creatinine, eGFR*, glucose, total protein, C reactive protein (CRP), urate, serum electrolytes [calcium (Ca), chloride (Cl), sodium (Na), phosphate (P), potassium (K), magnesium (Mg)], bicarbonate ($HCO_3$), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl-transferase (γ-GT/gamma-GT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH/LD), creatine kinase (CK), serum iron, thyroid stimulating hormone (TSH), free thyroxine (T4); also, brain natriuretic peptide (BNP) or N-terminal (NT)-pro hormone BNP (proNT-BNP) |
| **Serum pregnancy test** | beta human chorionic gonadotropin (β-hCG) |

**eGFR using CKD-EPI will be calculated in ml/min per 1.73m$^2$ via the following weblink:* https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi

**7.6.2 XBD173 assay**

Plasma levels of XBD173 will be quantified by an external laboratory. Sample-related data (labelling information) will be pseudonymised (coded).

**7.6.3 Genotyping**

A sample at baseline will be taken for DNA extraction and analysed by polymerase chain reaction (PCR) using appropriate primers for single nucleotide polymorphisms (SNPs) related to TSPO activity. Sample-related data (labelling information) shared with Imperial College will be pseudonymised (coded).

**7.6.4 Research blood samples**

Blood samples will be collected for measuring biomarkers such as sVCAM1 and proNT-BNP and for future research studies. Research blood samples will be processed at the site of collection to extract plasma serum and cells, which will be stored locally in -80°C laboratory freezers. Frozen samples will be shipped to the central laboratory at Imperial College London (Pulmonary Hypertension Biobank), where they will be deposited for

future research focused on PAH and/or XBD173 studies. Data shared with Imperial College London to accompany research blood samples will be pseudonymised (coded). For selected measurements (e.g. proteomic analyses), samples or products of them shall be sent to accredited central laboratory/laboratories overseas (e.g. USA) contracted to perform proteomic analysis. Any data shared with these third parties will be anonymised. Details on preparation, labelling, storage and shipment of these samples can be found in the relevant section of the laboratory manual.

### 7.6.5 Volume of blood collection

The approximate blood volume collected from each individual during all scheduled visits is described in the table below. In addition, a further 4mL is required at screening for TSPO genotyping.

| assessment | ml/collection | number of collections | total (ml) |
|---|---|---|---|
| haematology | 3.0 | 4 | 12.0 |
| clinical chemistry | 10.0 | 4 | 40.0 |
| serum pregnancy test | 1.5 | 1 | 1.5 |
| XBD173 assay | 5.0 | 2 | 10.0 |
| research blood | 10.0 | 5 | 50.0 |
| | | **total volume:** | 113.5 ml |

### 7.8 Electrocardiogram (ECG)

A single 12-lead ECG will be conducted at baseline assessment, and at the following assessments on Weeks 4 and 8 (and at any unscheduled assessment, as needed). A qualified physician will be responsible for interpreting the ECGs. Any ECG finding that is judged by the site investigator as a clinically significant change (worsening) will be considered an Adverse Event.

### 7.9 Remote monitoring and management system of haemodynamic data

The CardioMEMS™ Heart Failure System (27) provides pulmonary artery hemodynamic data used for monitoring and management of Heart Failure patients. The system includes an implantable wireless sensor with delivery catheter, a remote monitoring electronics system, and a System database.

The wireless sensor is implanted into the distal pulmonary artery. Once implanted, the CardioMEMS Pulmonary Artery Sensor provides non-invasive hemodynamic data that is collected in the System database. The dataset includes details on the pulmonary artery pressure waveform, systolic, diastolic, and mean pulmonary artery pressure and cardia rhythm (heart rate). This hemodynamic data is transferred online to a secure website that serves as the System database, so that monitoring information is available at all times.

## 8. ADVERSE EVENTS

### 8.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

8.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

8.3.1 Non serious AEs

All such events, whether expected or not, should be recorded

8.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, worsening of disease, death due to PAH, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

**Contact details for reporting SAEs**
**RGIT@imperial.ac.uk**
**CI: m.wilkins@imperial.ac.uk**
**Please send SAE forms to:**
**Martin Wilkins**
**ICRF, Ground Floor ICTEM, Hammersmith Hospital**
**Du Cane Road, London W12 0HS**
**Tel: 0203 313 8070 (Mon to Fri 09.00 – 17.00)**

## 9. DOCUMENTATION OF DATA

### 9.1 Data collection

The data collection tool for this study will be paper CRFs. Paper CRFs will contain study data which are verifiable to the source data (i.e., original recordings, laboratory reports, and subject records). In addition, all source data should be attributable (signed and dated). Only the site Investigator and authorised co-workers are entitled to make entries on the CRFs. Concomitant medications may be entered as they appear in the participant's record or as per local standards (generic or trade names may be entered). It is the responsibility of the site Investigator to ensure that the CRFs are kept up-to-date so that they always contain the latest observations on the subjects enrolled.

Pathology and imaging results outside the normal range will be identified and reviewed by the site Investigator. If they are deemed of clinical significance, they will be reported to the clinical care team. Other data than those requested by this protocol may be recorded as "additional data" in the comments section of the CRF; the clinical significance of any additional data should be described. Subjects' data will be stored in a validated database, developed and maintained by the Imperial College Trials Unit.

### 9.2 Data monitoring

The site Investigator is responsible for ensuring that the study is monitored appropriately in order to ensure compliance with GCP and local regulatory guidelines.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

## 10. STATISTICS, SAMPLE SIZE AND DATA ANALYSIS

To maximize study efficiency, the design compares measures following treatment with those at baseline. The entry criteria will select patients that are clinically stable (No 6: no change in medication for over the preceding 1 month). It is assumed that any change in measures over the dosing period is a consequence of the intervention. While the study design is open label, the reliance on objective endpoints is intended to minimise bias in measurement and interpretation. This is a pilot study and therefore has not been formally powered. A 10% reduction in total pulmonary resistance would be of biological interest and will be related to change in endothelial markers.

Estimated frequencies and proportions will be summarized with descriptive analysis. Change in total pulmonary resistance and plasma levels will be presented as mean ± standard deviations for continuous variables. The threshold for statistical significance will be established at 5%

Professor Martin Wilkins (CI) performed the statistical review of the study.

## 11. ADMINISTRATIVE AND LEGAL CONSIDERATIONS

### 11.1 General Legal Requirements

### 11.2 Ethical approvals

The ICL RGIT CTIMP Committee have confirmed that this study does not require MHRA authorisation.

The Study Coordination Centre has obtained approval from the London - West London & GTAC Research Ethics Committee Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also

receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 11.3 Informed consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

### 11.4 Patient confidentiality

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

The site Investigators affirm and uphold the principle of the subject's right to protection against invasion of privacy. Personal health data will be kept confidential.

On paper CRFs or other documents, subjects will be identified by their subject ID only. However, each site Investigator will keep in his/her file a Subject Identification List. With respect to the processing of data, every subject has to agree with this in writing. This agreement should be documented together with the written informed consent for trial participation.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be pseudonymised

### 11.5 Protocol Amendments

Any changes in the protocol will require a formal approval.

### 11.6 Premature Termination of the Study

The Chief Investigator reserves the right to terminate the trial for well-documented reasons.

Further recruitment of subjects will not take place under the following conditions:

- Premature termination of the trial.
- Drug-related events, i.e. SUSARs, emerging AEs that are serious and the risk/benefit ratio is unacceptable.
- Procedure-related events, i.e., the recruitment rate is too low or the number of dropouts for administrative reasons is too high.
- The model predicts that the lowest dose has a toxicity above the TTL with 90% certainty.

**11.7 Funder**
This project is funded by Imperial College London.

**11.8 Sponsor**

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

**11.9 Indemnity**

***Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study*11.10 Record Retention**

The site Investigator must retain all study records by the applicable regulations in a secure and safe facility. The site Investigator/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g. subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

The site Investigator/institution should retain subject identifiers for at least 10 years after the completion or premature termination of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 10 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements. It is the responsibility of PI to inform the institution as to when these documents no longer need to be retained.

If a site Investigator moves, withdraws from an investigation, retires, requests to move records to another location or to assign these records to another party or (e.g. other Investigator) who will accept the responsibility, written notice of this transfer must be made to and agreed upon by each party.

**11.11 Confidentiality**

***Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study*11.12 Publications**

The expectation is that the study will be published in full in peer reviewed scientific journals. The results may also be published in internal reports and conference presentations

**11.13 Audits and Inspections**

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

**11.14 Participants' Expenses and Payments**

Any reasonable journey costs (costs of fuel, bus or railway tickets) and subsistence costs will be reimbursed to individual patients, provided they are supported by valid receipts. Participants will not receive any other payment for taking part in this clinical study. Travel arrangements can be made as needed through the research site at no cost to the patient. Reasonable travel costs and expenses for going to hospital/clinic for the study visits will be reimbursed ss long as those costs and expenses follow the travel policy for the study site and all necessary receipts to the clinical study team.

# STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr David Owen (d.owen@imperial.ac.uk, Tel :07801140800

## REFERENCES


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2. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global view of pulmonary hypertension. Lancet Respir Med. 2016; 4: 306-322.

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| STUDY PERIOD | Pretreatment | Dosing | Assessments | | | | | Follow up | |
|---|---|---|---|---|---|---|---|---|---|
| **Assessment Name** | Assessment 1 (screening) | Assessment 2 (baseline) | Telephone assessment | Assessment 3 | Telephone assessment | Assessment 4 | Assessment 5 | Assessment 6 | Unscheduled visit |
| **Location** | Clinic | Clinic/Home | ☎ | Clinic | ☎ | Clinic | Clinic | Clinic/Home | Unscheduled assessment |
| **Time (weeks)** | Before Week 0 | Week 0 | Week 1 | Week 2 | Week 3 | Week 4 | Week 8 | Week 12 | Clinic/Home |
| **Assessment Window (days)** | 0 | Within 7 days baseline | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | when needed |
| Inclusion/Exclusion criteria | **X** | – | – | – | – | – | – | – | n/a |
| Written informed consent | **X** | – | – | – | – | – | – | – | – |
| Demographics | **X** | – | – | – | – | – | – | – | – |
| Medical and medication history | **X** | – | – | – | – | – | – | – | **X** |
| Physical examination | **X** | - | – | – | – | **X** | **X** | - | **X** |
| Concomitant medications | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| Vital signs | **X** | - | – | – | – | **X** | **X** | - | **X** |
| WHO Functional Class | **X** | – | – | – | – | – | – | – | – |
| Six-minute walk test (6MWT) | **X** | - | – | – | – | – | – | – | – |
| Borg Dyspnoea Index | **X** | - | – | – | – | – | – | – | – |
| Haematology blood tests | **X** | - | – | **X** | – | **X** | **X** | - | **X**[b] |
| Clinical chemistry tests | **X** | - | - | **X** | - | **X** | **X** | - | **X**[b] |
| TSPO genotype test | **X** | | | | | | | | |
| Serum pregnancy test | **X**[a] | – | – | – | – | – | – | – | – |
| Urinary pregnancy test | | **X**[a] | | **X**[a] | | **X**[a] | **X**[a] | | **X**[a] |
| Home body weight and ankle swelling self-check | – | – | **X** | - | **X** | – | – | – | – |
| XBD173 assay | – | - | – | - | – | **X** | **X** | - | – |
| Research blood samples | – | **X** | – | **X** | – | **X** | **X** | **X** | – |
| Electrocardiogram (ECG) | **X** | - | – | – | – | **X** | **X** | - | – |
| **Administration of XBD173** | – | **X** | – | – | – | – | – | – | **X**[b] |
| Review of the diary, XBD173 collection and reconciliation | – | – | – | – | – | **X** | **X** | **X** | – |
| Report of Adverse Events , if any | – | **X** | **X** | **X** | **X** | **X** | **X** | **X** | – |

Appendix 1: Schedule of Events

[a]For women of childbearing potential.

[b]If clinically required.

Appendix 2: NCI Common Terminology Criteria for Adverse Events (adapted), See separate file