TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A microdose Study to Evaluate the Biodistribution of [11C]-GSK2256098 in the Lungs and Heart of Healthy Subjects and Pulmonary Arterial Hypertension (PAH) Patients using Positron Emission Tomography (PET)

Compound Number: GSK2256098

Development Phase: I

Effective Date: 22-APR-2016

Protocol Amendment Number: 03

Author (s): PPD (Clinical Statistics); PPD (AcDPU); PPD PPD (CPSSO); PPD (Respiratory TAU); PPD (AcDPU); PPD (II DPU Clinical Imaging)

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N237824_00	2015-JUN-15	Original
2015N237824_01	2015-JUL-03	Amendment No. 1
To amend the eligibility criteria		
2015N237824_02	2015-NOV-24	Amendment No. 2
To clarify some ambiguous text in the protocol		
2015N237824_03	2016-APR-22	Amendment No. 3
To include iPAH patients with QTcF interval up to and including 500 msec.		

SPONSOR SIGNATORY

PPD

22/APR/2016

Duncan Richards, MD Date

VP and Head Academic Discovery Performance Unit

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
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Sponsor Legal Registered Address:

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): 2015-002626-40

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204746.

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described 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 receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204746

Rationale

Pulmonary Arterial Hypertension (PAH) used to be considered primarily a consequence of abnormal pulmonary vasoconstriction, but is now regarded as a disease caused mainly by pulmonary vascular remodelling with features analogous to carcinogenesis [Guignabert, 2013].

The currently available PAH therapies are vasodilators and provide symptomatic support but do not fully address the underlying remodelling aspects of the disease where there is a significant unmet need for a specific disease modifying PAH therapy.

In 2011, Novartis submitted an application for use of imatinib (Ruvise), a tyrosine kinase inhibitor, as an add-on therapy for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity in patients with pulmonary vascular resistance who remain symptomatic on dual vasodilator therapy. This was based on early clinical data indicating improvements in PVR/PAP. This medicine would have been the first disease-modifying treatment for PAH, but failed to receive a positive opinion (lack of sufficient positive risk/benefit evidence) and Novartis withdrew their application in January 2013.

GSK has identified the FAK inhibitor, GSK2256098, currently in development for glioblastoma as a candidate for repurposing for PAH.

Focal adhesion kinase (FAK) is a non-receptor kinase intracellular signalling node which is important for the initiation and maintenance of vascular smooth muscle cell (SMC) switching to the synthetic phenotype. GSK also has *in vitro* tissue cell data showing pulmonary artery smooth muscle cell migration effects, further demonstration of the target in disease relevant tissues is important before proceeding to a clinical Ph II study in PAH patients.

Therefore, a PET imaging study using a microdose of a ^{11}C-radiolabelled FAK tyrosine kinase inhibitor (TKI) GSK2256098 will enable identification of the cardiopulmonary sites where there is both expression of autoactivated, signalling-ready, FAK and drug exposure. The uptake of ^{11}C –GSK2256098 within the lung and / or heart will inform the decision as to whether a follow-on phase 2 trial should be initiated to investigate the therapeutic utility of GSK2256098 in iPAH.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the uptake of [^{11}C]-GSK2256098 in the heart and lungs of PAH patients versus the heart and lungs of healthy control subjects	• Uptake of [^{11}C]-GSK2256098 in the heart and lung (assessed as the volume of distribution(V_T) and/or standardised uptake values (SUV)) as measured by PET
Exploratory	
• To explore the spatial distribution of [^{11}C]-GSK2256098 uptake in the heart and lungs of PAH patients versus the heart and lungs of healthy control subjects.	• Qualitative assessment of the spatial distribution of [^{11}C]-GSK2256098 uptake in the heart and lungs

Overall Design

- This will be a cross-sectional study exploring the uptake of [^{11}C]-GSK2256098 in PAH patients and in healthy (age and gender-matched) volunteers.

- This is a non-randomised, open label study where all volunteers will receive one microdose of the radiolabelled compound.

Treatment Arms and Duration

- The total duration of the study for each subject will be approximately 2 months from screening to follow-up. The screening period will be followed by 1 scanning day and the follow-up visit.

- All subjects will receive one microdose of [^{11}C]-GSK2256098. The maximum amount of radioactivity injected during the –PET scan will be 500 MBq and maximum mass of [^{11}C]-GSK2256098 administered will be $\leq$10µg.

- Subject completion for the primary endpoint is defined as a subject who completes the PET-CT scan visit.

Type and Number of Subjects

- Up to 12 healthy subjects and 12 PAH patients will be enrolled to provide sufficient PET data to quantify the uptake of [^{11}C]-GSK2256098 in the heart and lungs.

- If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the Investigator/GSK Medical Monitor

Analysis

Hypotheses

Although a valid scientific hypothesis underpins this study, as expressed in the study objectives (viz: "FAK inhibitor uptake is substantially higher in patients than in (relatively) well-matched healthy control subjects"), no statistical hypothesis testing will be conducted, nor will any p-values be generated. (It would make no sense to "reject" a null hypothesis of "no difference in FAK expression between patients and healthy volunteers (HVs)" in the absence of a pre-specified threshold of clinical relevance.)

Instead, we will adopt an estimation approach, and use simple Bayesian methods to quantify the evidence which the study generates about the endpoints themselves, and about contrasts (probably ratios) of those endpoints. We will evaluate the evidence in as close to real-time as is feasible.

Sample Size Considerations

There is little known about the likely mean values of the PET-derived functional primary endpoints (Volume of distribution, and/or some form of integrated SUV) in this population. Therefore our sample size is driven by a mixture of (i) what is known about between-subject variability from relevant, recent PET studies, (ii) feasibility, and (iii) flexibility.

An ongoing study investigating the validation and dosimetry of a PET ligand in healthy subjects and patients with IPF (study RES116235) has been able to draw firm conclusions about similar endpoints (in terms of the estimation methods we describe below) using around 5 subjects. Therefore we will set five patients and five age- and gender-matched HVs as our initial target sample size.

From that point onwards, the data will be monitored continuously (or as near as possible given practicalities of study operationalisation), and at each step the following decisions will be made:

- Stop, and conclude that there is strong evidence of differential FAK uptake (as measured by the study endpoints) between patients and HVs.

- Stop, and conclude that there is insufficient evidence of any great difference, and furthermore (conditional on observed data i.e. in a formal Bayesian sense) there is low probability that an increase in sample size will reverse such a conclusion

- Continue to enrol patient-HV pairs, and re-evaluate the decision.

This iterative cycle will be followed up until a maximum of twelve patients and twelve HVs have been recruited into the study.

2. INTRODUCTION

GSK2256098 is a FAK inhibitor being considered for the treatment PAH.

2.1. Study Rationale

Focal adhesion kinase (FAK) is a non-receptor kinase intracellular signalling node which is important for the initiation and maintenance of vascular SMC switching to the synthetic phenotype. GSK also has *in vitro* tissue cell data showing pulmonary artery smooth muscle cell migration effects, further demonstration of the target in disease relevant tissues is important before proceeding to a clinical Ph II study in PAH patients.

Therefore, a PET imaging study using a microdose of a ^{11}C-radiolabelled FAK tyrosine kinase inhibitor (TKI) GSK2256098 will enable identification of the cardiopulmonary sites where there is both expression of autoactivated, signalling-ready, FAK and drug exposure. The uptake of ^{11}C –GSK2256098 within the lung and / or heart will inform the decision as to whether a follow-on phase 2 trial should be initiated to investigate the therapeutic utility of GSK2256098 in iPAH.

2.2. Brief Background

Pulmonary Arterial Hypertension (PAH) used to be considered primarily a consequence of abnormal pulmonary vasoconstriction, but is now regarded as a disease caused mainly by pulmonary vascular remodelling with features analogous to carcinogenesis [Guignabert, 2013].

The currently available PAH therapies are vasodilators and provide symptomatic support but do not fully address the underlying remodelling aspects of the disease where there is a significant unmet need for a specific disease modifying PAH therapy. This is particularly important since increasing pulmonary artery pressures leads to progressive, and sometimes maladaptive, right ventricle remodelling which increases the risk of QTcF interval prolongation (Rich, 2013), and is probably one of the factors which contributes to the increased risk of sudden death in this population.

In 2011, Novartis submitted an application for use of imatinib (Ruvise), a tyrosine kinase inhibitor, as an add-on therapy for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity in patients with pulmonary vascular resistance who remain symptomatic on dual vasodilator therapy. This was based on early clinical data indicating improvements in PVR/PAP. This medicine would have been the first disease-modifying treatment for PAH, but failed to receive a positive opinion, due to lack of positive risk/benefit and Novartis withdrew their application in January 2013.

GSK has identified the FAK inhibitor, GSK2256098, currently in development for glioblastoma as a candidate for repurposing for PAH.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To compare the uptake of [^{11}C]-GSK2256098 in the heart and lungs of PAH patients versus the heart and lungs of healthy control subjects	• Uptake of [^{11}C]-GSK2256098 in the heart and lung (assessed as the volume of distribution(V_T) and/or standardised uptake values (SUV)) as measured by PET
Exploratory	
• To explore the spatial distribution of [^{11}C]-GSK2256098 uptake in the heart and lungs of PAH patients versus the heart and lungs of healthy control subjects.	• Qualitative assessment of the spatial distribution of [^{11}C]-GSK2256098 uptake in the heart and lungs

4. STUDY DESIGN

4.1. Overall Design

- This will be a cross-sectional study exploring the uptake of [^{11}C]-GSK2256098 in PAH patients and in healthy (age and gender-matched) volunteers.

- This is a non-randomised, open label study where all volunteers will receive one microdose of the radiolabelled compound.

4.2. Treatment Arms and Duration

- The total duration of the study for each subject will be approximately 2 months from screening to follow-up. The screening period will be followed by 1 scanning day and the follow-up visit.

- All subjects will receive one microdose of [^{11}C]-GSK2256098. The maximum amount of radioactivity injected during the –PET scan will be 500 MBq and maximum mass of [^{11}C]-GSK2256098 administered will be ≤10μg.

4.3. Type and Number of Subjects

- Up to 12 healthy subjects and 12 PAH patients (including those with a prolonged QTcF interval ≤ 500ms) will be enrolled to provide sufficient PET data to quantify the uptake of [^{11}C]-GSK2256098 in the heart and lungs.

- If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects at the discretion of the Investigator/GSK Medical Monitor.

4.4. Design Justification

The study will be open-label and non-randomised as there is no intention of performing inference about the safety or efficacy profile of an NCE or other test therapeutic vs any form of control. A sufficient number of subjects will be recruited, based on feasibility, to permit adequate quantification of the uptake of [^{11}C]-GSK2256098 in target organs within the patient population, and those levels of expression will be compared with those measured in a set of age and gender-matched healthy controls. This form of case matching is intended to reduce the variance in the estimate of uptake by imposing a form of biological control on the signal derived from the subjects.

4.5. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2256098 can be found in the Investigator's Brochure. Of note the amount of GSK2256098 administered is a tracer dose and is not expected to result in any clinically significant pharmacology. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.5.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Subjects will be exposed to an additional dose of ionising radiation as a consequence of their participation in this study	The majority of the radiation dose comes from the administered radioligand, while a smaller portion comes from a low dose CT scan performed to estimate tissue attenuation.	Subjects < 40 years will not be eligible for the study. In addition, the study will exclude subjects who have previously participated in a research protocol involving nuclear medicine, PET and/or HRCT or radiological investigations or occupational exposure resulting in radiation exposure greater than 10 mSv over the past 3 years or greater than 10 mSv in a single year including the proposed study (clinical exposure from which the subject receives potential direct benefit is not included in these calculations). The study will exclude women of childbearing potential. The maximal dose of ionising radiation that subjects in this study may be exposed to is outlined in Appendix 5.
Arterial cannulation	Arterial blood for quantitative analysis will be sampled from a cannula in the radial artery.	Subject suitability to undergo radial artery cannulation will be assessed by means of an Allen's test assessment and testing the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		subjects blood coagulation profile. Arterial cannulation will be performed by suitably trained staff under local anaesthetic, using best practice. On completion of the PET scan, the radial artery cannula will be removed and subjects observed until haemostasis obtained. The PAH patients will be at an increased risk of bruising and will not be discharged until the Investigator is happy with the cannulation site. The total amount of blood collected for all of the study procedures will not exceed 500 mL. Warfarin will be discontinued in subjects on prophylactic doses about 5 days before the arterial cannulation. Arterial cannulation will be performed with an INR ideally ≤ 2. In situations where, anticoagulation is administered with a therapeutic intent (rather than simply prophylaxis), warfarin will be substituted by Low Molecular weight heparin starting up to 5 days prior to until a time after completion of the PET scan when therapeutic anti-coagulation is considered to have been achieved in the views of the clinician.

4.5.2. Benefit Assessment

- Participating in this study will contribute to the process of developing new therapies for PAH – an area of unmet need.

4.5.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to subjects participating in this study, the potential risks identified in association with study participation are justified by the anticipated benefits that may be afforded in the future to PAH patients

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

5.1.1. Healthy Volunteers

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Healthy subjects enrolled between 40 to 70 years inclusive at the time of signing the informed consent. Healthy subjects will be recruited to be age (± 5 years) and gender matched to PAH patients.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
3. Normal spirometry at Screening (FEV_1 and FVC ≥ 80% of predicted – measurements to be taken in triplicate and the highest value must be ≥ 80% of predicted).
4. A subject with a clinical abnormality or laboratory parameter(s) outside the reference range for the population being studied may be included only if the investigator, in consultation with the medical monitor if deemed necessary, agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
5. Subject is ambulant and capable of attending for PET-CT imaging.
6. A negative Allen's test in at least one arm for arterial blood sampling (indicating adequate collateral circulation to the hand from both the radial and ulnar arteries).

WEIGHT
7. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5 – 35 kg/m2 (inclusive).

SEX
8. Male or Female Males: Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 3 months after the scan. In addition, they must not plan to father a child, or donate sperm, for 3 months after the scan. a. Vasectomy with documentation of azoospermia. b. Male condom plus partner use of one of the contraceptive options below: • Contraceptive subdermal implant • Intrauterine device or intrauterine system • Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a] • Contraceptive vaginal ring [Hatcher, 2007a] • Percutaneous contraceptive patches [Hatcher, 2007a] This is an all-inclusive list of those methods that meet the following GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. For non-product methods (e.g., male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2) 2009].” The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. **Females**: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy • Documented Bilateral Oophorectomy

- Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
9. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.1.2. PAH Patients

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. PAH patients enrolled between 40 to 70 years inclusive at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subjects medically diagnosed with idiopathic or inherited PAH, and clinically Functional Class II-IV, as defined in the guidelines of the ESC and ERS; Table 4, Categories 1.1 and 1.2 [Galiè, 2009].
3. Subject is ambulant and capable of attending for PET-CT imaging.
4. A negative Allen's test in at least one arm for arterial blood sampling (indicating adequate collateral circulation to the hand from both the radial and ulnar arteries).

WEIGHT
5. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5 – 35 kg/m2 (inclusive).

SEX
6. Male or Female Males: a. Male subjects with female partners of child bearing potential must comply with the following contraception requirements from scan until 3 months after the last dose of study medication. In addition, they must not plan to father a child, or donate sperm, for 3 months after the scan. b. Vasectomy with documentation of azoospermia. c. Male condom plus partner use of one of the contraceptive options below: • Contraceptive subdermal implant • Intrauterine device or intrauterine system • Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a] • Contraceptive vaginal ring [Hatcher, 2007a] • Percutaneous contraceptive patches [Hatcher, 2007a] This is an all-inclusive list of those methods that meet the following GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. For non-product methods (e.g., male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2) 2009]." The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. **Females**: A female subject of non-child bearing potential is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy • Documented Bilateral Oophorectomy • Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating

hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
7. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

5.2.1. Healthy Volunteer Subjects

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Presence or history, of any significant or uncontrolled medical condition which in the opinion of the investigator would increase the potential risk to the subject or affect the study outcomes. 2. Previous pulmonary embolus 3. Current or chronic history of intrinsic liver disease, or known hepatic or biliary abnormalities, including coagulation abnormalities (with the exception of Gilbert's syndrome). 4. Established diagnosis of systemic hypertension or known Left Ventricular Hypertrophy (LVH). 5. Estimated GFR <60mL/min based on clinical chemistry

CONCOMITANT MEDICATIONS
6. Use of prohibited medication (Section 6.9)

RELEVANT HABITS
7. Current smoker or a history of smoking within 6 months of Screening, or a total pack year history of >10 pack years. [number of pack years = (number of cigarettes per day/20) x number of years smoked] 8. Subjects that do not wish to consume alcohol by I.V administration for personal reasons. 9. The subject has a positive pre-study drug/alcohol screen. A minimum list of drugs that will be screened for include cannabinoids, amphetamines, barbiturates, cocaine and opiates. The detection of drugs (e.g. benzodiazepines, opiates) taken for a legitimate medical purpose would not necessarily be an exclusion to study participation. The detection of alcohol would not be an exclusion at screening but would need to be negative pre-dose and during the study 10. History of regular alcohol consumption within 6 months of the study defined as: For UK sites: an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits

CONTRAINDICATIONS
11. History of sensitivity to heparin or heparin-induced thrombocytopenia. 12. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
13. Subject with QTcF of >450ms (or QTcF of > 480msec in subjects with Bundle Branch Block) or other 12-lead ECG abnormalities (with the exception of right bundle-branch block) which, in the opinion of the investigator, is clinically significant (e.g. LVH) in that they may increase safety risk or affect study outcomes. 14. Have donated blood or have taken part in a study of an experimental medicine in the last 3 months, or plan to do so in the 3 months after this study. 15. Have had a serious reaction to any medicine. 16. Unable or unfit to undergo PET scans, or found to be unsuitable for PET scanning in the opinion of the Investigator. 17. History of or suffers from claustrophobia or subject feels unable to lie flat and still on their back for a period of up to 2 hours in the PET/CT scanner. Previous inclusion in a research and/or medical protocol involving nuclear medicine, PET or radiological investigations or occupational exposure resulting in radiation exposure greater than 10 mSv over the past 3 years or greater than 10 mSv in a single year including the proposed study. Clinical exposure from which the subject receives a direct benefit is not included in these calculations.

5.2.2. PAH Patients

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Presence of any uncontrolled co-morbid condition (e.g. unstable coronary artery disease or systemic hypertension) which in the opinion of the investigator would increase the potential risk to the subject
2. Airways or interstitial lung disease, including adult asthma, COPD, emphysema, bronchiectasis, pulmonary fibrosis or chronic thromboembolic disease.
3. Current or chronic history of intrinsic liver disease (with the exception of Gilbert's syndrome or gallstones)
4. LVH on 2D-Echocardiogram in the past 12 months
5. Estimated GFR < 40mL/min based on clinical chemistry
6. Change in PAH medication within 28 days of scanning
7. A syncopal episode within 28 days of scanning
8. Subjects who require continuous oxygen.

CONCOMITANT MEDICATIONS
9. Use of prohibited medication (Section 6.9)

RELEVANT HABITS
10. Current smoker or a history of smoking within 6 months of Screening, or a total pack year history of >10 pack years. [number of pack years = (number of cigarettes per day/20) x number of years smoked]
11. Subjects that do not wish to consume alcohol by I.V administration for personal reasons.
12. The subject has a positive pre-study drug/alcohol screen. A minimum list of drugs that will be screened for include cannabinoids, amphetamines, barbiturates, cocaine and opiates. The detection of drugs (e.g. benzodiazepines, opiates) taken for a legitimate medical purpose would not necessarily be an exclusion to study participation. The detection of alcohol would not be an exclusion at screening but would need to be negative pre-dose and during the study
13. History of regular alcohol consumption within 6 months of the study defined as: For UK sites: an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits

CONTRAINDICATIONS
14. History of sensitivity to heparin or heparin-induced thrombocytopenia.

15. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
16. Subjects with QTcF of > 500ms (irrespective of bundle branch block status),or other 12-lead ECG abnormalities (with the exception of right bundle-branch block) which, in the opinion of the investigator is clinically significant in that they may increase safety risk. 18. Have donated blood or have taken part in a study of an experimental medicine in the last 3 months, or plan to do so in the 3 months after this study. 19. Have had a serious reaction to any medicine. 20. Unable or unfit to undergo PET scans, or found to be unsuitable for PET scanning in the opinion of the Investigator. 21. History of or suffers from claustrophobia or subject feels unable to lie flat and still on their back for a period of up to 2 hours in the PET/CT scanner. 22. Previous inclusion in a research and/or medical protocol involving nuclear medicine, PET or radiological investigations or occupational exposure resulting in radiation exposure greater than 10 mSv over the past 3 years or greater than 10 mSv in a single year including the proposed study. Clinical exposure from which the subject receives a direct benefit is not included in these calculations.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently scanned. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.5).

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last

known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.5. Subject and Study Completion

Subject completion for the primary endpoint is defined as a subject who completes the PET-CT scan visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments. In this study, the 'study treatment' is considered a microdose.

Product Name:	[^{11}C]-GSK2256098 Injection
Formulation description:	Up to 5% Ethanol in saline
Dosage Form:	IV
Unit dose strength:	Up to 500 MBq of [^{11}C]-GSK2256098
Route:	IV / single dose
Unit mass:	< 10 µg of GSK2256098
Administration:	Intravenous bolus over about 30 seconds
Physical description:	IV infusion, 20 mL
Manufacturer / source of procurement:	Imanova, London, UK[1]

1. According to the appropriate current Good Manufacturing Practice (cGMP) guidelines for the preparation of radio-pharmaceutical products to be administered to humans.

6.2. Blinding

This will be an open-label study.

6.3. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.4. Preparation/Handling/Storage/Accountability

A description of the methods required for the preparation of [^{11}C]GSK2256098 will be detailed in Imanova manufacturing documentation and will be accompanied by a Quality agreement.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.5. Compliance with Study Treatment Administration

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

[^{11}C]-GSK2256098 will be intravenously administered to subjects at the site. Administration will be documented in the source documents and reported in the CRF.

6.6. Treatment of Study Treatment Overdose

For this study, any dose of [^{11}C]-GSK2256098 > 10µg within a 24 hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose

6.7. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.8. Lifestyle Restrictions

6.8.1. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.8.2. Alcohol

Subjects will abstain from alcohol for 24 hours prior to each study visit.

6.9. Concomitant Medications and Non-Drug Therapies

6.9.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses of up to 2 grams/day is permitted for use any time during the study. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor.

Use of prescription contraceptives and HRT are permitted during the study.

PAH patients may continue all their usual treatment (except warfarin).

6.9.2. Prohibited Medications and Non-Drug Therapies

PAH patients on continuous oxygen are excluded from the study. Patients on warfarin will be asked to discontinue for a period prior to the scanning day to ensure appropriate INR values.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 7.1).

The timing and number of planned study assessments, including safety, or other assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring. The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment. The IRB/IE will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form. No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Procedure	Screening (up to 30 days prior to scan)	Scanning visit	Follow-up (2-4 weeks post-last dose)	Notes
Informed consent	X			
Inclusion and exclusion criteria	X			
Demography	X			
Brief physical	X	X	X	On the scanning day, to be completed pre-scan, prior to the administration of the peptide.
Medical / Medical history	X			
Vital signs	X	X		On the scanning day, to be conducted pre and post scan.
12-lead ECG	X			
Alcohol breath test	X	X		
Urine drug and cotinine screen	X			
Healthy subjects only: spirometry	X			
Coagulation profile	X			This will include PT (Prothrombin time), APTT (Activated Partial Thromboplastin Time) and Thrombin Time (TT)
PAH patients only (who have been on Warfarin): INR		X		Sample to confirm suitability for scanning day can be done up to 3 days prior to the day of the scan
HIV, Hep B and Hep C screen	X			If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Clinical chemistry and Haematology	X			
Urinalysis	X			
Allen's test	X	X		
i.v dose of [^{11}C]-GSK2256098		X		
PET scan		X		PET scanning will be started at the same time as injection of the radioligand and PET data will be collected for up to 90 minutes post administration.

Procedure	Screening (up to 30 days prior to scan)	Scanning visit	Follow-up (2-4 weeks post-last dose)	Notes
Attenuation CT scan		X		Lasting seconds to minute prior to start of PET scan. If subject gets off the bed for a comfort break midway through the PET scan, another CT scan will be performed prior to re-starting acquisition of PET data
Genetics sample		X		Genetic Informed consent must be obtained before collecting a sample
Samples for plasma radioactivity measurements & whole blood		X		Blood samples will be collected during scanning for plasma and whole blood radioactivity measurements.
AE/SAE review		X	X	
Concomitant medication review	X	X	X	

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management (e.g. MRI, INR) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of the PET scan until the follow-up contact (see Section 7.3.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the

event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

7.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.5.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.3.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. Pregnancy

- Details of all pregnancies in female partners of male subjects will be collected after the PET scan and until the follow-up visit.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

7.3.3. Physical Exams

- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.3.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

7.3.5. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the site SOPs. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the site SOPs for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 1.

Table 1 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit	MCHC	Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium		Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Pregnancy test • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, benzidiazepines and cannabinoids)			

7.3.7. Positron Emission Tomography (PET)

Prior to the commencement of the PET scan a venous cannula will be inserted in to the subjects arm for administration of [^{11}C]-GSK2256098. A radial arterial cannula will also be inserted prior to the scan start under local anaesthesia from which blood samples will be collected throughout the scan to enable the quantification of the total unmetabolised [^{11}C]-GSK2256098 related radioactivity in the whole blood and plasma throughout the duration of the PET scan. Initially an X-ray topogram of the area will be performed to localise the area to be scanned followed by a low- dose CT attenuation scan of the area to

be scanned. Thereafter the PET scan will commence with the administration of [^{11}C]-GSK2256098 intravenously and the emission data will be acquired for up to 90 minutes post-administration. The data provided from the arterial blood samples collected will be used to derive an input function for the analysis of emission PET data. At the end of the scan, the cannulae will be removed.

Ideally, subjects will complete the PET scan without a break. However, subjects may be removed from the scanner once for a period of rest and repositioned to continue the PET scan if absolutely necessary. The primary discomfort arises from the need for subjects to lie supine during the scan. The scan will be stopped or abandoned if the subject is unable to complete the scan.

The subjects will be monitored for approximately one hour after completion of the scan and will be allowed home at the Investigator's discretion.

7.3.8. Blood Sample Collection

Continuous and discrete arterial samples will be collected during this study. Samples collected during the [^{11}C]-GSK2256098 scan will be assayed for total blood and plasma radioactivity. Some of the discrete blood samples will be assayed to determine the fraction of labelled parent and metabolites of [^{11}C]-GSK2256098 in plasma, over time, using HPLC and/or TLC.

7.4. Genetics

Information regarding genetic research is included in Appendix 2.

8. DATA MANAGEMENT

- For this study data will be double-entered into a clinical database management system (ClinPlus Version 3.3).
- Management of clinical data will be performed in accordance with applicable HMR standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Original CRFs will be retained by GSK, while HMR will retain a copy. Subject initials will not be collected or transmitted to GSK according to GSK policy

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

Although a valid scientific hypothesis underpins this study, as expressed in the study objectives (viz: "FAK uptake is substantially higher in patients than in (relatively) well-matched healthy control subjects"), no statistical hypothesis testing will be conducted, nor will any p-values be generated. (It would make no sense to "reject" a null hypothesis

of "no difference in FAK expression between patients and HVs" in the absence of a pre-specified threshold of clinical relevance.)

Instead, we will adopt an estimation approach, and use simple Bayesian methods to quantify the evidence which the study generates about the endpoints themselves, and about contrasts (probably ratios) of those endpoints. We will evaluate the evidence in as close to real-time as the study operationalisation permits.

9.2. Sample Size Considerations

There is little known about the likely mean values of the PET-derived functional primary endpoints (Volume of distribution, and/or some form of integrated SUV) in this population. Therefore our sample size is driven by a mixture of (i) what is known about between-subject variability from relevant, recent PET studies, (ii) feasibility, and (iii) flexibility.

An ongoing study investigating the validation and dosimetry of a PET ligand in healthy subjects and patients with IPF (study RES116235) has been able to draw firm conclusions about similar endpoints (in terms of the estimation methods we describe below) using around 5 subjects. Therefore we will set five patients and five age matched HVs as our initial target sample size.

From that point onwards, the data will be monitored continuously (or as near as possible given practicalities of study operationalisation), and at each step the following decisions will be made:

- Stop, and conclude that there is strong evidence of differential FAK expression (as measured by the study endpoints) between patients and HVs.

- Stop, and conclude that there is insufficient evidence of any great difference, and furthermore (conditional on observed data i.e. in a formal Bayesian sense) there is low probability that an increase in sample size will reverse such a conclusion

- Continue to enrol patient-HV pairs, and re-evaluate the decision.

This iterative cycle will be followed up until a maximum of twelve patients and twelve HVs have been recruited into the study.

9.2.1. Sample Size Re-estimation or Adjustment

The first statistical evaluation of the data will occur once five patients and five healthy volunteers have been studied in the PET scanner, and the relevant functionals of their scan data (such as V_T) derived by Imanova scientists. At this point, the statistical analysis (set out below) will be carried out, and, based on those results, the team may decide to recruit more subjects, up to a total of twelve patients and twelve healthy volunteers.

9.3. Data Analysis Considerations

9.3.1. Interim Analysis

No formal interim "testing" of any statistical hypothesis will be performed. But we will be reviewing the strength of evidence in the data (about differential expression levels between patients and HVs) as data accrue (and as practicalities of data management permit).

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

For any important endpoint, we describe our uncertainty concerning its true value with a probability density function, p(t), say. (Suppose 't' represents Volume of Distribution, derived from the PET and blood sample data. The following argument will apply to any such endpoint which takes numerical values on the real line.) Pre-study start, we will characterise p(t) in such a way that our "prior belief" about the true endpoint's value is entirely diffuse over the real line (this approach implies that all conclusions about the endpoint are driven only by the data gathered in the study.)

We will gather evidence about the endpoint in the data from the study, which we will characterise via its likelihood function (derived from the relevant sampling distribution, l(x|t), say, where 'x' stands for 'data') From the likelihood function are derived the usual summary statistics for the endpoint.

It is highly likely, based on similar PET studies, that a Normal likelihood function will be suitable (that is will provide a reasonable fit to the observed data.) A conjugate Normal prior density function with mean zero and a vast variance will be adopted, leading to the standard Normal posterior density functions for the endpoints of interest. (Should the data not support a Normal likelihood function, alternative parametric forms, such as a log-Normal density, will be investigated.)

We will apply Bayes' theorem to derive the (constantly evolving) posterior density function p(t | x), and use this to produce the following quantities of inferential interest:

- What is currently (as a function of accruing data) the most probable true value of the endpoint? These point estimates, given the vagueness of the prior density, will be both the maximum likelihood, and the Bayesian maximum a posteriori, estimates of the parameters (the true values of the endpoints.)

- What is a range of plausible values for the true value of the endpoint, such that there is a 95% chance that the true value lies within that range? These intervals will be the 95% highest posterior density intervals for each parameter.

- What is the probability that the ratio of the endpoint in patients compared to the endpoint in HVs exceeds one, given the current data? Similarly, we will derive the 95% highest posterior density range for that ratio. Since the ratio of two Normally-distributed endpoints will not itself be Normally distributed, it is likely that some

simple Monte Carlo Markov Chain methods will be applied to derive these point and interval estimates.

- What does the graph of "probability that this ratio exceeds x", plotted against x, look like, for x in the range 0.5 to 2 (say – other ranges may be explored as data permits)?

- Given the current sample size, how likely, were we to recruit a further n patients, are those estimates to change substantially, for n in the range 2, 4, 6...up to a maximum sample size of 12. For this question, we will derive the predictive posterior density function for the ratio.

Full details of these approaches will be provided in the RAP.

9.4.2. Other Analyses

All other data will be listed and summarized as per GSK standards.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11. REFERENCES

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464 Gorin MB.

Galiè, Nazzareno, Hoeper, M.M., et al., 2009. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *European heart journal*, 30(20), pp.2493–2537.

Gorin, N.B. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

Guignabert C, Tu L, Le Hiress M, Ricard N, Sattler C, Seferian A, Huertas A, Humbert M and Montani D. 2013. Pathogenesis of Pulmonary Arterial Hypertension: lessons from cancer. *Eur Respir Rev.* 22(130):543-551.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28.

ICH GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS M3(R2). 11 June 2009.

Rich J.D., Thenappan T, Freed B., Patel A.R., Thisted R.A., Childers R., Archer S.L. 2013. QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension. International Journal of Cardiology, 167 (2013) 669–676.

12. APPENDICES

12.1. Appendix 1:Abbreviations and Trademarks

Abbreviations

µg	Microgram
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
cGMP	Current Good Manufacturing Practice
Cmax	Maximum observed concentration
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary disease
CPDS	Clinical Pharmacology Data Sciences
CPK	Creatine phosphokinase
CRF	Case Report Form
CS	Clinical Statistics
CT	Computed Tomography
CV	Coefficient of variance
ECG	Electrocardiogram
FAK	Focal adhesion kinase
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First time in humans
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
HPLC	High-performance liquid Chromatography
HR	Heart rate
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IU	International Unit
IUD	Intra Uterine Device
IUS	Intra Uterine System

IV	Intravenous
Kg	Kilogram
LFTs	Liver function tests
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
NCBP	Non Child Bearing Potential
NCE	New chemical entity
PAH	Pulmonary artery hypertension
PAP	Pulmonary arterial pressure
PET	Positron Emission Tomography
PVR	Pulmonary vascular resistance
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
REC	Research Ethics Committee
SAE	Serious adverse event(s)
SAO_2	Oxygen saturation levels
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
SUV	Standardized uptake values
T	Infusion duration
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
TKI	Tyrosine kinase inhibitor
TLC	Thin Layer Chromatography
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
vSMC	Vascular smooth muscle cell
V_T	Volume of distribution
WBC	White blood cells
τ	Dosing interval

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2:Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- GSK2256098 binding affinity, response to medicine, including GSK22560982 or any concomitant medicines;
- PAH susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies of PAH or related conditions to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected, after the subject has been enrolled and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample

destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.3. Appendix 3:Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' 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.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4:Collection of Pregnancy Information

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.5. Appendix 5:Radiation Dose

Subjects will be exposed to an additional dose of ionising radiation as a consequence of their participation in this study. The ionising radiation dose from PET/CT scanning comes from two sources. The majority of the radiation dose comes from the administered radiotracer ([^{11}C]GSK2256098). The remaining radiation dose coming from a low dose CT scan performed in order to correct the PET data for tissue attenuation. If the subject needs to be removed from the scanner and repositioned during the scan than a second low dose CT scan may be performed.The doses chosen for this study aim to deliver a minimal radiation exposure, compatible with a good quality PET and CT signal.

Each subject will have a single PET-CT scan. The dosimetry estimate for a study such as this, involving a novel tracer, is necessarily uncertain but a conservative approach has been taken by using a dose conversion factor of 6 μSv/MBq injected activity based on preclinical data. This results in an effective dose of 3 mSv for a 500 MBq administration. A low-dose attenuation CT scan of the lung results in an effective dose of 1.2 mSv. If the subject leaves the scanner during the scan and is repositioned, the CT scan will be repeated which would result in a further effective dose of 1.2 mSv . The total effective dose to each participant will therefore be up to 3.0 + 2.4 = 5.4 mSv. All of this exposure is over and above standard practice.

This total exposure of 5.4 mSv is equivalent to just under 2 and a half times the average yearly exposure (2.3 mSv) from natural background radiation in the United Kingdom. For an adult in good health this exposure would result in a risk of around 1 in 3700 of contracting a fatal cancer. The reduced life expectancy of the study patient group will result in a lower risk for these individuals.

The total exposure falls into category IIb (upper limit 10 mSv) of the guidance published by the International Committee for Radiation Protection (ICRP). There is no dose limit for research purposes in the UK, but like many EU member states, the UK follows the ICRP 62 guidance that recommends 10 mSv (or less) per study where research subjects are not expected to benefit personally.

12.6. Appendix 6:Protocol Changes

Amendment 01

The purpose of this amendment is to correct the eligibility criteria.

Summary of Changes

Section 5.2.1 Healthy Volunteer Subjects (Exclusion)

CHANGE FROM

4. Established diagnosis of systemic hypertension or known Left Ventricular Hypertrophy (LVH).
    a. Or undiagnosed subjects with the average of triplicate BP readings which is > 140 / 90 at screening

CHANGE TO

4. Established diagnosis of systemic hypertension or known Left Ventricular Hypertrophy (LVH).

Section 5.2.2 PAH patients (Exclusion)

CHANGE FROM

1. Presence of any uncontrolled co-morbid condition (e.g. severe or unstable coronary artery disease) which in the opinion of the investigator would increase the potential risk to the subject.
2. Airways or interstitial lung disease, including adult asthma, COPD, emphysema, bronchiectasis and pulmonary fibrosis or any secondary cause of PAH.
3. Previous significant pulmonary embolus
4. Current or chronic history of intrinsic liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome).
5. Systemic hypertension.
6. Estimated GFR <40mL/min based on clinical chemistry
7. Change in vasodilator and/or diuretic medication / dosage within 12 weeks of the scanning visit.
8. A syncopal or presyncopal episode within 4 weeks of screening.
9. Subjects who require continuous oxygen.

CHANGE TO

1. Presence of any uncontrolled co-morbid condition (e.g. unstable coronary artery disease or systemic hypertension) which in the opinion of the investigator would increase the potential risk to the subject
2. Airways or interstitial lung disease, including adult asthma, COPD, emphysema, bronchiectasis, pulmonary fibrosis or chronic thromboembolic disease.
3. Current or chronic history of intrinsic liver disease (with the exception of Gilbert's syndrome or gallstones)
4. LVH on 2D-Echocardiogram in the past 12 months
5. Estimated GFR < 40mL/min based on clinical chemistry
6. Change in PAH medication within 28 days of scanning
7. A syncopal episode within 28 days of scanning
8. Subjects who require continuous oxygen.

Amendment 02

The purpose of this amendment is to correct some typographical errors in the study title and the eligibility criteria. These changes do not impact subject safety, the study design or the integrity of the design. Therefore, this amendment is considered non-substantial.

Summary of Changes

Title

CHANGE FROM

A microdose Study to Evaluate the Biodistribution of [11C]- GSK2256098 in the Lungs and Heart of Healthy Subjects and Idiopathic Pulmonary Arterial Hypertension (PAH) Patients using Positron Emission Tomography (PET).

CHANGE TO

A microdose Study to Evaluate the Biodistribution of [11C]- GSK2256098 in the Lungs and Heart of Healthy Subjects and Pulmonary Arterial Hypertension (PAH) Patients using Positron Emission Tomography (PET)

Section 5.1.1 Healthy Volunteer Subjects (Inclusion)

CHANGE FROM

1. Healthy subjects enrolled between 40 to 70 years inclusive at the time of signing the informed consent. Healthy subjects will be recruited to be age (± 5 years) and gender matched to idiopathic PAH patients

CHANGE TO

1. Healthy subjects enrolled between 40 to 70 years inclusive at the time of signing the informed consent. Healthy subjects will be recruited to be age (± 5 years) and gender matched to PAH patients

Section 5.1.2 PAH Patients (Inclusion)

CHANGE FROM

2. Subjects medically diagnosed with idiopathic and inherited PAH, and clinically Functional Class II-IV, as defined in the guidelines of the ESC and ERS; Table 4, Categories 1.1 and 1.2 [Galiè, 2009].

CHANGE TO

2. Subjects medically diagnosed with idiopathic or inherited PAH, and clinically Functional Class II-IV, as defined in the guidelines of the ESC and ERS; Table 4, Categories 1.1 and 1.2 [Galiè, 2009].

Section 5.2.1 Healthy Volunteer subjects (Exclusion)

CHANGE FROM

7. Current smoker or a history of smoking within 6 months of Screening, or a total pack year history of >5 pack years.
   [number of pack years = (number of cigarettes per day/20) x number of years smoked]

CHANGE TO

7. Current smoker or a history of smoking within 6 months of Screening, or a total pack year history of >10 pack years.
   [number of pack years = (number of cigarettes per day/20) x number of years smoked]

Section 5.2.2 PAH patients (Exclusion)

CHANGE FROM

10. Current smoker or a history of smoking within 6 months of Screening, or a total pack year history of >5 pack years.
    [number of pack years = (number of cigarettes per day/20) x number of years smoked]

CHANGE TO

10. Current smoker or a history of smoking within 6 months of Screening, or a total pack year history of >10 pack years.
    [number of pack years = (number of cigarettes per day/20) x number of years smoked].

Amendment 03

The purpose of this amendment is to amend the QTc exclusion criteria (criteria number 16) for PAH patients only to a QTcF interval up to and including 500 msec. Te amendment is considered substantial.

Summary of Changes

Section 2.2 Brief Background

PREVIOUS TEXT

The currently available PAH therapies are vasodilators and provide symptomatic support but do not fully address the underlying remodelling aspects of the disease where there is a significant unmet need for a specific disease modifying PAH therapy.

REVISED TEXT

The currently available PAH therapies are vasodilators and provide symptomatic support but do not fully address the underlying remodelling aspects of the disease where there is a significant unmet need for a specific disease modifying PAH therapy. **This is particularly important since increasing pulmonary artery pressures leads to progressive, and sometimes maladaptive, right ventricle remodelling which increases the risk of QTcF interval prolongation (Rich et al, 2013), and is probably one of the factors which contributes to the increased risk of sudden death in this population.**

Section 4.3 Type and Number of Subjects

CHANGE FROM

- Up to 12 healthy subjects and 12 PAH patients will be enrolled to provide sufficient PET data to quantify the uptake of [^{11}C]-GSK2256098 in the heart and lungs.

CHANGE TO

- Up to 12 healthy subjects and 12 PAH patients (including those with a prolonged QTcF interval $\leq$ 500ms) will be enrolled to provide sufficient PET data to quantify the uptake of [^{11}C]-GSK2256098 in the heart and lungs.

Section 5.2.2 PAH patients (Exclusion)

CHANGE FROM

16. Subject with QTcF of >450ms (or QTcF of > 480msec in subjects with Bundle Branch Block) or other 12-lead ECG abnormalities (with the exception of right bundle-branch block) which, in the opinion of the investigator is clinically significant in that they may increase safety risk.

CHANGE TO

16. Subjects with QTcF of > 500ms (irrespective of bundle branch block status),or other 12-lead ECG abnormalities (with the exception of right bundle-branch block) which, in the opinion of the investigator is clinically significant in that they may increase safety