TITLE PAGE

Protocol Title: A study of single doses to evaluate the safety, tolerability, pharmacokinetics and target engagement of nebulised GSK3008348 in idiopathic pulmonary fibrosis patients, using positron emission tomography (PET) imaging

Protocol Number: 204715

Protocol Amendment Number: 02

Short Title: Single doses of GSK3008348 in IPF patients using PET imaging

Compound Number: GSK3008348

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): 2016-003674-41

Approval Date: 24-JAN-2018

SPONSOR SIGNATORY:

PPD

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24/01/18.

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	24-JAN-2018
Amendment 01	09-Mar-2017
Original Protocol	05-Dec-2017

Amendment 02 24-JAN-2018

Overall Rationale for the Amendment:

To correct the description of the primary endpoint and provide further guidance on the follow up visit and lung function requirements. Other typographical errors have also been corrected.

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis: Objectives and Endpoints	The wording 'and blood' has been removed from the primary endpoint pertaining to the volume of distribution (V_T)	To provide clarity and correct the definition of the primary endpoint pertaining to the volume of distribution (V_T). The V_T is generated using a kinetic model that includes a blood compartment and is therefore implicitly corrected for blood volume
Section 1 Synopsis: Treatment Group and Follow up	Additional wording has been included in the follow up section for participants who withdraw from the study prior to the final dose	To provide further guidance for participants withdrawing from the study prior to the final dose
Section 2 Schedule of Activities (SoA)	The requirement to measure height at the follow up visit has been removed	A substantial change in height is not expected to be observed over a short time period
Section 4 Objectives and	The wording 'and blood' has been removed from the primary endpoint	The volume of distribution (V_T) is generated using a

Section # and Name	Description of Change	Brief Rationale
Endpoints Section 10.3.1 Pharmacodynamic Analyses	pertaining to the volume of distribution (V_T)	kinetic model that includes a blood compartment and is therefore implicitly corrected for blood volume
Section 4 Objectives and Endpoints: Exploratory	The wording 'with and without correction' has been added and the wording 'corrected' has been removed to describe the standardised uptake values [SUV] and V_T, for air and/or blood volume)	To correct and provide clarity on the standardised uptake value (SUV) which cannot be readily corrected for blood volume
Section 5.2 Number of Participants	Additional wording on the number of participants required to be dosed and considered complete when PET data at 30min post dose has been collected	To provide clarity on the numbers of participants required to meet the primary endpoint of: Changes in the uptake of [^{18}F]-FBA-A20FMDV2 in the whole lung at approximately 30 min post-dose compared to pre-dose, as measured by PET
Section 6.4 Screen Failures	Re-screened participants should be assigned a new participant number The following has been removed from Section 6.4: Rescreened participants should be assigned the same participant number as for the initial screening	Correction to the protocol
Section 9.4 Safety Assessments	New wording inserted in Section 9.4.6 Lung Function Tests	To provide guidance on lung function tests which was previously omitted from the protocol

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1. SYNOPSIS

Protocol Title: A study of single doses to evaluate the safety, tolerability, pharmacokinetics and target engagement of nebulised GSK3008348 in idiopathic pulmonary fibrosis patients, using positron emission tomography (PET) imaging

Short Title: Single doses of GSK3008348 in IPF patients using PET imaging

Rationale: GSK3008348 is a potent and selective inhibitor of the integrin receptor αvβ6, and is being developed as a treatment for idiopathic pulmonary fibrosis (IPF). It has been shown to engage αvβ6 integrin and inhibit downstream fibrogenic mechanisms in mouse and human lung cells and tissue. The first-time-in-human study (GSK Document Number 2014N201929_01, Study 200262) showed that single nebulised doses of 1−3,000 µg GSK3008348 in healthy volunteers were well tolerated, with pharmacokinetic (PK) exposures within the defined limits set by the protocol. The proposed study is intended to evaluate the safety, tolerability and pharmacokinetics of the molecule in patients with IPF not currently treated with pirfenidone or nintedanib, and obtain preliminary information on target engagement to support progression to repeat dose and proof of mechanism studies. Target engagement will be measured by positron emission tomography (PET) using a radiolabelled αvβ6-specific ligand, [^{18}F]-FBA-A20FMDV2 (GSK2634673).

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate target engagement in the lung after single nebulised doses of GSK3008348 in IPF patients	• Changes in the uptake of [^{18}F]-FBA-A20FMDV2 in the whole lung (assessed as the volume of distribution [V_T], not corrected for air volume) at approximately 30 min post-dose compared to pre-dose, as measured by PET
• To evaluate the safety and tolerability of single nebulised doses of GSK3008348 in IPF patients	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and pulmonary function tests
Secondary	
• To evaluate the pharmacokinetic profile of single nebulised doses of GSK3008348 in IPF patients	• Derived pharmacokinetic parameters for GSK3008348 including, but not limited to, area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}),

Objective	Endpoint
	and terminal half-life ($T_{1/2}$) following single nebulised doses, where data allow
• To evaluate duration of target engagement after single nebulised doses of GSK3008348 in IPF patients	• Changes in the uptake of [^{18}F]-FBA-A20FMDV2 in the lung (assessed as the V_T) up to 28 h post-dose compared to pre-dose, as measured by PET

Overall Design:

This is a multi-centre, 2-cohort, study of single doses to investigate the safety, tolerability, PK and target engagement of nebulised GSK3008348, in patients with IPF. Hospital-based clinical units will recruit and enrol participants; PET imaging will be done at a specialist imaging unit. All participants will be screened up to 30 days before their first dose, will have 2 planned dosing periods, and will have a follow-up visit at 7–14 days post-last dose.

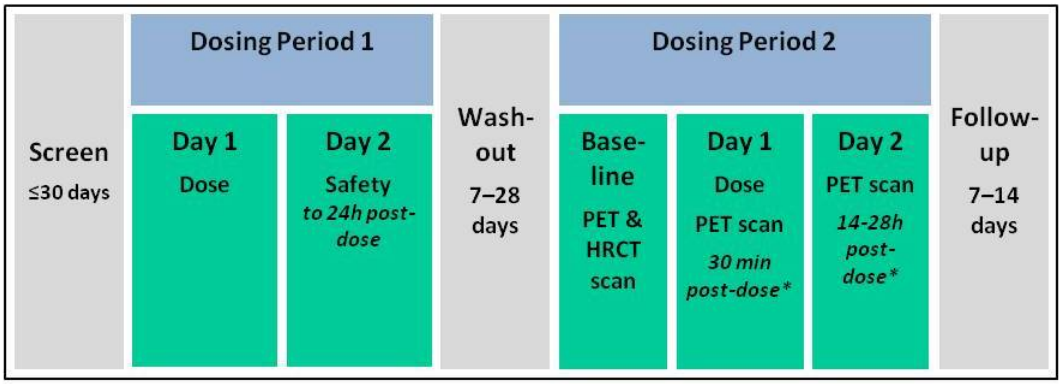
Cohort 1 will be a randomised, double-blind (sponsor unblind), placebo-controlled group of 7 participants, randomised 5:2 to receive 1,000 µg GSK3008348 or placebo. Safety and tolerability will be assessed in dosing period 1, and PET scans in dosing period 2 will be used to assess target engagement of GSK3008348.

After completion of Cohort 1, safety, PET and PK data will be reviewed.

Cohort 2 is optional, and will be designed to further explore the safety and to provide additional information on the target engagement profile of GSK3008348, such that each participant has up to 3 PET scans and 2 planned doses of GSK3008348.

Refer to Figure 1 for a schematic illustrating the study design.

Figure 1 Study Schematic



** PET scan time points may change in Cohort 2 depending on accumulated data*

Number of Participants:

It is anticipated that up to 21 participants will be randomized.

Treatment Groups and Duration:

	Cohort 1	Cohort 2
Screening	Within 30 days of the first dose.	
Dosing Period 1	After pre-dose assessments at the clinical unit, participants will be admitted to the clinical unit the day of dosing (Day 1), stay overnight and be discharged after 24 h post-dose safety and PK assessments (Day 2).	After pre-dose assessments at the clinical unit, participants will attend the clinical unit for dosing (Day 1) and stay for at least 8 h post-dose for safety and PK assessments. Participants will return on Day 2 for 24 h post-dose safety and PK assessments.
Washout Period	At least 7 days and no more than 28 days between doses.	
Baseline PET scan	At least 7 days after the first dose, and no more than 14 days before the first post-dose PET.	
Dosing Period 2	Participants will have pre-dose assessments at the clinical unit. They will attend the imaging unit for dosing and a 30 min post-dose PET scan, and stay for at least 4 h post-dose. Participants will return to the imaging unit on Day 2 for a 24 h PET scan, and safety and PK assessments.	Participants will have pre-dose assessments at the clinical unit. They will attend the clinical or imaging unit for dosing and will stay for at least 4 h post-dose. Participants will have up to 2 post-dose PET scans on Days 1 or 2, at times to be determined after review of Cohort 1 data.
Follow-up	At least 7 days and no more than 14 days after the final dose. If warranted, additional follow-up visits may be scheduled. If a participant withdraws from the study prior to the final dose, the follow up visit should occur within 14 days of withdrawal unless a separate timepoint is agreed by the principal investigator and medical monitor	
Study Duration	Up to 62 days	
Treatment Arms	Participants will receive a single nebulised dose of GSK3008348 or placebo during each of 2 planned dosing periods. Participants will receive up to 3 microdose administrations of [^{18}F]-FBA-A20FMDV2 for the PET scanning. The maximum amount of radioactivity injected during each PET scan will be 150 MBq and maximum mass of [^{18}F]-FBA-A20FMDV2 administered across the 3 administrations will be 100 µg.	

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening	Dosing period 1			Wash-out (7-28 days between doses)	Dosing period 2				Follow-up (7-14 days post-final dose)	Comments
	Day ≤-30	Day –1[1]	Day 1	Day 2		Baseline PET[2]	Day –1[1]	Day 1[2]	Day 2[2]		1. Visit may take place on Day -1 or on Day 1 before dosing. 2. Visits will take place at imaging unit; all other visits will take place at clinical units.
Informed consent	x										
Inclusion and exclusion criteria	x										
Demography	x										
Medical history	x										
Past and current medical conditions	x	x									
Full physical exam including height and weight	x									x[3]	3. Height not required at follow up visit
Brief medical exam		x		x		X[4]	x	x[4]	x[4]		4. Pre-PET scan, per imaging site SOPs; timing may change in Cohort 2 depending on PET timing.
Pregnancy test	x	x				x[5]		x[5]	x[5]		Pregnancy tests in females, when required, in serum or urine, as per site SOPs. 5. Pre-PET scan; time points may change in Cohort 2 depending on PET timing.
Hepatitis B and Hepatitis C screen	x										
Laboratory assessments (include liver chemistries)	x	x		x[6]			x		x[6]	x	6. 24 h post-dose
12-lead ECG	x	x	x[7]	x[8]			x	x[9]	x[8]	x	7. 30 min and 2, 4 and 8 h post-dose 8. 24 h post-dose (pre-PET scan in Dosing period 2) 9. Post-PET scan and before leaving imaging unit Timings may change in Cohort 2. Vital signs include blood pressure, heart rate, respiration rate and temperature.
Vital signs	x	x	x[7]	x[8]			x	x[9]	x[8]	x	
Oxygen saturation monitoring			x								Continuous monitoring from pre-dose to 4 h post-dose.
Lung function tests (FEV_1,FVC)	x	x	x[10]	x[11]			x			x	10. 1 h post-dose 11. 24 h post-dose

Procedure	Screening	Dosing period 1			Wash-out (7-28 days between doses)	Dosing period 2				Follow-up (7-14 days post-final dose)	Comments
	Day ≤-30	Day –1[1]	Day 1	Day 2		Baseline PET[2]	Day –1[1]	Day 1[2]	Day 2[2]		1. Visit may take place on Day -1 or on Day 1 before dosing. 2. Visits will take place at imaging unit; all other visits will take place at clinical units.
DLCO	x	x		x[12]							12. 24 h post-dose.
Randomisation			x								
GSK3008348 dosing			x					x			All post-dose time points are relative to start of nebulisation
PK blood sample			x	x				x	x		In Dosing period 1, pre-dose, and at 15 and 30 min, 1, 2, 4, 8, 12, 18 and 24 h after the start of nebulisation. In Dosing period 2, pre-dose; on Day 1 at 15 and 30 min, 2 and 4 h post-dose; and on Day 2 on arrival and discharge from imaging unit. Time points may change in Cohort 2.
PK urine collection			x								Spot urine sample to be taken from pre-dose void. Total urine collection from pre-dose to 8 h post-dose.
Biomarker blood sample			x[13]	x[14]							13. Samples at pre-dose, and at 2 and 8 h post-dose. 14. Sample at 24 h post-dose.
PET ligand administration & PET scan						x[15]		x[16]	x[17]		15. At least 7 days post-first dose, and no more than 14 days before next PET scan. 16. Approx. 30 min (between 20–60 min) post-dose. 17. Approx. 24 h (between 14−28 h) post-dose. Timing of post-dose PET scans may change in Cohort 2; participants will have a max of 3 PET scans in total.
HRCT						x					
Immunogenicity blood sample						x[18]				x	18. Pre-PET scan.
Genetic sample		x									
AE/SAE & CV event review			x	x	x	x	x	x	x	x	
Concomitant medication review		x	x	x	x	x	x	x	x	x	

ECG: Electrocardiogram, DLCO: Diffusing capacity of the lungs for carbon monoxide, FEV1: Forced expiratory volume in 1 second, FCV: Forced vital capacity, PET: Positron emission tomography, HRCT: High resolution computed tomography, AE: Adverse event, SAE : Serious adverse event, CV: Cardiovascular, PK: Pharmacokinetics

- The timing and number of planned study assessments, including safety, pharmacokinetic, imaging, immunogenicity and biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The ethics committee will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the information and consent form (ICF).
- Acceptable time deviation windows are listed in the Study Reference Manual (SRM).

3. INTRODUCTION

3.1. Study Rationale

GSK3008348 is a potent and selective inhibitor of the integrin receptor αvβ6, and is being developed as a treatment for idiopathic pulmonary fibrosis (IPF). It has been shown to engage αvβ6 integrin and inhibit downstream fibrogenic mechanisms in mouse and human lung cells and tissue. The first-time-in-human study (GSK Document Number 2014N201929_01 Study 200262) showed that single nebulised doses of 1−3,000 µg GSK3008348 in healthy volunteers were well tolerated, with pharmacokinetic (PK) exposures within the defined limits set by the protocol. The proposed study is intended to evaluate the safety, tolerability and PK of the molecule in patients with IPF not currently treated with pirfenidone or nintedanib, and obtain preliminary information on target engagement to support progression to repeat dose and proof of mechanism studies. Target engagement will be measured by positron emission tomography (PET) using a radiolabelled αvβ6-specific ligand, [^{18}F]-FBA-A20FMDV2 (GSK2634673).

3.2. Background

IPF is a form of chronic fibrosing interstitial pneumonia, limited to the lung and associated with the histological appearance of usual interstitial pneumonia (UIP) on surgical lung biopsy. The aetiology of IPF is unknown; it progresses in a relentless and often insidious manner that may be difficult to detect using parameters such as symptomatology, chest radiographic findings, or spirometry alone. Spontaneous remissions do not occur, and mean survival ranges from 2 to 4 years (5-year survival range, 30 to 50%).

In the United Kingdom, data from general practice shows that the 12 month prevalence is 15−18/100,000 person and an incidence of about 5/100,000 person-years. Approximately 2,000 new cases of IPF are diagnosed each year in England and Wales [Navaratnam, 2013].

No therapy has been demonstrated to reverse the progression of IPF and it remains a major indication for lung transplantation. Two oral therapies are currently marketed for IPF, pirfenidone (Roche), the mechanism of action for which is incompletely understood and nintedanib (Boehringer Ingelheim), a kinase inhibitor. Both of these treatments demonstrate a reduction in the rate of decline in lung function (forced vital capacity [FVC]) over one year [King, 2014; Richeldi, 2014]. Pirfenidone is associated with phototoxicity, and both agents have significant gastrointestinal effects. In a real-world study, treatment with pirfenidone led to discontinuation in approximately one third of patients due to adverse events [Hughes, 2016].

The association of transforming growth factor (TGF)β activity with fibrosis has been established in many disease settings. TGFβ is secreted in an inactive form, and requires activation post-translationally. Substantial evidence suggests that the αvβ6 integrin performs a key TGFβ activation function at sites of damaged epithelium [Margadant, 2010]. Activation of TGFβ by αvβ6 has been shown to play an important role in lung

fibrosis: β6 knockout mice are resistant to bleomycin-induced pulmonary fibrosis [Munger, 1999] and treatment with an αvβ6 neutralising antibody ameliorates bleomycin [Horan, 2008] and radiation-induced pulmonary fibrosis [Puthawala, 2008].

Immunohistochemistry of lung biopsy has shown that αvβ6 is significantly increased in the fibrotic areas of the lungs of IPF patients [Horan, 2008]. Expression levels of αvβ6 in IPF lungs predict mortality, with highest expression levels in IPF patients who progress rapidly [Saini, 2013]. In addition, animal models of pulmonary fibrosis have shown that the expression of αvβ6 correlates with the severity of the fibrotic response, and blockade of this target reduces the fibrosis [Horan, 2008; Puthawala, 2008]. Inhibition of αvβ6 is considered to be advantageous over direct TGFβ inhibition because αvβ6 expression is highly regulated and localised to damaged epithelial sites. Thus, inhibition of integrin-mediated TGFβ activation should minimise the risk of potential side effects caused by direct TGFβ inhibition, e.g. pro-inflammatory responses.

GSK3008348 is being progressed as a twice-daily small molecule anti-fibrotic medicine, to be delivered to IPF patients' lungs by nebulisation. On reaching the peripheral areas of the lung, where the fibrosis occurs, GSK3008348 will bind to αvβ6 on the damaged epithelium. Our non-clinical work indicates that binding leads to internalisation of the integrin, inhibiting αvβ6-mediated activation of TGFβ. The ability of TGFβ to promote collagen production by activated myofibroblasts is thereby limited. It is hypothesised that GSK3008348 will slow or stop the progression of fibrosis, with the potential to provide significant benefit to patients in terms of reduction, avoidance or delay of symptoms, disability and death.

A 20 amino acid peptide (A20FMDV2), derived from the foot and mouth disease virus (FMDV2), has been synthesised and shown to bind selectively to αvβ6 (K_D =0.22nM). The radiolabelled peptide, [^{18}F]-FBA-A20FMDV2, will be used in this study to quantify levels of αvβ6 expression and GSK3008348 receptor engagement in the lungs of IPF patients. A single photon emission computed tomography (SPECT) analogue, [^{111}In]-FBA-A20FMDV2, has been shown non-clinically to bind specifically to αvβ6 in the lungs of mice [John, 2013] and similar results have been obtained using the PET ligand in rats [internal GSK data on file]. [^{18}F]-FBA-A20FMDV2 has also been administered to humans and shown to provide a signal that allows the distinction between IPF patients and healthy participants (GSK Document Number 2013N163906_00 Study RES116235).

3.3. Benefit/Risk Assessment

Information on the key potential risk associated with GSK3008348 and the strategies to mitigate this risk are detailed below in Section 3.3.1. Further details about the potential risks and expected benefits of GSK3008348 may be found in the Investigator's Brochure (IB).

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3008348]		
Potential local irritancy	**Non-clinical:** Upper respiratory tract irritancy was observed in the 4-week inhalation toxicity studies in rats and dogs. Principal changes included epiglottic cartilage necrosis, regeneration/ remodelling at 5850 and 12000 µg/kg/day in rats; and soft palate or laryngeal ulcerations in dogs at 3070 and 8710 µg/kg/day. No Observed Adverse Effect Levels (NOAELs) were identified at the lowest doses tested (1420 and 899 µg/kg/day in rats and dogs, respectively). Lower respiratory tract irritancy was also observed in the 4-week inhalation toxicity study in dogs. Adverse mixed inflammation and alveolar macrophage aggregates were observed at 3070 and 8710 µg/kg/day. These findings were also present in some animals from the lowest dose tested (899 µg/kg/day – the NOAEL), including control. Changes in local draining lymph nodes of GSK3008348-treated dogs were considered to be a non-adverse secondary response to the pulmonary inflammation. Non-adverse alveolar macrophage aggregates were seen at a low incidence in the lungs of all treated groups and also in control males in the 4-week inhalation study in rats. A minor test article-related effect could not be entirely discounted in female rats.	In this planned first-time-in-patient study, IPF patients will only receive single doses. Appropriate inclusion/exclusion criteria (e.g., exclusion for current upper or lower respiratory tract infection) will be implemented in clinical protocols. Potential adverse events associated with irritancy (e.g., sore throat, cough, dyspnoea, wheezing) are readily monitored, and will be monitored during the study. Interpretation of these AEs may be compromised in IPF patients where cough or dyspnoea may be symptoms of their respiratory diseases. Therefore patients' baseline symptoms will be recorded as part of the current conditions assessment, and physical measurements including respiratory rate and oxygen saturation monitoring reviewed, to aid interpretation of any new symptoms. It is anticipated that symptoms secondary to irritancy will be more acute in nature, which will help distinguish from chronic symptoms due to IPF. Symptoms of clinical concern may be investigated further in collaboration with an Ear, Nose and Throat

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical: No symptoms or other clinical findings indicative of upper respiratory tract irritancy were observed in the first-time–in-human study 200262 in healthy volunteers following single doses up to 3,000 µg.	(ENT) specialist.
Study Procedures		
Participants exposed to ionising radiation as a consequence of patient's participation in this study.	The ionising radiation exposure comes from the administered radioligand, a high resolution CT (HRCT) for anatomical localization and low dose CT scans performed in order to correct the PET data for tissue attenuation. The maximum effective dose of ionising radiation that participants in this study may be exposed to is 20.9 mSv. This is equivalent to approximately 9 times the average yearly exposure (2.3 mSv) from natural background radiation in the United Kingdom. The additional risk of developing a fatal malignancy as a result of these exposures has been estimated as approximately 1 in 1,000 for an adult in normal health. The reduced life expectancy of IPF patients will result in a lower risk for these individuals. Within the UK the guidance set out by International Commission on Radiological Protection (ICRP) 62 is generally followed in setting research study dose constraints. The level of risk may therefore be assumed to broadly fall within the ICRP 62 intermediate Category IIb, where the benefit should be more directly aimed at the cure or prevention of disease.	The study has been designed to keep the radiation dose as low as reasonably practicable whilst obtaining images of sufficient quality to meet the objectives. Male participants < 50 years and female participants < 55 years will not be eligible. To avoid recruitment of radiation worker or serial study volunteers, participants who have been exposed to ionising radiation in excess of 10mSv above background over the previous 3 year period as a result of occupational exposure to radiation or as a result of research studies are excluded. Clinically justified (therapeutic or diagnostic) exposures are not included in the exposure calculation. Participants are asked about any occupational exposure or previous participation in research studies at screening so that dose estimates can be obtained where necessary. The study will exclude women of childbearing potential. The maximal dose of ionising radiation that participants

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		in this study may be exposed to is outlined in Appendix 8.
Potential risk of immunogenicity related to A20FMDV2	There is a low theoretical risk that [^{18}F]-FBA-A20FMDV2 may be immunogenic in humans. This could potentially lead to reduced signal in PET scans from neutralising anti-drug antibodies. There is also potential for anaphylactic and other immune mediated reactions. Neither of these phenomena has been observed in previous administrations of [^{18}F]-FBA-A20FMDV2 to humans (ongoing GSK Study RES116235). [Of note, assay for measurement of antibodies to [^{18}F]-FBA-A20FMDV2 produced positive results in two participants in study RES116235. One healthy participant was positive pre- and post-dosing, and one IPF participant was positive after the first scan and negative after the second scan. No clinical effects were attributed to effects of antibodies.]	Exclusion of participants with prior exposure to farm animals that may harbour FMDV2. Exclusion of participants from countries where FMDV2 is endemic. Short period between repeat PET scans. Collection of serum samples for measurement of antibodies to [^{18}F]-FBA-A20FMDV2. PET scans performed in an imaging unit with immediate access to emergency measures. Refer to Appendix 9 for more detail on the immunogenicity risk assessment and mitigation.
Potential bystander exposure to GSK3008348	Unintended inhalation of GSK3008348 (irritant potential). Since clear NOAELs were established in the nonclinical toxicity studies (with adequate safety margins) and the concentration in the room will be significantly less than direct exposure to GSK3008348, the risk for irritancy for bystanders is considered to be low. No events in bystanders were reported in the study in healthy volunteers following single doses up to 3,000 µg.	Appropriate precautions will be taken to minimise bystander exposure in the study. Nebulised drug should not be administered in a confined and/or unventilated space.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Ensuring sufficient medical oversight for safety monitoring and transport between sites	In dosing period 2 of Cohort 1, the doses will be administered to participants in the imaging unit, so that the PET can be carried out at approximately 30 minutes post-dose. However, in Cohort 2, there is the option to administer those doses in the hospital clinical unit, if required for logistical or safety reasons. In that case, participants would be transported after dosing to the imaging site for the PET scans.	In both Cohorts 1 and 2, the first dosing period will be conducted in a hospital-based clinical unit, under the supervision of a chest physician, with immediate access to facilities for the treatment of medical emergencies, facilities for stabilizing individuals in an acute emergency and ready availability of Intensive Care Unit facilities. Following Principal Investigator (PI) and GSK medical monitor review of the individual safety and tolerability data from the completed first dosing period, the patient will continue to the baseline PET visit and second dosing period. In the second dosing period, the same dose will be administered by clinical staff in the imaging unit, alongside an appropriately trained research nurse. If in Cohort 2 doses are to be administered in the clinical unit before transporting participants to the imaging unit in dosing period 2, patients will be observed for at least 4 hours post-dose before being transported to the imaging unit.

3.3.2. Benefit Assessment

Participants will receive single doses of GSK3008348, which is being developed as a treatment for IPF. It is not anticipated that this single dose study will provide any clinical benefit to participants. The results will inform the evaluation of GSK3008348 as a treatment for IPF, so participants may contribute to the process of developing new therapies for IPF and related conditions. Participants will be monitored throughout the study for any worsening of IPF symptoms or decline in general health.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with single doses of GSK3008348 and with study procedures are justified by the anticipated benefits from active treatment that may be afforded to patients in the future, in developing GSK3008348 as a new therapy for IPF.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate target engagement in the lung after single nebulised doses of GSK3008348 in IPF patients	• Changes in the uptake of [^{18}F]-FBA-A20FMDV2 in the whole lung (assessed as the volume of distribution [V_T], not corrected for air volume) at approximately 30 min post-dose compared to pre-dose, as measured by PET
• To evaluate the safety and tolerability of single nebulised doses of GSK3008348 in IPF patients	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and pulmonary function tests
Secondary	
• To evaluate the pharmacokinetic profile of single nebulised doses of GSK3008348 in IPF patients	• Derived pharmacokinetic parameters for GSK3008348 including, but not limited to, area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), and terminal half-life ($T_{1/2}$) following single nebulised doses, where data allow

Objectives	Endpoints
• To evaluate duration of target engagement after single nebulised doses of GSK3008348 in IPF patients	• Changes in the uptake of [^{18}F]-FBA-A20FMDV2 in the lung (assessed as the V_T) up to 28 h post-dose compared to pre-dose, as measured by PET
Exploratory • To explore the pharmacodynamic effects of single nebulised doses of GSK3008348 in IPF patients using additional PET analyses techniques	• Changes in the uptake of [^{18}F]-FBA-A20FMDV2 in the whole lung (assessed using standardised uptake values [SUV] and V_T, with and without correction for air and/or blood volume) at various time points post-dose compared to pre-dose, as measured by PET
• To explore the spatial distribution of the effects of single nebulised doses of GSK3008348 in IPF patients and to compare it to the spatial distribution of disease	• Qualitative assessment of the distribution of the uptake of [^{18}F]-FBA-A20FMDV2 in the lungs post-dose compared to pre-dose, as measured by PET and compared to the spatial distribution of disease as indicated by HRCT
• To explore pharmacodynamic effects of GSK3008348 in blood	• Exploratory pharmacodynamic biomarkers of the αvβ6/TGFβ mechanism which may include but are not limited to: mRNA, microRNA and proteins in blood
• To explore potential biomarkers of IPF disease and/or treatment response	• Exploratory biomarkers in blood

5. STUDY DESIGN

5.1. Overall Design

This is a multi-centre, 2-cohort, study of single doses to investigate the safety, tolerability, PK and target engagement of nebulised GSK3008348, in patients with IPF. Hospital-based clinical units will recruit and enrol participants; the PET imaging will be done at a specialist imaging unit.

Participants will be screened up to 30 days before their first dose, and will have a follow-up visit at 7–14 days post-last dose.

Refer to Figure 1 for a schematic illustrating the study design.

5.1.1. Cohort 1

Cohort 1 will be a randomised, double-blind (sponsor unblind), placebo-controlled group of 7 participants, randomised 5:2 to receive 1,000 µg GSK3008348 or placebo. All participants will have 2 planned dosing periods, and receive the same dose in each period.

Dosing period 1 aims to assess safety and tolerability, and dosing period 2 aims to assess target engagement using PET imaging.

In dosing period 1, participants will be admitted to the clinical unit on the morning of Day 1 for pre-dose health assessments and a pharmacogenetic sample; these assessments may also take place on Day –1. On Day 1, they will remain in the clinical unit overnight, to enable safety assessments to be carried out for at least 24 h after receiving their nebulised dose. PK and exploratory biomarker samples will also be taken. Participants will then be discharged from the clinical unit.

There will be a washout of between 7 and 28 days between doses in periods 1 and 2. Participants will attend the imaging unit for a baseline PET scan and a high resolution computerised tomography (HRCT) scan, at least 7 days after their first dose, and a maximum of 14 days before their first post-dose PET scan in dosing period 2.

In dosing period 2, participants will first attend the clinical unit for pre-dose health assessments, on Day 1 or Day −1. If they pass the health assessments, participants will attend the imaging unit for dosing and a PET scan starting approximately 30 min post-dose (i.e., post the start of nebulisation). Participants will remain in the imaging unit for safety observation for at least 4 h post-dose on Day 1, and then return on Day 2 for a PET scan at approximately 24 h post-dose (post the start of nebulisation). Safety assessments and PK sampling will be done throughout those visits.

Cohort 1 will be considered complete when PET data at 30 min post-dose has been collected from 7 participants. After completion of Cohort 1, blinded safety and PK data will be reviewed by a data review team, consisting of the investigators, medical monitor, statistician, clinical pharmacokineticist, pharmacovigilance representative, and clinical study team members, as appropriate. The statistician will also perform an unblinded review of the PET data.

5.1.2. Cohort 2

Cohort 2 is optional, and will proceed only if there is evidence of target engagement at 30 min post-dose in Cohort 1. It will be designed to further explore the safety and to provide additional information on the target engagement profile of GSK3008348. Decisions on whether to proceed with Cohort 2, and on the most informative design for Cohort 2, will be based on Cohort 1 data. Cohort 2 data may be reviewed in-stream and the design of Cohort 2 adjusted to maximise the value of the data obtained. Cohort 2 will be designed such that each participant will have up to 3 PET scans and 2 planned doses of GSK3008348, and within the logistical limitations of dosing, safety monitoring, PET ligand radiochemistry and PET scanning. For example:

- If there is no evidence of target engagement at 30 min post-dose in Cohort 1, then Cohort 2 will not go ahead.
- If the variability in PET measurements is higher than anticipated, participants in Cohort 2 may follow the same dosing and scanning regime as in Cohort 1, to increase the sample size.

- If significant target engagement is observed at 30 min in Cohort 1, but there is no evidence of target engagement at 14−28 h, then Cohort 2 may explore time points between 30 min and 28 h after a 1,000 µg dose.
- If significant target engagement is observed at 30 min and at 14−28 h, then Cohort 2 may explore target engagement at time points between 30 min and 28 h after a dose lower than 1,000 µg.

A decision-making flowchart is shown in Appendix 10.

Cohort 2 may be open-label, in which case up to 10 participants may receive single doses of GSK3008348 in an open-label manner. If Cohort 1 data suggests that including a placebo control would be beneficial, for example for safety reasons, Cohort 2 will be carried out in a double-blind (sponsor unblind) fashion, with up to 14 participants randomised 5:2 to receive GSK3008348 or placebo.

The dose level will be 1,000 µg or lower, and may be changed at any time depending on previous or emerging data. Participants may receive a lower dose in dosing period 2 compared to dosing period 1. The length of post-dose safety monitoring in the clinic will be decided based on previous or emerging data, but participants will be monitored for at least 8 h post-first dose.

Participants will have 2 planned dosing periods, both on an outpatient basis, with an additional visit for baseline imaging, as follows.

- Dosing period 1: participants will have pre-dose health assessments and a pharmacogenetics sample at the clinical unit on the morning of Day 1. They will remain in the clinical unit for at least 8 h after receiving their nebulised dose for safety observations, and then return to the clinical unit on Day 2. Safety assessments will be done, and PK and exploratory biomarker samples taken.

- Baseline PET scan and HRCT scan at least 7 days after the first dose, and a maximum of 14 days before the first post-dose PET scan.

- Dosing period 2: participants will attend the clinical unit for health assessments before dosing, on Day 1 or Day −1. If participants pass the health assessments, they will attend the imaging unit, have their dose administered, and have up to 2 post-dose PET scans. Alternatively, dosing may take place at the clinical unit before the patient is transferred to the imaging unit for their PET scan, depending on the PET scan timing; however, the participant must be observed for at least 4 h post-dose without changing location. The timing of the post-dose PET scans will be determined based on emerging study data. Doses will be separated by a washout of between 7 and 28 days.

5.1.3. Changes to Cohorts 1 or 2

Participants in Cohorts 1 and 2 will have 2 planned dosing periods. However, if a PET scan cannot be performed (e.g. because of technical issues, PET ligand synthesis radiochemistry failure, or because the participant cannot be scanned for safety reasons), participants may repeat the visit or dosing period, and repeat procedures in order to

obtain a full dataset for each endpoint. Participants may be administered an additional dose of GSK3008348 after a 7-day washout, such that they receive a maximum of 3 single doses in total during the study. Participants will not, however, be administered an additional dose of [^{18}F]-FBA-A20FMDV2; they will receive a maximum of 3 doses of the radiotracer during the study.

If a participant experiences unexpected and/or potentially serious side effects after their first or second dose, they will be referred to the clinical site investigator for assessment and ongoing care. That may include admission to a clinical bed, if deemed appropriate by the investigator, as per routine clinical practice.

5.2. Number of Participants

It is anticipated that up to 21 participants will be randomised, as follows.

- Cohort 1 – 7 participants will be randomised. (7 participants will be randomised, dosed and considered complete when PET data at 30 min post-dose has been collected)

- Cohort 2 – up to 10 participants may be randomised if an open-label design is chosen; or up to 14 participants may be randomised if a double-blind design is chosen.

Refer to Section 10.2 for definitions of participants who will be considered evaluable and therefore included in the analyses.

If participants prematurely discontinue the study, additional replacement participants may be recruited and randomised to the same treatment at the discretion of the Sponsor in consultation with the investigator. Replacement participants will start the study at dosing period 1, in order to establish tolerability of the study medication before entering the PET scanning dosing period.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study, including the baseline PET scan, at least 1 post-dose PET scan, and the last follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

- Cohort 1 includes a placebo control to allow assessment of safety and tolerability, as reporting of adverse events in patients receiving placebo will facilitate the differentiation between ‘disease’ and ‘intervention’ adverse events.
- Cohort 1 will be conducted in a double-blind (sponsor unblind) fashion. Safety and PK data reviews will be conducted without treatment group assignment or subject numbers, so that the investigators and data review team remain blinded. The

statistician will perform an unblinded review of PET data as part of the pre-planned interim analysis, to allow appropriate decision-making. The sponsor (including the medical monitor) may also undertake separate in-stream review of unblinded data to help determine the most appropriate response to emerging data.

- The number of patients to be enrolled in Cohort 1 (7 participants) is based on the probability of detecting a change in αvβ6 internalisation at approximately 30 min post-dose compared to pre-dose of 6% or greater, as measured by the uptake of [^{18}F]-FBA-A20FMDV2 in the lungs reported as the volume of distribution [V_T]. This predetermined change is equivalent to approximately half the difference in [^{18}F]-FBA-A20FMDV2 PET signal observed between healthy volunteers and IPF patients in a previous study RES116235. If GSK3008348 cannot achieve that reduction in αvβ6-associated PET signal and the endpoint variability is as expected, then the study will end.
- The design for Cohort 2 will be defined following completion of Cohort 1, to ensure the most informative doses of GSK3008348 are selected and the PET scans are timed appropriately. Cohort 2 data may be reviewed in-stream and the design of Cohort 2 adjusted to maximise the value of the data obtained. The aim is to assess target engagement while exposing the smallest possible number of patients to ionising radiation from the PET procedure.

5.5. Dose Justification

The first-time-in-human study 200262 showed that single nebulised doses of 1–3,000 µg GSK3008348 were well tolerated in healthy participants, with PK exposures within the defined limits set by the protocol.

The 1,000 µg dose was selected for this study as the preliminary geometric mean C_{max} and $AUC_{(inf)}$ observed in healthy volunteers in study 200262 provided 22- and 11-fold margins, respectively, over the systemic exposures observed in the most sensitive preclinical species (Day 1 exposures from the Rat 1 month good laboratory practice [GLP] study at the 12000 µg/kg/day dose level; the no effect level for systemic toxicity).

Additionally, the 1,000 µg dose maintains adequate safety coverage over the NOAEL based on the deposited lung dose (36-fold over the rat and 26-fold over the dog, 1 month GLP toxicity studies). The proposed dose therefore allows significant safety margins in the event that systemic exposure is greater in IPF patients than in healthy volunteers.

In addition, the observed PK in study 200262 demonstrated peak systemic unbound concentrations significantly in excess of the *in vitro* Kd for GSK3008348. Given that GSK3008348 is inhaled, it is reasonable to assume that lung tissue exposures were at least as high as those observed in plasma and so are expected to engage with αvβ6 to a significant extent.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Male participants aged ≥ 50 years, and female participants aged ≥ 55 years, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosis of definite or probable IPF as determined by a responsible and experienced chest physician and based on established criteria defined by the American Thoracic Society/European Respiratory Society Internationale Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias [Raghu, 2011].
3. Ambulant and capable of attending outpatient visits.
4. FVC > 50 % predicted and DLCO > 40 % predicted.

Weight

5. Body weight ≥ 45 kg and body mass index (BMI) within the range 18.0–35.0 kg/m^2 (inclusive).

Sex

6. Male and female

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the study and for at least 90 days after the follow-up visit, and refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is not pregnant, not breastfeeding, and not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. ALT and bilirubin > 1.5x upper limit of normal (ULN; isolated bilirubin > 1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
3. QTc > 450 msec, or QTc > 480 msec in participants with Bundle Branch Block.
4. Current IPF exacerbation, or upper or lower respiratory tract infection on admission to the clinical unit.
5. History of or suffers from claustrophobia, or unable to lie flat and still on their back for up to 2 h in the PET scanner.
6. Extent of emphysema greater than the extent of fibrotic change on HRCT scan, based on investigator judgement.
7. Forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio < 0.70 at screening (post-bronchodilator).
8. History of sensitivity to the study treatment, or components thereof, or a history of drug or other allergy that, in the opinion of the investigators or Medical Monitor, contraindicates their participation.
9. Any current oro-pharygneal disease or disorders as judged by the investigator.

Prior/Concomitant Therapy

10. Currently taking pirfenidone or nintedanib, or received pirfenidone or nintedanib within 30 days of the first dose of study treatment.
11. Taken, within 7 days or 5 half-lives (whichever is longer) before the first dose of study treatment, organic anion transporter (OAT) substrates with a narrow therapeutic index (eg methotrexate and tenofovir), vitamins, or dietary or herbal supplements, unless in the opinion of the investigator and sponsor the supplement will not interfere with the study medication.
12. Long-term continuous home oxygen therapy (use of oxygen that is only intermittent and for symptom relief is acceptable).

Prior/Concurrent Clinical Study Experience

13. Participation in a clinical trial and receipt of an investigational medicinal product within the following time period before the first dose in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
14. Exposure to more than 4 new investigational medicinal products within 12 months before the first dose.

Diagnostic assessments

15. Presence of Hepatitis B surface antigen (HBsAg) at screening, or positive Hepatitis C antibody test result at screening or within 3 months before the first dose of study treatment (Note: participants with a positive Hepatitis C antibody test because of previous, resolved disease can be enrolled if a confirmatory negative Hepatitis C RNA test is obtained).
16. Previous or current exposure to animals that may harbour FMDV2.
17. Previous long term (≥ 3 months) residence in a country where FMDV2 is endemic (such as certain areas of Africa, Asia and South America, see Appendix 11).
18. Where participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days
19. History of drug or alcohol abuse that in the opinion of the investigator affects their participation in the study

Other Exclusions

20. Exposure to ionising radiation in excess of 10 mSv above background over the previous 3 year period as a result of occupational exposure or previous participation in research studies. Clinically justified (therapeutic or diagnostic) exposures are not included in the exposure calculation.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- During each dosing session, participants will be fasted for 4 hours before dosing. Water will be allowed. The time of the first meal after dosing will be recorded.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 12 hours before the start of dosing until after collection of the final PK sample in that period.
- During each dosing period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample in that period.
- Participants who use tobacco products will be instructed that use of nicotine-containing products will not be permitted while they are in the clinical or imaging units. Nicotine patches are allowed.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized due to failure to meet inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	**GSK3008348**	**Placebo**	**[^{18}F]-FBA-A20FMDV2**
Dosage formulation:	Solution for nebulisation	Solution for nebulisation	Intravenous (IV)
Formulation description:	Formulated at 250 µg/ml with 5% mannitol, citric acid, sodium citrate and water for injection	5% mannitol, citric acid, sodium citrate and water for injection	Formulated in 0.9% saline
Unit dose strength(s)/Dosage level(s):	1,000 µg	N/A	Up to 150 MBq of [^{18}F]-FBA-A20FMDV2 per administration; ≤ 100 µg total of [^{18}F]-FBA-A20FMDV2 per participant
Route of Administration	Inhaled via nebulisation	Inhaled via nebulisation	IV
Dosing instructions:	4mL administered by nebulisation	4mL administered by nebulisation	Intravenous bolus over about 30 seconds

Study Treatment Name:	**GSK3008348**	**Placebo**	**[^{18}F]-FBA-A20FMDV2**
Physical description:	Clear colourless to pale yellow coloured solution in a 5mL vial with 20mm stopper and aluminium seal	Clear colourless to pale yellow coloured solution in a 5mL vial with 20mm stopper and aluminium seal	IV infusion, 20 mL
Storage conditions:	Refer to SRM	Refer to SRM	N/A
Device:	European Conformity mark (CE) marked nebuliser	CE marked nebuliser	N/A

7.2. Dose Modification

The proposed dose for Cohorts 1 and 2 is 1,000 µg GSK3008348. The dose may be decreased in Cohort 2 at any time, depending on previous or emerging data. The decision will be made by the data review team based on available preliminary safety, tolerability, PK and PET data obtained from preceding participants. The dose will not be increased above 1,000 µg.

7.3. Method of Treatment Assignment

Participants will be randomised to a subject number in accordance with the randomisation schedule generated by GSK Clinical Statistics before the study start, using validated internal software (RANDALL NG). Each participant in Cohort 1 will be randomised 5:2 to receive either GSK3008348 or placebo. Participants in Cohort 2 will receive GSK3008348 in an open-label manner, unless it is decided that a placebo control would be beneficial, in which case participants will be randomised 5:2 to receive either GSK3008348 or placebo.

All participants will be centrally randomised using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number or log in information and directions will be provided to each site.

Study treatment for both dosing periods will be dispensed by appropriately trained pharmacy staff.

Returned study treatment should not be re-dispensed to the participants.

7.4. Blinding

Cohort 1 will be double-blind (sponsor unblind). Cohort 2 may be open-label, or may be double-blind (sponsor unblind) if required. For double-blind cohorts, the following will apply.

An unblinded monitor, if required, and in the event of a Quality Assurance audit, the auditors, will be allowed access to unblinded study treatment records at the sites to verify that randomisation and dispensing has been done accurately.

The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken by the investigator or treating physician in the case of an emergency, or if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The investigator is encouraged to discuss with the GSK Medical Monitor or appropriate GSK study personnel before the blind is broken. If GSK is not notified before the blind is broken, they must be notified as soon as possible after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

A participant may continue in the study if their treatment assignment is unblinded, at the discretion of the Medical Monitor. If a participant is withdrawn after their treatment code is unblinded by the investigator or treating physician, the primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

For an open-label cohort, all participants will be randomised to active study treatment.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorised 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 authorised site staff.
- The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (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.

7.6. Treatment Compliance

Participants will be dosed at the sites, and 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 participant 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.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

Participants must not be taking pirfenidone or nintedanib, or must abstain from taking pirfenidone or nintedanib within 30 days before their first dose of study treatment until completion of the follow-up visit.

There is an unknown risk of interaction with OAT substrates with a narrow therapeutic index (eg methotrexate and tenofovir). Therefore, participants must abstain from taking these agents within 7 days or 5 half-lives (whichever is longer) before their first dose of study treatment until completion of the follow-up visit. Participants must also abstain from taking vitamins and dietary or herbal supplements for the same period, unless, in the opinion of the investigator and sponsor, the supplement will not interfere with the study medication.

Other concomitant medication, including paracetamol at doses of ≤ 4 grams/day, is permitted for use any time during the study. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study. The investigators are responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

8. DISCONTINUATION CRITERIA

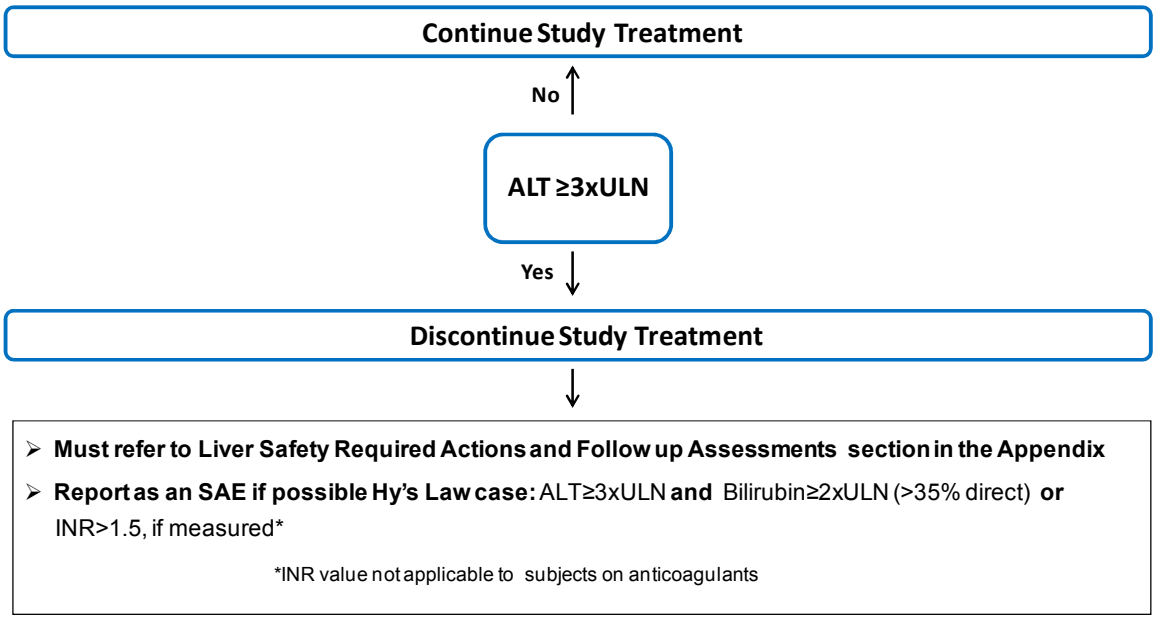
8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7.

8.1.2. QTc Stopping Criteria

A participant who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc > 500 msec **OR** Uncorrected QT > 600 msec
- Change from baseline of QTc > 60 msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

8.1.3. Individual Adverse Event Stopping Criteria

A participant will be withdrawn from the study if they experience:

1. An SAE that is at least possibly related to the study treatment
2. An IPF exacerbation, upper or lower respiratory tract infection or other systemic infection
3. A clinically significant change in a laboratory value or vital sign
4. Failure to recover from an adverse event

A participant can be discontinued from therapy if the investigator decides that the patient should be withdrawn.

Participants who are withdrawn will complete the follow-up visit, as described in the SoA.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at follow-up for evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. All post-dose time points are relevant to the start of nebulisation.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the first dose of study treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the first dose of study treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the first dose of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

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

The CV eCRFs are presented as queries in response to reporting of certain CV Medical dictionary for regulatory activities (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 eCRF 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.

9.2.6. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until the follow-up visit.

- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

For this study, any dose of GSK3008348 greater than 1,000 µg within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

21. Contact the Medical Monitor immediately.
22. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3008348 can no longer be detected systemically (at least 2 days).
23. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
24. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems, and the oropharynx. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, oropharynx, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Single readings of temperature, heart rate, respiratory rate, and blood pressure will be assessed.

- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured in a semi-supine position after 5 minutes rest.

9.4.3. Peripheral capillary oxygen saturation

- Peripheral capillary oxygen saturation (SpO2) levels will be continuously monitored with a completely automated device.

9.4.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained and recorded in the eCRF as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

9.4.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SRM and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

9.4.6 Lung Function Tests

- Spirometry measurements will be obtained using standard spirometry equipment available at sites, to include FEV_1 and FVC.
- DLCO will be measured according to local procedures.

- For calculating % predicted FEV_1, FVC and DLCO, the Quanjer 2012 calculation is to be used.
- All subjects will have spirometry and DLCO performed at Screening to assess eligibility and at time points as described in the time and events table.
- Participants must perform 3 acceptable blows, all within 5% of each other. The difference between the highest FEV_1 and the second highest should be within 150 mL. A maximum of 8 attempts can be made for each time point.
- Only the highest FEV_1 and FVC measurements should be recorded.
- At each time point, measurements of FEV1 and FVC should be compared to baseline. Any clinically significant decreases in either measurements compared to baseline, as judged by the investigator, will be recorded as an AE.

9.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3008348 as specified in the SoA. A maximum of 5 additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided in the SRM. The actual date and time (24 hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK3008348. Samples collected for analyses of GSK3008348 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.
- Once the plasma has been analyzed for GSK3008348, any remaining plasma may be analysed for other compound-related metabolites and the results reported under a separate protocol.
- Urine samples will be analysed qualitatively for drug-related components and the results reported under a separate Platform Technology and Science-Product Development and Supply, GlaxoSmithKline study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.6. Positron Emission Tomography (PET)

Before each PET scan, participants will have a low dose CT scan to provide data to enable correction of the PET data for tissue attenuation. [^{18}F]-FBA-A20FMVD2 will then be injected into a cubital or forearm vein through an intravenous cannula, and emission data acquired for up to 90 minutes. One rest period will be permitted during the scan, if required.

An additional venous cannula in a cubital or forearm vein will be used to collect blood samples throughout the PET scan for quantification of the total and unmetabolised [^{18}F]-FBA-A20FMDV2-related radioactivity in whole blood and plasma. The data will be used to derive an input function for the analysis of emission PET data. The cannula may be flushed with saline to keep it patent, if required; HepSal will not be used. At the end of the scanning day, the cannula will be removed.

At the baseline visit only, an HRCT scan will also be performed for anatomical localisation.

In the event of a problem that prevents the PET scan going ahead after the study treatment has been administered, such as a quality control failure of the synthesised tracer, the scan may be rescheduled. An additional dose of study treatment may be administered to the participant if required, at the discretion of the investigator and GSK Medical Monitor, as described in Section 5.1.3.

9.7. Genetics

A 6 mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

Blood samples will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence IPF, and/or medically related conditions, as well as the biological and clinical responses to GSK3008348. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events. These analyses are exploratory in nature, and will be reported separately from the results of the clinical trial.

Samples will be collected at the timepoints indicated in the SoA. The actual date and time of each blood sample collection will be recorded. The timing of the collections may be adjusted on the basis of emerging PK or pharmacodynamic (PD) data from this study or other new information in order to ensure optimal evaluation of the endpoints.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with IPF or medically related conditions and/or the action of study treatment may be identified by the potential application of:

- Ribonucleic acid (RNA) transcriptome analysis of blood samples.

- Measurement of the levels of a subset of RNA species in blood.
- Proteome analysis in plasma and blood samples.
- Measurement of the levels of a subset of proteins in plasma and blood samples which may include but are not limited to chemokine (C-C motif) ligand 18 (CCL18) [Prasse, 2009] and collagen degradation biomarkers [Jenkins, 2015].

Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to αvβ6, IPF disease processes, pathways associated with IPF and/or mechanism of action of GSK3008348.

All samples will be retained for a maximum of 15 years after the last participant completes the trial.

9.9. Immunogenicity Assessments

Serum samples will be analysed for the presence of anti-[^{18}F]-FBA-A20FMDV2 antibodies. Approximately 7 mL of blood will be collected into serum separator (SST) tubes (no anti-coagulant) at the timepoints indicated SoA.

9.10. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

This study is designed to assess the level of receptor engagement as measured by the effect of nebulised GSK3008348 on the αvβ6-associated PET signal (V_T). The PET data from the 5 participants in Cohort 1 receiving GSK3008348 will be used. This sample size has been chosen based on considerations given to: a) the probability of declaring a successful study for reductions in αvβ6-associated PET signal deemed to be representative of the expected receptor engagement activity, and b) the within-subject variability of the PET signal.

The chosen study success criteria is defined as Prob ($\theta < 0$ | Study Data, Prior (θ)) ≥80%, where θ is the unknown true logarithm of the ratio of αvβ6-associated PET signal post-dose / pre-dose in patients receiving GSK3008348, and the prior distribution for θ is non-informative. Assuming the within-subject standard deviation is as previously observed in study RES116235 (within-subject standard deviation following two PET scans was estimated to be 0.15, 95% CI [0.099, 0.34]), consideration was given to the probability of achieving the study success criteria for a range of true reductions in αvβ6-associated PET signal with GSK3008348. In addition, the minimum detectable effect (MDE), i.e., the minimum observed reduction in αvβ6-associated PET signal leading to the success

criteria being achieved, was also derived. In particular, if the true reduction in αvβ6-associated PET signal is 14% then there is 86% probability of achieving the above success criteria, and the MDE is a 6.2% reduction in αvβ6-associated PET signal.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All participants	All participants who are screened and for whom a record exists on the study database.
Enrolled	All participants who are screened and enrolled into the study.
Intent-To-Treat (ITT)	All randomised participants who receive at least one dose of study treatment. This population will be based on the treatment they actually received.
Per-Protocol	All participants in the ITT population who comply with the protocol and that have at least one evaluable PET measurement post baseline.
Pharmacokinetic	All participants in the ITT population receiving active dose for whom a pharmacokinetic sample was obtained and analysed.

10.3. Statistical Analyses

10.3.1. Pharmacodynamic Analyses

Endpoint	Statistical Analysis Methods
Volume of distribution [V_T] in whole lung, not corrected for air volume	The logarithm of the αvβ6-associated PET signal as measured by V_T will be analysed assuming that it follows a normal distribution. The mean or median signal level pre- and post-dose, as appropriate depending on the posterior distribution, along with the median difference post-dose – pre-dose, will be estimated and the corresponding 95% credible intervals will be produced. The posterior probability that the true difference in the logarithm of αvβ6-associated PET signal post-dose vs pre-dose is less than 0 will be calculated. Non-informative priors will be used for all the parameters in the statistical model.
Secondary	Will be described in the reporting and analysis plan (RAP)
Exploratory	Will be described in the RAP

10.3.2. Safety Analyses

All safety analyses will be performed on the ITT Population. Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

10.3.3. Pharmacokinetic analyses

Plasma concentration-time data of GSK3008348 will be displayed in listings, summary tables and/or graphically. Summary data will use nominal/planned sample times, listings will display planned and actual times. Plasma concentration-time data may be used to derive PK parameters (such as AUC and C_{max}) using standard non-compartmental analysis according to current working practices and using Phoenix WNL, or other currently validated software. All calculations of non-compartmental parameters will be based on actual sampling times.

Additionally, plasma concentration-time data may be used to derive population PK parameters/models using NONMEM or other currently validated software. Any population PK analysis will be presented separately from the main clinical study report (CSR).

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline.

10.3.4. Other Analyses

Exploratory PD and biomarker analyses will be described in the RAP, and will be presented separately from the main CSR.

10.3.5. Interim Analyses

An interim analysis will be performed for futility or sample size re-estimation based on the variability of the PET signal (V_T) and the level of receptor engagement at the end of Cohort 1 and prior to the start of Cohort 2. The PET data from the 5 participants in Cohort 1 receiving GSK3008348 will be used. The logarithm of the αvβ6-associated PET signal as measured by V_T will be analysed assuming that it follows a normal distribution.

10.3.5.1. Interim Analysis for Futility

Assuming that the variability is as anticipated, if the posterior probability Prob ($\theta < 0$ | Study Data, Prior (θ)) < 80%, where θ is the unknown true logarithm of the ratio of αvβ6-associated PET signal post-dose / pre-dose in patients receiving 1,000 µg GSK3008348 in Cohort 1, and the prior distribution for θ is non-informative, then the study will stop for futility. If the study is stopped at the end of Cohort 1, then Cohort 2 will not proceed.

10.3.5.2. Interim Analysis for Sample Size Re-estimation

If the variability in V_T is higher than expected, then sample size re-estimation will be performed and additional participants receiving 1,000 µg GSK3008348 will be recruited into Cohort 2. Sample size re-estimation will be primarily based on the posterior predictive distribution of the data given the information collected at the interim, and the predictive probability of end-of-study success. This probability will be calculated for a range of sample sizes up to a maximum of 10 additional participants receiving 1,000 µg GSK3008348 in Cohort 2.

Further details of the interim analysis will be provided in the RAP.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area under the plasma drug concentration versus time curve
AUC(0-t)	Area under the plasma concentration-time curve from zero (0) hours to time (t)
AUC(0-∞)	Area under the plasma concentration-time curve from zero (0) hours to infinity (∞)
BMI	Body Mass Index
CCL18	Chemokine (C-C motif) ligand 18
CE	European Conformity mark
C_{max}	Maximum observed plasma drug concentration
CL	Clearance
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatinine Phosphokinase
CSR	Clinical Study Report
CT	Computed Tomography
CV	Cardiovascular
DLCO	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENT	Ear, Nose and Throat
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume
FMDV2	Food and Mouth Disease Virus
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety & Pharmacovigilance
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HRCT	High-Resolution Computed Tomography
IB	Investigator Brochure
ICF	Information and consent form
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiological Protection
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board

ITT	Intent-To-Treat
IVRS/IWRS	Interactive Voice/Web Response System
MCH	Mean Cell Haemoglobin
MCV	Mean Cell Volume
MDE	Minimum detectable effect
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mm	Millimeter
MM	Medical Monitor
MSDS	Material Safety Data Sheet
mSV	Millisievert
NOAEL	No Observed Adverse Effect Level
OAT	Organic anion transporter
PD	Pharmacodynamic
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetics
QTc	Corrected QT Interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SoA	Schedule of Assessments
SPECT	Single Photon Emission Computed Tomography
SpO2	Peripheral Capillary Oxygen Saturation
SRM	Study Reference Manual
SST	Serum-separator Tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised Uptake Volume
$T_{1/2}$	Terminal half-life
TGFβ	Transforming Growth Factor Beta
T_{max}	Time to maximum concentration
UIP	Usual Interstitial Pneumonia
ULN	Upper Limit of Normal
V	Volume of Distribution (of GSK3008348)
V_T	Volume of Distribution (of PET radioligand)
WBC	White Blood Cells
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
HepSal
MedDRA
NONMEM
Phoenix WNL
RANDALL NG

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Total and direct bilirubin	Total Protein
	Creatinine	Sodium	CPK	Albumin
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	Gamma glutamyl transferase (gamma GT)
	Aspartate aminotransferase (AST)		Alanine aminotransferase (ALT)	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • If blood or protein is abnormal, a mid-stream urine sample will be collected for further urinalysis, to include microscopy, culture and sensitivities			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed)[2] • Serology (hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody; hepatitis C RNA test, if required after a positive antibody test)			

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 7. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- 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 participants, as appropriate.
- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• 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 participant'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 participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that

leads to the procedure is the AE.

- Situations in which 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

- 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 (eg, sprained ankle) which may interfere with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include 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.

Recording AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant 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 eCRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study treatment (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

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 or courier service. • Initial notification via 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 reporting can be found in the SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

25. Premenarchal

26. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

27. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 2 when having penile-vaginal intercourse with a woman of childbearing potential

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Men must refrain from donating sperm for duration of study and for 90 days after study completion.

Female participants

Female participants of childbearing potential are not eligible to participate.

Table 2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- Women should only be included after a negative highly sensitive urine or serum pregnancy test
- Additional pregnancy testing will be performed before each PET scan, as required locally

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours 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.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek

this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3008348 or IPF and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3008348 (or study treatments of this drug class), and IPF. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3008348 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3008348 (or study treatments of this class) or IPF continues but no longer than 15 years after the last visit of the last subject, or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 3xULN
If ALT ≥ 3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Report the event to GSK within 24 hours
• Complete the liver event eCRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
<u>If</u> ALT ≥ 3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> > 1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td colspan="2">• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained as soon as possible after the event, and within 36 h of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event</td></tr>
</table>

If ALT ≥ 3xULN AND bilirubin < 2xULN and INR ≤ 1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	alcohol intake case report form **If ALT ≥ 3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally,if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**,indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excludingstudies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.8. Appendix 8: Radiation Dose Risk Assessment

Participants will be exposed to an additional dose of ionising radiation as a consequence of their participation in this study. The ionising radiation exposure from PET and CT scanning comes from three sources. A proportion of the radiation exposure comes from the administered radioligand ([^{18}F]-FBA-A20FMDV2). The remaining radiation dose comes from an HRCT for anatomical localisation (performed once only during the study) and low dose CT scans performed in order to correct the PET data for tissue attenuation. If the participant needs to be removed from the scanner and repositioned during the PET 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 participant will have up to three PET-CT scans. The effective dose for each radioligand administration will be 3.3 mSv based on a conversion factor of 21.7 μSv/MBq determined from study RES116235 and a maximum administered activity of 150 MBq. A low-dose attenuation CT scan of the lung results in an effective dose of 1.2 mSv. If the participant 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. In addition, each participant will have one HRCT scan, resulting in an effective dose of 3.8 mSv. The total effective dose to each participant will therefore be up to 3 x (3.3 + 2.4) + 3.8 = 20.9 mSv. All of this exposure is over and above standard practice.

The total maximum effective dose of 20.9 mSv in this study is equivalent to approximately 9 times the average yearly exposure (2.3 mSv) from natural background radiation in the United Kingdom. The additional risk of developing a fatal malignancy as a result of these exposures has been estimated as approximately 1 in 1,000 for an adult in normal health. The reduced life expectancy of IPF patients will result in a lower risk for these individuals.

Within the UK the guidance set out by ICRP 62 is generally followed in setting research study dose constraints. The level of risk may therefore be assumed to broadly fall within the ICRP 62 intermediate Category IIb, where the benefit should be more directly aimed at the cure or prevention of disease.

12.9. Appendix 9: Assessment of the Potential Immunogenicity Risk for [^{18}F]-FBA-A20FMDV2

Immunogenicity is a potential risk for exogenous peptides. However, we consider the risk to be low under the current circumstances where the peptide is synthetic and is not administered repeatedly for clinical benefit, but is used as an imaging tracer.

This potential risk may come from two sources:

g. pre-existing antibodies that may arise from prior exposure to the intact virus

h. induction of a *de novo* immune response by exposure to the peptide

The risk assessment and management strategy is summarised in Table 3.

Table 3 Summary of the assessment of the immunogenicity risk for [^{18}F]-FBA-A20FMDV2 in the PETAL Study

Potential risk	Relevant factors and comments	Assessment of risk	Risk mitigation /management	Risk level
Potential risk for pre-existing antibodies	Previous exposure to FMDV may have elicited an immune response in certain individuals that may recognise the peptide	FMD is notifiable in the UK and the last outbreak was in 2007 FMD is endemic in certain areas of Africa, Asia and South America	Participants with prior exposure to farm animals are excluded from the study. Participants resident in endemic countries are excluded from the study.	Low
Potential risk for induction of a *de novo* immune response	Route of administration	[^{18}F]-FBA-A20FMDV2 will be administered intravenously.	This route is less immunogenic than the subcutaneous route. Two participants in a previous study developed anti-peptide antibodies to this tracer but neither experienced any clinical event.	Low
	Number and frequency of dosing	[^{18}F]-FBA-A20FMDV2 will be administered 2 or 3 times to patients with IPF	The 3 doses will be administered a maximum of 4 weeks apart, reducing the potential for immune response maturation	Low
	Cross-reacting antibodies to [^{18}F]-FBA-A20FMDV2	Anti-[^{18}F]-FBA-A20FMDV2 antibodies may cross-react with non-redundant endogenous proteins and give rise to adverse events	Humans are likely to be tolerant to sequences containing RGD Development of anti- [^{18}F]-FBA-A20FMDV2 antibodies would require breaking tolerance	Low
	Physico-chemical properties of [^{18}F]-FBA-A20FMDV2	An effective immunogen must contain T cell epitopes presented in the presence of adjuvant	[^{18}F]-FBA-A20FMDV2 is chemically synthesised and there is no elevated concern for contaminating host cell products with adjuvant properties.	Low

Potential risk	Relevant factors and comments	Assessment of risk	Risk mitigation /management	Risk level
		GSK2634673F is predicted to contain two sequences that have binding capacity for MHC class II	Aggregation of the peptide is minimal Clinical relevance of *in silico* predictions is uncertain, however a relevant T cell epitope cannot be excluded In the absence of adjuvant a productive immune response is very unlikely	

Risk mitigation measures

Clinical management

Although the risk of immunogenicity is low, some immune responses can progress to hypersensitivity reactions, such as IgE-mediated allergic reactions (anaphylaxis). The impact of such a very rare event would be high. In order to manage this potential risk the following measures are in place at the site:

- Crash trolleys are available on site
- Suitably trained staff are available throughout the study
- SOPs have been developed and are current at the site
- Direct access to resuscitation teams and intensive care facilities are available immediately

Assay to measure anti-peptide antibodies

Immunogenicity assessment will be performed for serum samples collected as per the SoA. Results will be analysed when the study is completed and will be correlated with any clinical or imaging observations.

Conclusions

Currently, the evidence suggests that the immunogenicity risk of [^{18}F]-FBA-A20FMDV2, a synthetic 20 amino acid peptide, is predicted to be low. Mitigation strategies are incorporated into the protocol as described in the table above (such as exclusion of prior exposure to FMDV, short period between the 3 doses). In the unlikely event that anaphylaxis occurs, appropriate clinical management procedures are available immediately.

References

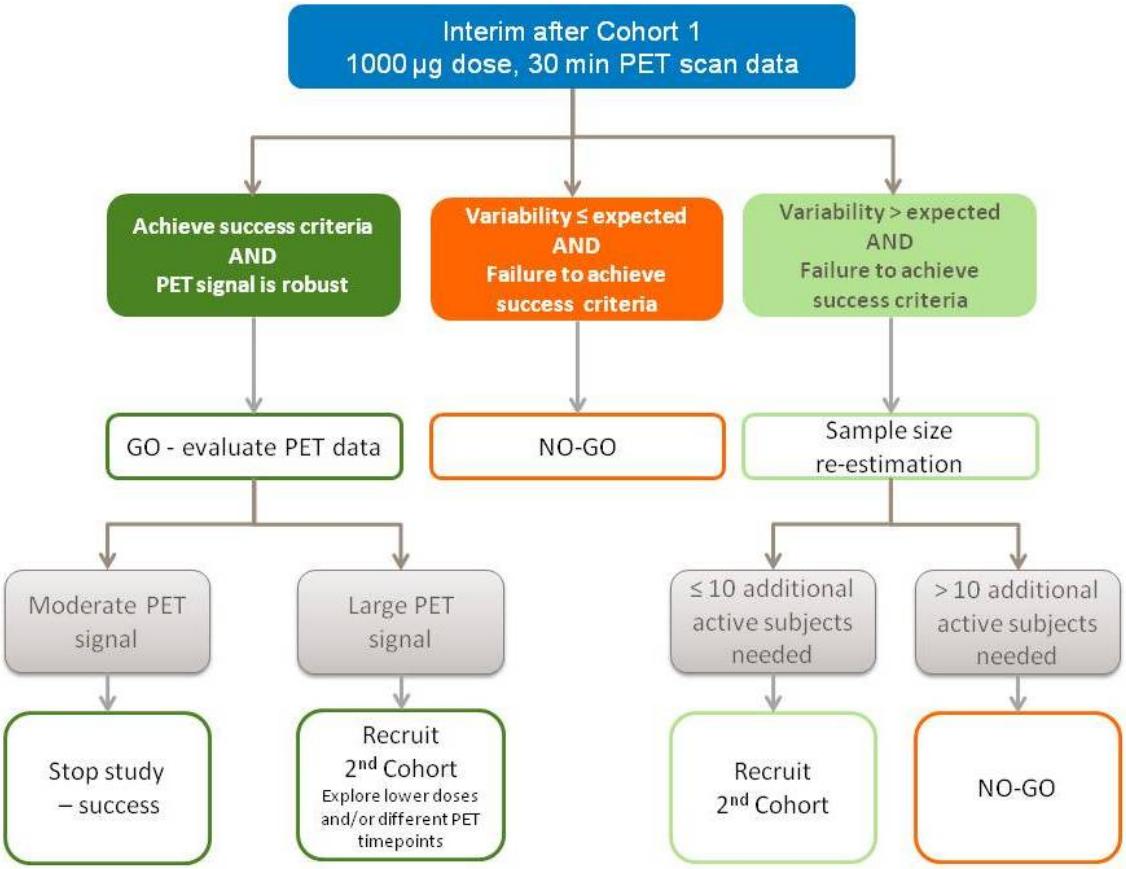
Francis, M. J., Fry, C. M., Rowlands, D.J., Brown, F., Bittle, J. L. , Houghten, R. A. , and Lerner R. A. Immunological Priming with Synthetic Peptides of Foot-and-Mouth Disease Virus. J. gen. Virol. 1985: 66; 2347-2354

Schellekens H. Immunogenicity of Therapeutic Proteins: Clinical Implications and Future Prospects. Clinical Therapeutics 2002: 24; 1720-40

12.10. Appendix 10: Diagram Summarising the Study Decision Making

The data from the 30 min post-dose PET scan will be used to make decisions on the design of Cohort 2, assuming Cohort 1 safety data supports proceeding to Cohort 2. Figure 2 below illustrates the decision making for the study.

Figure 2 Diagram illustrating study decision making



12.11. Appendix 11: Areas Endemic to Foot and Mouth Disease

Figure 3 Global Distribution of Foot and Mouth Disease

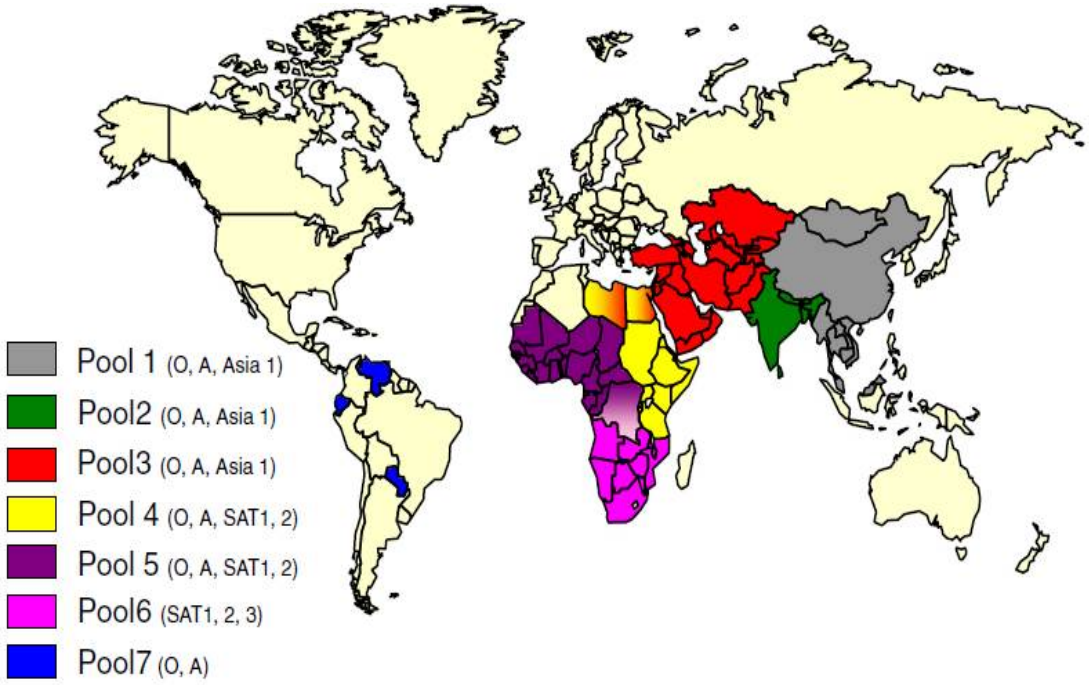


Figure 3 shows the geographical distribution of 7 pools of foot and mouth disease viruses (FMDV). Serotype O FMDV is the most widely distributed serotype. Countries which are normally free of the disease (North America, Europe, Russia, Australia and most of South America), and are therefore not included in any of the pools shown above, are marked in light yellow.

Reference

Jamal, S. M. & Belsham, G. J. Foot-and-mouth disease: Past, present and future. *Veterinary Research* **44,** (2013)

12.12. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 01

Overall Rationale for the Amendment: As part of their review of the clinical trial authorisation, the Medicines and Healthcare products Regulatory Agency (MHRA) requested a clarification to the emergency unblinding instructions in the protocol.

Section # and Name	Description of Change	Brief Rationale
7.4 Blinding	Clarified that the investigator may break the blind for a participant in an emergency, or if it is in the participant's best interest for the investigator to know the study treatment assignment, whether or not an antidote is available, and that the responsibility lies with the investigator. The investigator is encouraged to discuss with GSK personnel before breaking the blind, but if not, may inform GSK after the event.	As requested by the MHRA.