Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for 204715: 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.
Compound Number	:	GSK3008348
Effective Date	:	28-JAN-2019

Description:

- The purpose of this RAP amendment is to describe the planned analyses and outputs for the interim analysis which was conducted on 3rd September 2018. This RAP amendment also describes the planned analyses and outputs to be included in the Clinical Study Report for Protocol 204715.
- This RAP amendment is intended to describe the planned safety, tolerability, pharmacokinetics and target engagement analyses required for the study at the end of Cohort 1 only. At Interim Analysis and after review of Cohort 1 the study team agreed that the study will not progress to Cohort 2, therefore, all analyses pertaining to Cohort 2 as specified in the protocol will not be conducted. This RAP amendment will be provided to the study team members to convey the content of the Interim Analysis (IA) and final Statistical Analysis Complete (SAC) deliverable.
- All displays (Tables, Figures & Listings) will use the term 'Subjects'. However, RAP amendment text will refer to "Participants" in-line with the master RAP template and protocol.

Author(s):

Author	Date
PPD Principal Statistician (Respiratory, Clinical Statistics)	DD-MMM-YYYY
PPD Manager (Respiratory, Clinical Pharmacology Modelling and Simulation (CPMS))	DD-MMM-YYYY

RAP Team Review and Confirmations (Method: E-mail)

Reviewer	Date
PPD Programming Manager (Respiratory, Clinical Programming)	22-JAN-2019
PPD Clinical Development Manager (Respiratory, Respiratory TAU)	22-JAN-2019
PPD Director (Experimental Medicine Imaging)	22-JAN-2019

Clinical Statistics & Clinical Programming Line Approvals (Method: Pharma TMF eSignature)

Reviewer	Date
PPD Director (Respiratory, Clinical Statistics) On behalf of PPD Statistics Director (Respiratory, Clinical Statistics)	24-JAN-2019
PPD Programming Manager (Respiratory, Clinical Programming)	28-JAN-2019

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) amendment is to describe the analyses to be included in the Interim Analysis (IA) and Clinical Study Reports for Protocol: 204715

Protocol Revision Chronology:		
2016N291965_00	05-DEC-2016	Original
2016N291965_01	09-MAR-2017	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.
2016N291965_02	24-JAN-2018	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.

1.1. RAP Amendments

The original RAP was finalised prior to the Interim Analysis. At the Interim Analysis it was agreed to terminate the study and to not proceed to Cohort 2. This RAP amendment was written after the Interim Analysis and prior to final DBF and aims to clarify the contents of the SAC outputs.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

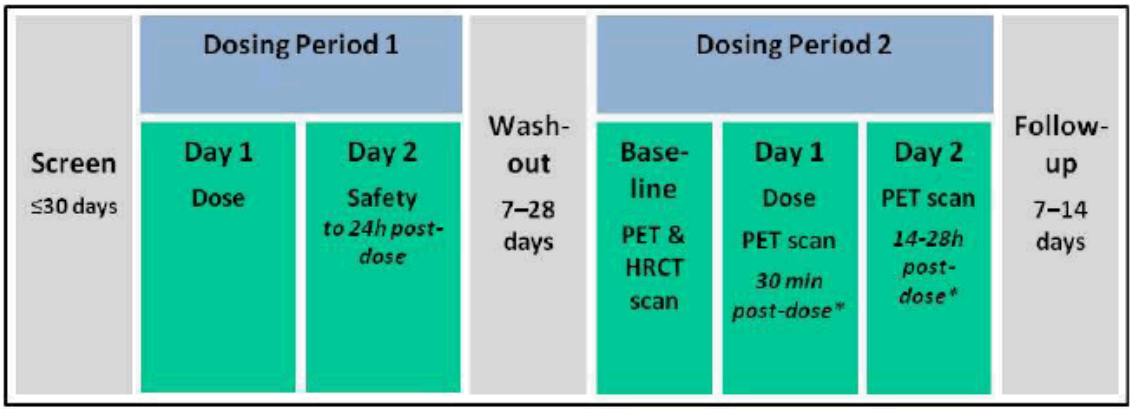
There are no changes or deviations to the originally planned statistical analysis specified in the protocol 2016N291965_02 (Dated: 24-JAN-2018). However, the protocol states that 'If the study is stopped at the end of Cohort 1, then Cohort 2 will not proceed', therefore, all analyses pertaining to Cohort 2 will not be conducted.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• 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 Objectives	**Secondary Endpoints**
• 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 ($AUC_{(0-t)}$, $AUC_{(0-inf)}$), 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
• 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 Objectives	**Exploratory Endpoints**
• 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	• 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

Objectives	Endpoints
and to compare it to the spatial distribution of disease	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

2.3. Study Design

Overview of Study Design and Key Features	
Cohort 1  	
Design Features	• 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. • **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. After screening (within 30 days of the first dose), all participants will have 2 dosing periods, and receive the same dose in each period as follows: o **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). o **Washout period:** At least 7 days and no more than 28 days between doses. o **Pre-dose scan:** At least 7 days after the first dose, and no more than 14 days before the first post-dose PET. o **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. • **Cohort 2** was not conducted**.** It was optional and would have been designed to further explore the safety of GSK3008348 and to provide additional information on the target engagement profile of GSK3008348. Based on Cohort 1 data, the decision was made to

Overview of Study Design and Key Features	
	terminate the study and not continue into cohort 2.
Dosing	• A single nebulised dose in each dosing period
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• **Cohort 1:** • 7 IPF patients will be enrolled. More IPF patients may be enrolled to achieve a target of 7 evaluable IPF patients. • Subjects in Cohort 1 will be randomised to receive either 1,000 µg GSK3008348 or placebo using a 5:2 ratio. •
Interim Analysis	• An interim analysis to assess safety and tolerability, exposure and receptor engagement will occur at the end of Cohort 1. • For safety assessments in Cohort 1, the review by the study team will include data on AEs, ECGs, pulmonary function, clinical laboratory values and VS.

2.4. Statistical Hypotheses / Statistical Analyses

All Parts:

- The assessment of the safety and tolerability of single doses of nebulised GSK3008348 in this study will not include any formal statistical comparisons.

Cohort 1:

- In Cohort 1, the primary comparison of interest is based on the 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.

3. PLANNED ANALYSES

3.1. Interim Analyses

Interim Analyses	Details
Pharmacodynamics **(Cohort 1)**	• The purpose of the interim analysis at the end of Cohort 1 was to provide the project team and key GSK stakeholders with data on receptor engagement to inform internal decision making. There were options to stop the study for success or to stop if it was deemed futile to proceed or to increase the sample size. • The interim occurred at the end of Cohort 1 when 5 IPF subjects receiving GSK3008348 had completed dosing period 2 and had a valid baseline and 30 minutes post-dose PET scan. • The primary endpoint for decision-making at the interim analysis was the change 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 • The review occurred on a clean database including the PET derived endpoints and the randomisation assignment. In addition, in-stream data reviews took place to ensure maximum data quality. • At the interim time point the change 30 minutes post-dose vs pre-dose in whole lung V_T for the 5 active subjects was analysed. The decision was made to stop the study due to success and evidence of receptor engagement, primarily based on the predefined success criterion, i.e. the posterior probability that there was a reduction in 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. • Appropriate data summaries were at the treatment group level and individual subject numbers were scrambled so treatment allocation was not obvious. The circulation of results was restricted to selected members of the GSK project team and key stakeholders. Interim results were discussed with site investigators following internal review at GSK.
PK	• The purpose of the interim PK analysis at the end of Cohort 1 was to provide the study team with data on

Interim Analyses	Details
(Cohort 1)	systemic exposure to inform dose selection for Cohort 2 and/or dose selection for future studies and occurred at the end of Cohort 1. • PK analysis was performed on the data prior to cleaning. Additionally, the analysis was performed using nominal times and interim analysis was conducted on data with scrambled individual subject numbers. These scrambled numbers were different from scrambled numbers for the PET endpoint. The critical PK endpoints for assessment of systemic exposure were AUC and C_{max}. AUC was assessed as 0-t in the event of insufficient data to determine $AUC_{(0\text{-inf})}$. Exposures relative to those observed at the NOAEL in toxicology studies were not calculated since we were not proceeding to Cohort 2.
Safety (Cohort 1)	• An informal review of safety data occurred at the end of Cohort 1. The purpose of this review was to compare safety parameters at the pre- and post-dose timepoints across both dosing periods and explore any safety signals that may have emerged. • The review by the study team included data on AEs, ECGs, pulmonary function, clinical laboratory values and VS. • It was not expected that this review would occur on a clean database. No data listings were produced, and no statistical analysis was performed on the data.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All participants	• All participants who are screened and for whom a record exists on the study database.	• Study Population
Enrolled	• All participants who are screened and enrolled into the study. • **Note:** Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
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. • **Note:** Any participants who receives a treatment randomisation number will be considered to have been randomised.	• PD • Study Population • Safety
Per-Protocol (PP)	• All participants in the ITT population who comply with the protocol and that have at least one evaluable PET measurement post baseline. • **Note:** Protocol deviations that would exclude participants from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1(Protocol Deviation Management and Definitions for Per Protocol Population). • **Note:** The ITT set will not be analysed if this population is the same as the PP population.	• PD
Pharmacokinetic (PK)	• All participants in the Intent-to-Treat population receiving active dose for whom a pharmacokinetic sample was obtained and analysed. • **Note:** Non-quantifiable [NQ] values will be considered as non-missing values.	• PK

Refer to Appendix 12: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

Protocol deviations will be tracked and reviewed by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (Final v1.0, Dated: 09-MAR-2017).

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

For the interim analysis, exclusions from the Per-Protocol Population based on the criteria detailed in Section 15.1.1 were agreed prior to un-blinding based on review of in-stream data by the study team.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		**Data Displays for Reporting**	
Code	**Description**	**Description**	**Order in TLF**
A	Placebo	Placebo	1
B	GSK3008348 1000 mcg	GSK3008348 1000 mcg	2

No treatment comparisons between GSK3008348 1000 mcg versus Placebo will be conducted.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	**Study Assessment Period**		
	1	**2**	
Baseline Used in Data Display	**Dosing Period 1 Day -1 or Day 1 (Pre-Dose)**	**Dosing Period 2 Day -1 or Day 1 (Pre-dose)**	**Dosing Period 2, Baseline scan (≤2 Weeks Pre-Dose)**
Pharmacodynamics			
Volume of Distribution (V_T), not corrected for air volume			X
Volume of Distribution (V_T), corrected for air volume			X
Standardised Uptake Values (SUV), not corrected for air volume			X
Standardised Uptake Values (SUV), corrected for air volume			X

Parameter	Study Assessment Period		
	1	2	
Baseline Used in Data Display	**Dosing Period 1 Day -1 or Day 1 (Pre-Dose)**	**Dosing Period 2 Day -1 or Day 1 (Pre-dose)**	**Dosing Period 2, Baseline scan (≤2 Weeks Pre-Dose)**
Safety			
12 Lead ECG	X	X	
Vital Signs	X	X	
Laboratory Assessments	X	X	
FEV_1 and FVC (absolute & % predicted)	X	X	
DLCO (absolute & % predicted)	X		

For all pharmacodynamics and safety displays, baseline will be labelled 'Pre-dose'.

If Pre-dose % predicted FVC in Period 2 is missing Pre-dose % predicted FVC in Period 1 will be used as baseline value instead for PET data analysis.

If Day -1 and Day 1 pre-dose values are missing, screening value for Period 1 will be used as baseline. Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

This is a single country, multicentre study and enrolment will be presented by investigative site/hospital.

Investigative site/Hospital	Country
University College London Hospital (UCLH)	United Kingdom
Royal Brompton Hospital (RBH)	United Kingdom

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Strata	None
Covariates	Age, Sex, Baseline % Predicted FVC (baseline in Period 2) and Baseline % Predicted DLCO (baseline in Period 1).

5.4.2. Examination of Subgroups

There is no examination of subgroups.

5.5. Multiple Comparisons and Multiplicity

In Cohort 1, the primary comparison of interest is based on the 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. No treatment comparisons between GSK3008348 1000 mcg versus Placebo will be conducted. Therefore, there are no planned adjustments for multiple comparisons or multiplicity.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
15.3	Appendix 3: Assessment Windows
15.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
15.5	Appendix 5: Data Display Standards & Handling Conventions
15.6	Appendix 6: Derived and Transformed Data
15.7	Appendix 7: Reporting Standards for Missing Data
15.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Intent-To-Treat (ITT) population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards.

Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. PHARMACODYNAMIC ANALYSES

7.1. Primary Pharmacodynamics Analyses

The three PET scans per subject will be denoted as 'Pre-dose' (Baseline PET in Period 2), 'PET1' (Period 2, Day 1, 30 minutes PET after dose of GSK3008348, allowable time window is 20-60 mins) and 'PET2' (Period 2, Day 2, 24 hours PET after dose of GSK3008348, allowable time window is 14-28 hrs).

7.1.1. Endpoint / Variables

Change 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. V_T is implicitly corrected for blood volume.

7.1.2. Summary Measure

Ratio (PET1/Pre-dose) in the volume of distribution (V_T), not corrected for air volume at approximately 30 min post-dose as measured by PET.

7.1.3. Population of Interest

The primary pharmacodynamic analyses will be based on the Per-Protocol (PP) population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Several post-randomisations events have been considered e.g. use of rescue medication, discontinuation of treatment, treatment switching and death. Due to the short duration of the study (and the time at which the pharmacodynamic endpoint is measured; baseline, 30mins and 14-28hrs post-dose) these post-randomisation events have been deemed to have little impact on the endpoint.

Therefore, a treatment policy approach will be adopted hence the actual values of the endpoint regardless of whether the intercurrent event has occurred will be analysed.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• V_T (whole lung, not corrected for air volume), at 1000 mcg GSK3008348
Timepoint
• The primary timepoint of interest is the 30 minutes post-dose PET scan timepoint.
Model Specification
• The distribution of V_T will be explored using graphical approaches. It is likely that this follows a log-normal distribution in which case the logarithm transformation will be applied, and a normal distribution assumed for log (V_T). • Only data from those subjects receiving 1,000 mcg GSK3008348 will be included in the primary analysis (i.e., no placebo data will be included) in Cohort 1. • The three PET scans per subject will be denoted by Pre-dose (Baseline PET in Period 2), PET1 (Period 2, Day 1, 30 minutes PET after dose of GSK3008348, allowable time window is 20-60 mins) and PET2 (Period 2, Day 2, 24 hours PET after dose of GSK3008348, allowable time window is 14-28 hrs). • The mean of the normal distribution will be allowed to vary per post-dose scan timepoint by defining the 3-dimensional array parameter ResponsebyVisit as follows: o ResponsebyVisit[1] = mean of log (Response) at 'Pre-dose' o ResponsebyVisit[2] = mean of log (Response) at 'PET1' o ResponsebyVisit[3] = mean of log (Response) at 'PET2' • In addition, the following 3 - dimensional array parameter ResponseRatio will also be created: o ResponseRatio[1] = PET1/Pre-dose o ResponseRatio[2] = PET2/Pre-dose o ResponseRatio[3] = PET2/PET1 • The inclusion of covariates Age, Sex, Baseline % predicted FVC, and Baseline % predicted DLCO (baseline from Period 2) will be explored in a sequential manner and included in the model if the 95% HPD credible interval for the corresponding regression coefficient excludes 0. • This endpoint will be analysed using Bayesian inference assuming non-informative priors of the form N(mean=0, SD = 1000) for all regression coefficients in the model. • An unstructured 3x3 variance-covariance matrix will be assumed to model the dependency between log (V_T) in the three PET scans. If the model fails to converge then additional structures such as the Toeplitz structure should be explored. Details of the prior distributions are presented in Section 12.2.
Model Checking & Diagnostics
• Refer to Section 12.2: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Plots of the posterior samples (chains) will be produced for all the parameters in the model as listings. • Posterior density plots for V_TRatio;

○ PET1/Pre-dose ○ PET2/Pre-dose ○ PET2/PET1 will be produced. • The adjusted posterior median values of V_TRatio (PET1/Pre-dose, PET2/Pre-dose and PET2/PET1) will be presented in tabular form together with the corresponding standard deviations and 95% HPD credible intervals. • Plots of individual subject data for PET1/Pre-dose, PET2/ Pre-dose and PET2/PET1 will be superimposed with the adjusted posterior median values of PET1/Pre-dose, PET2/Pre-dose and PET2/PET1 respectively. These plots should also include the corresponding 95% HPD credible intervals for PET1/Pre-dose, PET2/Pre-dose and PET2/PET1. • The posterior probability that the true ratio PET1/Pre-dose is less than 1 will be calculated.
Subgroup Analyses
• None
Sensitivity and Supportive Analyses
• Following review of the data, additional analyses may be conducted to further support the primary statistical analysis, if deemed appropriate. The posterior probability that the true ratio PET1/Pre-dose is less than 0.9, 0.8, 0.7 and 0.6, as appropriate depending on the observed data, will also be calculated. If the PP and ITT populations differ, the same statistical analysis using the ITT population will also be conducted.

7.2. Secondary Pharmacodynamic Analyses

The secondary pharmacodynamic analyses will be conducted in the same manner as the primary pharmacodynamic analyses. The only difference is that the timepoint of interest is now PET2. The output corresponding to the secondary pharmacodynamic analysis will be obtained from the primary pharmacodynamic analysis and corresponds to PET2/Pre-dose and PET2/PET1.

7.2.1. Endpoint / Variables

Changes in the uptake of [^{18}F]-FBA-A20FMDV2 in the whole lung (assessed as the V_T) up to PET2 post-dose compared to Pre-dose, as measured by PET.

7.2.2. Summary Measure

- Ratio (PET2/Pre-dose) in the volume of distribution (V_T), not corrected for air volume at 14-28 hrs post-dose as measured by PET.

7.2.3. Population of Interest

The secondary pharmacodynamic analyses will be based on the Per Protocol (PP) population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomisation) Events

Treatment policy approach will be adopted hence the actual values of the endpoint regardless of whether the intercurrent event has occurred will be analysed as outlined in the primary pharmacodynamic analyses.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• V_T (whole lung, not corrected for air volume), at 1000 mcg GSK3008348
Timepoint
• The secondary timepoint of interest is the PET2.
Model Specification
• Similar to the primary pharmacodynamic analyses
Model Checking & Diagnostics
• Similar to the primary pharmacodynamic analyses
Model Results Presentation
• Similar to the primary pharmacodynamic analyses
Subgroup Analyses
• Similar to the primary pharmacodynamic analyses
Sensitivity and Supportive Analyses
• Similar to the primary pharmacodynamic analyses

7.3. Exploratory Pharmacodynamic Analyses

There are four exploratory objectives and associated endpoints as outlined Section 2.2. For the exploratory pharmacodynamic analyses, only endpoints associated with the following objective will be described in this RAP:

- To explore the pharmacodynamic effects of single nebulised doses of GSK3008348 in IPF patients using additional PET analyses techniques

The following objectives and associated endpoints below will be described separately from this RAP:

- 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
- To explore pharmacodynamic effects of GSK3008348 in blood
- To explore potential biomarkers of IPF disease and/or treatment response

7.3.1. Endpoint / Variables

- Change 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 (PET1 and PET2) compared to pre-dose (Pre-dose), as measured by PET

7.3.2. Summary Measure

- Ratio (PET1/Pre-dose) in the volume of distribution (V_T), whole lung, corrected for air volume at approximately 30 mins post-dose as measured by PET.
- Ratio (PET2/Pre-dose) in the volume of distribution (V_T), whole lung, corrected for air volume at 14-28 hrs post-dose as measured by PET.
- Ratio (PET2/PET1) in the volume of distribution (V_T), whole lung, corrected for air volume at approximately 30 mins and 14-28 hrs post-dose as measured by PET.
- Ratio (PET1/Pre-dose) in the standardised uptake values (SUV), whole lung, not corrected for air volume) at approximately 30 mins post-dose as measured by PET.
- Ratio (PET2/Pre-dose) in the standardised uptake values (SUV), whole lung, not corrected for air volume at 14-28 hrs post-dose as measured by PET.
- Ratio (PET2/PET1) in the standardised uptake values (SUV), whole lung, not corrected for air volume at approximately 30 mins and 14-28 hrs post-dose as measured by PET.
- Ratio (PET1/Pre-dose) in the standardised uptake values (SUV), whole lung, corrected for air volume at approximately 30 mins post-dose as measured by PET.
- Ratio (PET2/Pre-dose) in the standardised uptake values (SUV), whole lung, corrected for air volume at 14-28 hrs post-dose as measured by PET.
- Ratio (PET2/PET1) in the standardised uptake values (SUV), whole lung, corrected for air volume at approximately 30 mins and 14-28 hrs post-dose as measured by PET.

7.3.3. Population of Interest

The exploratory pharmacodynamic analyses will be based on the Per Protocol (PP) population, unless otherwise specified.

7.3.4. Strategy for Intercurrent (Post-Randomisation) Events

Treatment policy approach will be adopted hence the actual values of the endpoint regardless of whether the intercurrent event has occurred will be analysed as outlined in the primary pharmacodynamic analyses.

7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.5.1. Statistical Methodology Specification

Endpoint / Variables
• Volume of distribution (V_T), (whole lung, corrected for air volume) at approximately 30 mins post-dose as measured by PET. • Volume of distribution (V_T), (whole lung, corrected for air volume) at 14-28 hrs post-dose as measured by PET. • Standardised uptake values (SUV), (whole lung, not corrected for air volume) at approximately 30 mins post-dose as measured by PET. • Standardised uptake values (SUV), (whole lung, not corrected for air volume) at 14-28 hrs post-dose as measured by PET. • Standardised uptake values (SUV), (whole lung, corrected for air volume) at approximately 30 mins post-dose as measured by PET. • Standardised uptake values (SUV), (whole lung, corrected for air volume) at 14-28 hrs post-dose as measured by PET.
Timepoints
• The exploratory timepoints of interest are PET1 and PET2.
Model Specification
• Similar to the primary pharmacodynamic analyses
Model Checking & Diagnostics
• Similar to the primary pharmacodynamic analyses
Model Results Presentation
• Similar to the primary pharmacodynamic analyses
Subgroup Analyses
• None
Sensitivity and Supportive Analyses
• Similar to the primary pharmacodynamic analyses

8. SAFETY ANALYSES

The safety analyses will be based on the Intent-To-Treat (ITT) population, unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review by the study team in place at the time of reporting. The details of the planned displays are provided in Appendix 12: List of Data Displays.

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs, pulmonary function and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 15.5.3 Reporting Standards for Pharmacokinetic)

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Nominal sampling times may be used during any interim analysis. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_{(0-t)}/D$	$AUC_{(0-t)}$ corrected for dose
$AUC_{(0-inf)}$	Area under the concentration-time curve extrapolated to infinity will be calculated as: AUC = $AUC_{(0-t)}$ + C(t) / lambda_z
$AUC_{(0-inf)}/D$	$AUC_{(0-inf)}$ corrected for dose
C_{max}	Maximum observed concentration, determined from the concentration-time data.
T_{max}	Time to reach C_{max}, determined directly from the concentration-time data.
C_{max}/D	C_{max} corrected for dose
Lambda_z[1]	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
Lambda_z_lower	First time point used in computing Lambda_z.
Lambda_z_upper	Last time point used in computing Lambda_z.
#pts	Number of points used in computing Lambda_z.
r-squared	R-squared of Lambda_z computation.
t½	Apparent terminal half-life will be calculated as: t½ = ln2 / Lambda_z

NOTES:
- Additional parameters may be included as required.

9.1.2. Summary Measure

PK treatment comparisons are not planned for this study.

9.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomisation) Events

In the event of a missing time point, PK parameters will be estimated from the available data on that day, unless the missing value compromises the accurate estimate of the parameter.

9.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 9.1.1 will be summarised by period using descriptive statistics, graphically presented (where appropriate) and listed.

9.1.5.1. Statistical Methodology Specification

No formal statistical modelling will be performed, only descriptive statistics will be produced.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

Plasma concentration-time data may be used to derive population PK parameters/models using NONMEM or other currently validated software. The timeline for this analysis and reporting will be independent of the analysis described in this RAP. In an event that GSK3008348 is terminated before these analyses are conducted, they will not be reported.

11. BIOMARKER ANALYSES

Analyses for exploratory pharmacodynamic biomarkers of the αvβ6/TGFβ mechanism which may include but are not limited to: mRNA, microRNA and proteins in blood will be independent of the analysis described in this RAP and will be reported separately.

12. PHARMACODYNAMIC INTERIM ANALYSES

12.1. Pharmacodynamic Interim Analyses

The interim analysis for pharmacodynamics in Cohort 1 was based on the Per Protocol population.

The interim analysis was conducted in the same manner as the primary pharmacodynamic analysis and the primary timepoint of interest was the 30 minutes post-dose scan timepoint. The secondary timepoint of interest was the 14-28hrs post dose scan point. The data was reported to the study team with scrambled individual subject numbers.

12.1.1. Endpoint / Variables

- Change 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.
- Change 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 14-28hrs post-dose compared to pre-dose, as measured by PET.

12.1.2. Summary Measures

- Ratio (PET1/Pre-dose) in the volume of distribution (V_T), whole lung, not corrected for air volume at approximately 30 mins post-dose as measured by PET.
- Ratio (PET2/Pre-dose) in the volume of distribution (V_T), whole lung, not corrected for air volume at 14-28 hrs post-dose as measured by PET.
- Ratio (PET2/PET1) in the volume of distribution (V_T), whole lung, not corrected for air volume at approximately 30 mins and 14-28 hrs post-dose as measured by PET.

12.1.3. Population of Interest

The pharmacodynamics interim analyses were based on the Per Protocol (PP) population.

12.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Treatment policy approach was adopted hence the actual values of the endpoint regardless of whether the intercurrent event had occurred were analysed as described for the primary pharmacodynamic analyses.

12.1.5. Statistical Analyses / Methods

Details of the planned displays were provided in Appendix 12: List of Data Displays and were based on GSK Data Standards and statistical principles.

Endpoints / variables defined in Section 12.1.1 were summarised using descriptive statistics, graphically presented (where appropriate) and listed.

12.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Change 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. • Change 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 14-28hrs post-dose compared to pre-dose, as measured by PET.
Timepoints
• PET1. • PET2.
Model Specification
• Same model specifications as in Section 7.1.5.1 for the primary pharmacodynamics analyses
Model Checking & Diagnostics
• Same model specifications as in Section 7.1.5.1 for the primary pharmacodynamics analyses
Model Results Presentation
• Same model specifications as in Section 7.1.5.1 for the primary pharmacodynamics analyses
Subgroup Analyses
• None
Sensitivity and Supportive Analyses
• Same model specifications as in Section 7.1.5.1 for the primary pharmacodynamics analyses

12.1.5.2. Table Illustrating Study Decision Making Used at Interim Analysis

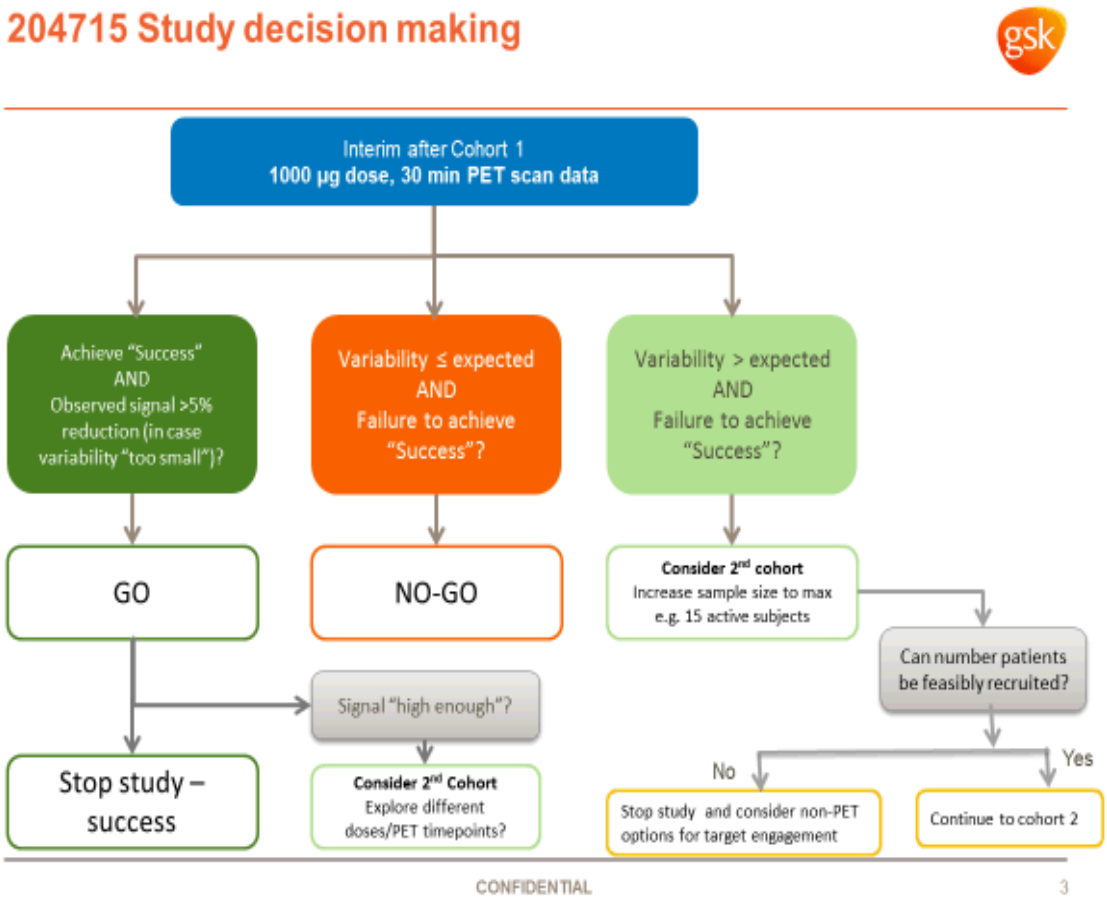
	Interim outcomes from 204715	Impact on development of GSK3008348	Traffic lights	Question for cohort 2	Cohort 2	Cohort 2 - Positive data	Cohort- 2 negative data
1)	No signal, variability as expected	Stop development					
2)	Signal more variable than expected, sample size increase required >10 subjects	Failure of PET endpoint not '348 continue to PD study (pSMAD2)		N/A			
3)	Signal more variable than expected, sample size increase required <10 subjects	Dependent on number additional subjects required. If the number of patients can be feasibly recruited, continue to cohort 2 to get definitive answer. If it is not feasible to increase the sample size- failure in sensitivity of PET endpoint continue to PD study (pSMAD2)		Can target engagement be established in the larger cohort? Is this only 10 or less subjects and can these be feasibly recruited?	If Answer to both questions yes, recruit additional subjects and confirm target engagement. Otherwise continue to PD study	1) invest API-3 and repeat dose IPF study	Still no robust target engagement- Stop development
4)	Signal at 30 minutes, but no or inconclusive signal at 24 hours (expected outcome)	Go ahead with API-3 and repeat dosing studies in IPF patients		Is GSK3008348 suitable for twice daily dosing? Can this be achieved in a number of participants that can be feasibly recruited?			

	Interim outcomes from 204715	Impact on development of GSK3008348	Traffic lights	Question for cohort 2	Cohort 2	Cohort 2 - Positive data	Cohort- 2 negative data
5)	Signal at both 30 mins and 24 hours	Go ahead with API-3 and repeat dose study with PD assessments in IPF patients		Investigate whether lower doses can be used?	Investigate lower doses	Use information to inform dose selection for repeat dosing in IPF study	Use information to inform dose selection for repeat dosing in IPF study

12.1.5.3. Table Explaining Programming Requirements Used at Interim Analysis

Study Decision	Description	Statistical Programming
Achieve Study Success Criteria **and** **PET Signal is Robust**	Achieve Study Success Criteria and PET Signal is ≥ 5% Inhibition	Study Success #1 = P (*log* [θ] < 0 | Study Data, Prior(θ)) ≥ 80%. θ = $PET1_{VT}$/$Pre\text{-}dose_{VT}$ and % Inhibition = (1-$PET1_{VT}$/$Pre\text{-}dose_{VT}$)*100
Sample Size Re-estimation	Include up to 10 active additional subjects and with each additional subject evaluate Study Success Rule #2. If this rule is not met with 10 additional subjects then NO-GO, else Recruit 2nd Cohort.	Study Success Rule #1 = P (*log* [θ] < 0 | Study Data, Prior(θ)) ≥ 80% θ = $PET1_{VT}$/$Pre\text{-}dose_{VT}$

12.1.5.4. Figure Illustrating Study Decision Making Used at Interim Analysis



12.2. Model Checking and Diagnostics for Statistical Analyses

12.2.1. General Considerations for Bayesian Analysis

- The following points are for guidance and illustration only and do not guarantee a successful model convergence. They cannot cover all eventualities and do not remove the requirement to do what is best for the specific set of observed data being modelled.
- Unless otherwise stated, data collected at screening and at unscheduled time points will not be included in the statistical analyses, i.e., only planned/scheduled post-screening data will be included except where screening data is used as baseline.
- All credible intervals reported will be 95% HPD intervals, unless otherwise specified.
- After Markov Chain Monte Carlo (MCMC) for Bayesian inference, estimated and monitored model parameters (variance components and fixed effects) were compared to corresponding estimated parameters from the linear mixed model. Confidence was gained if results were similar. Different initial values for fixed effects (but not

variance components) were used to assess convergence. Convergence for all the parameters in the model needs to be verified

- A separate seed for each MCMC chain will be set to ensure reproducibility.

12.2.1.1. Prior Distributions

Unless otherwise specified, the following will be the default approach to selecting prior distributions:

- Non-informative priors of the form Normal (0, Var=1E6) will be assigned to each fixed-effect parameter in the proposed statistical model.

- For repeated measures models, non-informative Inverse-Wishart priors of the form IW (υ, Σ) will be assigned for the Variance-Covariance (VC) matrix associated with the repeated measures timepoints. The parameter υ represents the dimension of VC (number of rows or columns) and the matrix Σ is an identity matrix of the same dimension as VC. The unstructured variance covariance structure for the repeated measurements will be assumed. In cases of non-convergence, the Toeplitz structure will be used.

    - If there are issues with these distribution parameters, then Σ may be a diagonal matrix that uses best guesses for the residual variance at each repeated measure timepoint (or the residual estimate from fitting simple models). This only needs to be of the correct order of magnitude.

- Non-informative inverse-gamma priors of the form IG(a=2.001, b=0.001) will be used for scale parameters (variances). If these parameters do not lead to convergence, then choose "a" small and "b" smaller than the expected standard deviation.

It is good practice to ensure that each prior distribution is visualized to ensure it appears sensible, i.e., that it allows parameter values that generate clinically plausible response values and that it is truly non-informative over the region of the likelihood function where the data lies.

Note:

- The Gamma(a,b) density function takes the form

$$p(u) = \frac{b(bu)^{a-1}e^{-bu}}{\Gamma(a)}, u > 0$$

  The mean is a/b and the variance is a/b^2.

- The IG(a,b) density function takes the form

$$p(u) = \frac{b^a u^{-(a+1)}e^{-b/u}}{\Gamma(a)}, u > 0$$

The mode is b/(a+1), the mean is b/(a-1), if a>1, and the variance is $b^2/[(a-1)^2(a-2)]$, if a>2.

- There is no requirement to formally report the prior visualisation outputs.

12.2.1.2. Initial Values

The two MCMC chains should be generated using over-dispersed initial values. To achieve this the sample standard deviation of the change from baseline in log(response), SD_hat, should be estimated. The two over-dispersed initial values for the parameters (ResponsebyVisit) should then be sampled from the following normal distribution N(0, SD = 10*SD_hat).

For the remaining model parameters over-dispersed initial values may be drawn at random from their respected prior distribution. If convergence of the Markov chain Monte Carlo (MCMC) algorithm is problematic then alternative estimates may be used (for example, these could be based on maximum likelihood estimates).

12.2.1.3. Convergence Diagnostics

To be able to perform Bayesian inference using MCMC simulations the posterior samples for all the parameters in the model need to be obtained from the corresponding target posterior distribution. To ensure that this is the case the following is a list of convergence diagnostics that can be applied for each parameter:

Comparing MCSE vs. posterior standard deviation:

- The Monte Carlo Standard Errors (MCSE) should be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to the simulation, i.e., the ratio MCSE/SD should be as small as possible, typically < 0.01.

- Adequate values for the number of MCMC samples / thinning / number of burn-in samples should be chosen to ensure that the ratio MCSE/SD for all the parameters in the model is < 0.01.

- In addition, if possible, the number of tuning units and maximum number of tuning iterations may be increased to find a better proposal distribution for the model parameters, which in turn may reduce the MCSE/SD ratio.

- Where possible the code should be written to allow the SAS compiler to identify and make use of conjugacy, since this can greatly reduce the corresponding MCSE/SD ratio.

- Models selected with MCSE/SD values > 0.01 would need a brief remark/justification added to the CSR to clarify why it was not possible to reach the target and why it is believed the subsequent model still has utility from an inference perspective.

Gelman & Rubin diagnostics:

- The Gelman & Rubin diagnostic assessment will be used to assess convergence of the multiple chains.

- The Gelman & Rubin diagnostic is based on running multiple Markov chains, say *m*, each with *n* draws, with the different chains started at initial values that should be overdispersed relative to the target posterior distribution. Thus, the *m* chains yield *m* possible inferences; to answer the question of whether these inferences are similar enough to indicate approximate convergence, Gelman, 1992 suggested comparing these to the inference made by mixing together the *m***n* draws from all the sequences as follows: the pooled variance across the chains is compared to the overall within-chain variance using a ratio, usually called the potential scale reduction factor, or $\hat{R}$.

- Values of $\hat{R}$ close to 1 indicate that each of the *m* sets of *n* simulated observations is close to the target posterior distribution.

- Although PROC MCMC in SAS does not provide the Gelman & Rubin $\hat{R}$, SAS has provided a macro, %gelman, for determining the statistic (note that for this to work at least two MCMC chains need to be generated, which means that PROC MCMC needs to be call as many times as the number of chains, with the different starting values).

Diagnostic plots and visual inspection:

- Trace plots of samples versus the simulation index can be used to assess some aspects of convergence. The centre of the chain should appear stable with very small fluctuations, i.e., the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant.

- Autocorrelation plots provide information on how slow or fast the Markov chain converges. If the autocorrelation does not decrease rapidly this means that the chain needs to be run for longer to achieve convergence.

- Examination of correlation structures between relevant posterior parameters should be used to provide information about what potential issues may be and also what corrective action(s) may be worthwhile attempting.

Convergence for all the parameters in the model needs to be verified (apart from subject-specific random effects).

12.2.2. General Considerations for All Analyses

Model assumptions will be applied, but appropriate adjustments may be made based on the data. If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

Distributional assumptions underlying the model used for analysis will be examined through graphical approaches by assessing the distribution of the residuals against the assumed distribution of the response, and by assessing the distribution of the residuals against the fitted response values.

Outputs of the residual plots as a check of the normality assumptions of the log(response) will be produced.

13. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

Pharmacodynamic and PK-time data may be used to derive population PKPD parameters/models using NONMEM or other currently validated software. The timeline for this analysis and reporting will be independent of the analysis described in this RAP. In an event that GSK3008348 is terminated before these analyses are conducted, they will not be reported.

14. REFERENCES

1. GlaxoSmithKline Document No.: 2016N291965_02: 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. Effective date: 24-JAN-2018.

2. Gelman, A. and Rubin, D.B. (1992) Inference from Iterative Simulation Using Multiple Sequences. Statistical Science, 7, 457-472.

15. APPENDICES

15.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

15.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population.

Number	Protocol Deviation	Full, Case by Case and Partial Exclusion [1]
01	Inclusion # 2 – Did not have correct diagnosis of definite or probable IPF	Full
02	Inclusion # 4 – Did not have qualifying lung function severity (Subjects who do not have FVC > 50 % predicted and DLCO > 40 % predicted).	Full
03	Exclusion # 7 - Forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio < 0.70 at screening (post-bronchodilator).	Full
04	PET scan at 30 mins post-dose non-evaluable	Full
05	Visit outside of protocol defined window	Case by case
06	Exclusion # 4 – Current IPF exacerbation or upper or lower respiratory tract infection on admission to the clinical unit.	Partial
07	Exclusion # 10 - Subjects who are currently taking Pirfenidone or Nintedanib or who have received Pirfenidone or Nintedanib within the 30 days prior to the first dosing day will be excluded from the study.	Partial

NOTES:

[1] Partial exclusions refer to patients for whom data will be excluded from the Per-Protocol population only from the study day at which the deviation takes place onwards. Full exclusions refer to patients for whom all the available data will be excluded from the Per-Protocol population. Other protocol deviations not listed in this section will be assessed on a case by case basis.

15.2. Appendix 2: Schedule of Activities

15.2.1. Protocol Defined Schedule of Events

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

15.3. Appendix 3: Assessment Windows

15.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target timepoint	Analysis time deviation Window		Analysis Timepoint
			Earliest Timepoint	Latest Timepoint	
ITT/PP	V_T	30 mins	20 mins	60 mins	Day 1
ITT/PP	SUV	30 mins	20 mins	60 mins	Day 1
ITT/PP	V_T	24 hours	14 hours	28 hours	Day 2
ITT/PP	SUV	24 hours	14 hours	28 hours	Day 2

15.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

15.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment.

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 1
Post-Treatment	Date > Study Treatment Stop Date + 1

15.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 7 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

15.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date +1 • For studies with greater than one treatment period (e.g., Period 1 and Period 2), if AE onset is during one period and worsens during a later period it would be counted in both periods. For the initial period the logic would be as above. For the later period the logic would use the treatment dates associated with the later period: • Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date + 1

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

15.4.3. Categorisation of adverse events into Dosing Periods

AEs will be categorised into 4 groups (Dosing Period 1, Dosing Period 1 follow up, Dosing Period 2 and Dosing Period 2 follow up) as shown in table below. AEs are assigned up to 72 hours for the dosing periods as GSK3008348 will be expected to have cleared the systemic circulation by 72 hours [GSK3008348 has a half-life of 8-10 hours and so 72 hours >5 half-lives]. Any AEs prior to dosing will be listed as screening AEs and will not be summarised.

Dosing Period 1	Start of first dose GSK3008348 to 72 hrs post start of dose
Dosing Period 1 Follow up (which will include washout and baseline scan)	72 hours post start of first dose of GSK3008348 (Period 1) to start of second dose of GSK3008348 (Period 2), or end of study follow up for subjects that were withdrawn before dosing period 2
Dosing Period 2	Start of second dose GSK3008348 to 72 hrs post start of second dose
Dosing Period 2 Follow up	72 hours post start of second dose of GSK3008348 (Period 2) to end of follow up for the study.

15.5. Appendix 5: Data Display Standards & Handling Conventions

All displays (Tables, Figures & Listings) will use the term 'Subjects'. However, RAP text will refer to "Participants" in-line with the master RAP template and protocol.

15.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area Interim	:\arprod\gsk3008348\mid204715\internal_01
HARP Area Dry-run	:\arprod\gsk3008348\mid204715\data_look_01
HARP Area SAC	:\arprod\gsk3008348\mid204715\final_01
QC Spreadsheet	: \arwork\gsk3008348\mid204715\ internal_01\Documents
QC Spreadsheet	: \arwork\gsk3008348\mid204715\final_01\Documents
QC Spreadsheet	:\arwork\gsk3008348\mid204715\data_look_01\documents
Analysis Datasets	
• Analysis datasets were created according to Legacy GSK A&R dataset standards (IDSL) for the interim analyses in Cohort 1. The same standards will be used for the final analyses.	
Generation of RTF Files	
• RTF files were generated for tables and figures for the IA. In addition, pdf files of the plots were generated at IA. Similarly, RTF files for tables and pdf files of the plots will be generated at Statistical Analysis Complete (SAC) reporting effort.	

15.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be in the modular appendices as ICH or non-ICH listings
Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.

• Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

15.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to Standards for the Transfer and Reporting of PK Data using HARP. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function maybe created if appropriate. The data specification and timeline for creation of this file will be independent of the analysis described in this RAP. In an event that GSK3008348 is terminated before these analyses are conducted, this file will not be created.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function maybe created, if

	appropriate. The data specification and timeline for creation of this file will be independent of the analysis described in this RAP. In an event that GSK3008348 is terminated before these analyses are conducted, this file will not be created.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	$AUC_{(0-t)}$/D, $AUC_{(0-inf)}$/D and C_{max}/D
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

15.6. Appendix 6: Derived and Transformed Data

15.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 15.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
• Calculated as the number of days from First Dose Date within a treatment period: o Ref Date = Missing → Study Day = Missing o Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date o Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

15.6.2. Safety

ECG Parameters
RR Interval
• ECGs are machine read, the RR value preceding the measurement QT interval was only collected during Imanova visits. Missing RR interval (msec) will not be derived.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fridericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • If RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as: $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{3\sqrt{\frac{RR}{1000}}}$

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing or replaced with a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field), the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x - 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x - 1. • If there is more than one value of a particular parameter for a subject for a visit, the scheduled value will be used in summary statistics; all values will be listed.

15.6.3. Pharmacokinetic

Dose-Normalised Parameters
$AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max}
• Derived as: PK parameter/ Inhaled dose (mg)

15.6.4. Pharmacodynamic

The V_T and SUV are already derived. These endpoints will be further natural log-transformed.

15.7. Appendix 7: Reporting Standards for Missing Data

15.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion is defined as a subject having reached Last Subject Last Visit (LSLV) at the end of Dosing Period 2 in Cohort 1. • Withdrawn subjects will be replaced in the study if they withdraw before successful completion of the 30mins PET scan in Dosing Period 2 of Cohort 1. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

15.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated using a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
PK	• Adjustments to the derivation of PK parameters where NQ values are present in the data will be performed according to how extensive the NQ values are and which treatment groups the NQ's are present in. Refer to the Standards for the Handling of NQ impacted PK Parameters documentation.
PET	• Missing PET measurements will not be imputed.

15.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day: First of the month will be used unless this

Element	Reporting Detail
	is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

15.7.2.2. Handling of Missing Data for Statistical Analysis

For statistical analysis purposes, data will be assumed to be Missing at Random (MAR) and no imputation will be conducted.

15.8. Appendix 8: Values of Potential Clinical Importance

15.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Haemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		30	
Calcium	mmol/L		2	2.75
Creatinine	umol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	2x ULN
AST/SGOT	U/L	High	2x ULN
AlkPhos	U/L	High	2x ULN
T Bilirubin	µmol/L	High	1.5xULN
T. Bilirubin + ALT	µmol/L	High	1.5xULN T. Bilirubin +

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
	U/L		2x ULN ALT

15.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		>60

15.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg		≥ 40		≥ 40
Diastolic Blood Pressure	mmHg		≥ 20		≥ 20
Heart Rate	bpm		≥ 30		≥ 20

15.9. Appendix 11: Abbreviations & Trade Marks

15.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
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)
$AUC_{(0-inf)}$	Area under the plasma concentration-time curve from zero (0) hours (to infinity (inf)
BMI	Body mass index
BQL	Below the quantification limit
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	Maximum observed plasma drug concentration
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CPSR	Clinical Pharmacology Study Report
CPSSO	Clinical Pharmacology Science and Study Operations
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
D	Dose
DM	Data Management
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FEV_1	Forced Expiratory Volume in 1 second

Abbreviation	Description
FVC	Forced Vital Capacity
GCSP	Global Clinical Safety & Pharmacovigilance
GSK	GlaxoSmithKline
µg	Microgram
HPD	Highest Posterior Density
HR	Heart rate
HRCT	High Resolution Computerised Tomography
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
ITT	Intent-To-Treat
λz	Terminal phase rate constant
LLQ	Lower limit of quantification
LSLV	Last Subject Last Visit
MCMC	Markov Chain Monte Carlo
MMRM	Mixed Model Repeated Measures
MCSE	Monte Carlo Standard Errors
msec	Milliseconds
mcg	Microgram
microRNA	Micro Ribonucleic acid
mRNA	Messenger Ribonucleic acid
NONMEM	Nonlinear Mixed Effects Modelling
NQ	Non-quantifiable concentration measured as below LLQ
PCI	Potential Clinical Importance
PCPS	Projects Clinical Platforms and Sciences
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PET	Positron Emission Tomography
PK	Pharmacokinetic
PKPD	Pharmacokinetic Pharmacodynamic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RandAll NG	RandAll New Generation
RAP	Reporting & Analysis Plan
RAMOS	Randomisation & Medication Ordering System
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event

Abbreviation	Description
SAS	Statistical Analysis Software
SI	System Independent
SD	Standard deviation
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SDTM IG	Standard Data Tabulation Model Implementation Guide
SOA	Schedule of Activities
SOP	Standard Operation Procedure
SUV	Standardised Uptake Values
T	Infusion duration
TA	Therapeutic Area
TAU	Therapeutic Area Unit
TFL	Tables, Figures & Listings
t OR tlast	Time of last observed quantifiable concentration
$t_{½}$	Terminal phase half-life
τ	Dosing interval
tlag	Lag time before observation of drug concentrations in sampled matrix
T_{max}	Time of occurrence of C_{max}
ULQ	Upper limit of quantification
ULN	Upper limit of normal
UK	United Kingdom
VC	Variance-Covariance
VS	Vital Signs
V_T	Volume of distribution
WBC	While Blood Cell Count

15.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

15.10. Appendix 12: List of Data Displays

15.10.1. Data Display Numbering

All data displays will combine Dosing Period 1 and Dosing Period 2 unless this has been explicitly described otherwise or the actual data display requires Dosing Period 1 and Dosing Period 2 as separate rows. For the interim analyses subject randomisation numbers were scrambled when individual data was shown while for the final analyses after breaking study blind actual randomisation numbers will be shown

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.16	N/A
Safety	2.1 to 2.12	2.1 to 2.4
Pharmacodynamic	3.1 to 3.8	3.1 to 3.8
Pharmacokinetic	4.1 to 4.3	4.1 to 4.4
Section	**Listings**	
ICH Listings	1 to 29	
Other Listings	30 to 41	

15.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacodynamic	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

15.10.3. Deliverables

Delivery [Priority] [1]	Description
IA SAC	Interim Analysis Statistical Analysis Complete
SAC	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

15.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	ES1	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.3.	ITT	ES4	Summary of Participant Disposition at Each Study Epoch	ICH E3	SAC
1.4.	All Participants	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.5.	Enrolled	NS1	Summary of Number of Participants by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.6.	All Participants	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.7.	All Participants	SP1	Summary of Study Populations	IDSL	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	All Participants	SP2	Summary of Exclusions from the Per Protocol Population	IDSL	SAC
Demographic and Baseline Characteristics					
1.9.	PP	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.10.	PP	DM11	Summary of Age Ranges	EudraCT	SAC
1.11.	PP	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.12.	ITT	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.13.	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
1.14.	Enrolled	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
Prior and Concomitant Medications					
1.15.	ITT	MH1	Summary of Current/Past Medical Conditions	ICH E3	SAC
1.16.	ITT	CM1	Summary of Concomitant Medications	ICH E3	SAC

15.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	ITT	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3, Overall and by Dosing period (Dosing Period 1, Dosing Period 1 follow up, Dosing Period 2 and Dosing Period 2 follow up)	SAC
2.2.	ITT	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3, Overall and by Dosing period (Dosing Period 1, Dosing Period 1 follow up, Dosing Period 2 and Dosing Period 2 follow up) As 2.1 notes	SAC
Laboratory: Chemistry					

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	ITT	LB1	Summary of Chemistry Changes from Baseline	ICH E3, By treatment and by Dosing period (Period 1, Period 2) Includes Baseline values. Includes pre-specified parameters repeated in conventional units.	SAC
Laboratory: Hematology					
2.4.	ITT	LB1	Summary of Hematology Changes from Baseline	ICH E3, By treatment and by Dosing period (Period 1, Period 2) Includes baseline values.	SAC
Laboratory: Urinalysis					
2.5.	ITT	UR3b	Summary of Urinalysis Dipstick Results by Planned Timepoint	ICH E3, By treatment and by Dosing period (Period 1, Period 2) Includes Baseline values.	SAC
ECG					

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	ITT	EG1	Summary of ECG Findings	IDSL, By treatment and by Dosing period (Period 1, Period 2) As above for Chemistry, using ECG findings categories (and change from baseline categories, if applicable).	SAC
2.7.	ITT	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL, By treatment and by Dosing period (Period 1, Period 2) Includes Baseline values.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
2.8.	ITT	VS1	Summary of Change from Baseline in Vital Signs	ICH E3, By treatment and by Dosing period (Period 1, Period 2) Includes Baseline values.	SAC
Lung Function Tests: (FEV_1, % Predicted FEV_1, FVC and % Predicted FVC)					
2.9.	ITT	PFT1	Summary of Pulmonary Function Test Data	Absolute and % Predicted, by Visit	SAC
2.10.	ITT	PFT3	Summary of Change from Baseline Pulmonary Function Test Data	Absolute and % Predicted, by Visit	SAC
Diffusing capacity of the lungs for carbon monoxide (DLCO) and % Predicted DLCO					
2.11.	ITT	PFT1	Summary of Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO).	Absolute and % Predicted, by Visit	SAC
2.12.	ITT	PFT3	Summary of Change from Baseline Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO).	Absolute and % Predicted,	SAC

15.10.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Lung Function Tests (FEV_1, % Predicted FEV_1, FVC and % Predicted FVC)					
2.1.	ITT	PK16a	Individual Patient Profiles of Pulmonary Function Test Data	Longitudinal patient profile (y axis is the response and x axis the Visit). All patients in the same plot. Linear Plot only. By endpoint and Dosing Period, add separate colours for GSK3008348 1000mcg or Placebo.	SAC
2.2.	ITT	PK16a	Individual Patient Profiles of Change from Baseline Pulmonary Function Test Data	Longitudinal patient profile (y axis is the response and x axis the Visit). All patients in the same plot. Linear Plot only. By endpoint and Dosing Period, add separate colours for GSK3008348 1000mcg or Placebo.	SAC
Diffusing capacity of the lungs for carbon monoxide (DLCO) and % Predicted DLCO					
2.3.	ITT	PK16a	Individual Patient Profiles of Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO),	Longitudinal patient profile (y axis is the response and x axis the Visit). All patients in the same plot. Linear Plot only. By endpoint and Dosing Period, add separate colours for GSK3008348 1000mcg or Placebo.	SAC

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.4.	ITT	PK16a	Individual Patient Profiles of Change from Baseline Diffusing Capacity of the Lungs for Carbon Monoxide Changes from Baseline (DLCO)	Longitudinal patient profile (y axis is the response and x axis the Visit). All patients in the same plot. Linear Plot only. By endpoint and Dosing Period, add separate colours for GSK3008348 1000mcg or Placebo.	SAC

15.10.7. Pharmacodynamic Tables

Pharmacodynamic Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Volume of Distribution (V_T, mL/cm^3)					
3.1.	PP	Non-Standard PD_T1	Summary of Volume of Distribution (V_T, mL/cm^3) of [18F]-FBA-A20FMDV2 not Corrected for Air Volume.	Summary statistics by visit	IA SAC, SAC
3.2.	PP	Non-Standard PD_T2	Summary of Volume of Distribution (V_T, mL/cm^3) of [18F]-FBA-A20FMDV2 Corrected for Air Volume.	Summary statistics by visit	SAC
3.3.	PP	Non-Standard PD_T3	Summary of Statistical Analysis of Volume of Distribution (V_T, mL/cm^3) of [18F]-FBA-A20FMDV2 not Corrected for Air Volume (Cohort 1, GSK3008348 1000mcg).	Excludes placebo group Footnote table with details of the model, covariates and priors, etc.	IA SAC, SAC

Pharmacodynamic Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.4.	PP	Non-Standard PD_T4	Summary of Statistical Analysis of Volume of Distribution (V_T, mL/cm^3) of [18F]-FBA-A20FMDV2 Corrected for Air Volume (Cohort 1, GSK3008348 1000mcg).	Excludes placebo group Footnote table with 'The covariates: sex, age, baseline % predicted FVC and baseline % predicted DLCO were independently considered in the model *but all were removed because the HPD CrI includes 0*.	SAC

Pharmacodynamic Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Standardised Uptake Values (SUV, g/mL)					
3.5.	PP	Non-Standard PD_T1	Summary of Standardised Uptake Values (SUV, g/mL) of [18F]-FBA-A20FMDV2 not Corrected for Air Volume.	Summary statistics by visit	SAC
3.6.	PP	Non-Standard PD_T2	Summary of Standardised Uptake Values (SUV, g/mL) of [18F]-FBA-A20FMDV2 Corrected for Air Volume.	Summary statistics by visit	SAC
3.7.	PP	Non-Standard PD_T3	Summary of Statistical Analysis for Standardised Uptake Values (SUV, g/mL) of [18F]-FBA-A20FMDV2 not Corrected for Air Volume (Cohort 1, GSK3008348 1000mcg).	Excludes placebo group Footnote table with; 'The covariates: sex, age, baseline % predicted FVC and baseline % predicted DLCO were independently considered in the model *but all were removed because the HPD CrI includes 0.*	SAC

Pharmacodynamic Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.8.	PP	Non-Standard PD_T4	Summary of Statistical Analysis for Standardised Uptake Values (SUV, g/mL) of [18F]-FBA-A20FMDV2 Corrected for Air Volume (Cohort 1, GSK3008348 1000mcg).	Excludes placebo group Footnote table with; 'The covariates: sex, age, baseline % predicted FVC and baseline % predicted DLCO were independently considered in the model *but all were removed because the HPD CrI includes 0.*	SAC

15.10.8. Pharmacodynamic Figures

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Volume of Distribution (V_T, mL/cm^3)					
3.1	PP	Non-Standard PD_F1	Plot of Unadjusted Geometric Means (95% CI) of Volume of Distribution (V_T, mL/cm^3) of [^{18}F]-FBA-A20FMDV2 not Corrected for Air Volume.	Plot for GSK3008348 1000mcg arm only with raw data superimposed. Also add raw placebo data in different colour on the same graph. Placebo subject's data should be jittered on the x axis and with a different symbol. Individual subject numbers were scrambled at interim analysis only, so treatment allocation was not obvious but after unblinding they will be unscrambled for final analyses + the interim outputs. Add footnote: 1. Note: Pre-dose = Baseline PET, PET1= 20-60 mins and PET2= 14-28 hrs PET 2. Unadjusted Geometric Means (95% CI) from GSK3008348 1000mcg arm only.	IA SAC, SAC

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.2	PP	Non-Standard PD_F2	Plot of Adjusted Medians and Adjusted Median Ratios of Volume of Distribution (V_T, mL/cm^3) of [^{18}F]-FBA-A20FMDV2 not Corrected for Air Volume.	Add different colours for GSK3008348 1000mcg and placebo patients. Individual subject numbers were scrambled at interim analysis only, so treatment allocation was not obvious but after unblinding they will be unscrambled for final analyses + the interim outputs. Add footnote: 1. Note: Pre-dose = Baseline PET, PET1= 20-60 mins and PET2= 14-28 hrs PET 2. Unadjusted Geometric Means (95% CI) from GSK3008348 1000mcg arm only. Footnote added: 'The covariates: sex, age, baseline % predicted FVC and baseline % predicted DLCO were independently considered in the model but all were removed because the HPD CrI includes 0'.	IA SAC, SAC

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.3	PP	Non-Standard PD_F3	Plot of Unadjusted Geometric Means (95% CI) of Volume of Distribution (V_T, mL/cm^3) of [^{18}F]-FBA-A20FMDV2 Corrected for Air Volume.	Plot for GSK3008348 1000mcg arm only with raw data superimposed. Also add raw placebo data in different colour on the same graph. Placebo subject's data should be jittered on the x axis and with a different symbol. Individual subject numbers were scrambled at interim analysis only, so treatment allocation was not obvious but after unblinding they will be unscrambled for final analyses + the interim outputs. Add footnote: 1. Note: Pre-dose = Baseline PET, PET1= 20-60 mins and PET2= 14-28 hrs PET 2. Unadjusted Geometric Means (95% CI) from GSK3008348 1000mcg arm only.	SAC

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.4	PP	Non-Standard PD_F4	Plot of Adjusted Medians and Adjusted Median Ratios of Volume of Distribution (V_T, mL/cm^3) of [^{18}F]-FBA-A20FMDV2 Corrected for Air Volume.	Add different colours for GSK3008348 1000mcg and placebo patients. Placebo subject's data should be jittered on the x axis and with a different symbol. Individual subject numbers were scrambled at interim analysis only, so treatment allocation was not obvious but after unblinding they will be unscrambled for final analyses + the interim outputs. Add footnote: 1. Note: Pre-dose = Baseline PET, PET1= 20-60 mins and PET2= 14-28 hrs PET 2. Unadjusted Geometric Means (95% CI) from GSK3008348 1000mcg arm only. Add footnote: 'The covariates: sex, age, baseline % predicted FVC and baseline % predicted DLCO were independently considered in the model but all were removed because the HPD CrI includes 0'.	SAC

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Standardised Uptake Values (SUV, g/mL)					
3.5	PP	Non-Standard PD_F1	Plot of Unadjusted Geometric Means (95% CI) of Standardised Uptake Values (SUV, g/mL) of [^{18}F]-FBA-A20FMDV2 not Corrected for Air Volume.	Plot for GSK3008348 1000mcg arm only with raw data superimposed. Also add raw placebo data in different colour on the same graph. Placebo subject's data should be jittered on the x axis and with a different symbol. Individual subject numbers were scrambled at interim analysis only, so treatment allocation was not obvious but after unblinding they will be unscrambled for final analyses + the interim outputs. Add footnote: 1. Note: Pre-dose = Baseline PET, PET1= 20-60 mins and PET2= 14-28 hrs PET 2. Unadjusted Geometric Means (95% CI) from GSK3008348 1000mcg arm only.	SAC

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6	PP	Non-Standard PD_F2	Plot of Adjusted Medians and Adjusted Median Ratios of Standardised Uptake Values (SUV, g/mL) of [^{18}F]-FBA-A20FMDV2 not Corrected for Air Volume.	Add different colours for GSK3008348 1000mcg and placebo patients Add footnote: 'The covariates: sex, age, baseline % predicted FVC and baseline % predicted DLCO were independently considered in the model but all were removed because the HPD CrI includes 0'.	SAC
3.7	PP	Non-Standard PD_F3	Plots of Unadjusted Geometric Means (95% CI) of Standardised Uptake Values (SUV, g/mL) of [^{18}F]-FBA-A20FMDV2 Corrected for Air Volume.	Plot for GSK3008348 1000mcg arm only with raw data superimposed. Also add raw placebo data in different colour on the same graph. Placebo subject's data should be jittered on the x axis and with a different symbol. Individual subject numbers were scrambled at interim analysis only, so treatment allocation was not obvious but after unblinding they will be unscrambled for final analyses + the interim outputs. Add footnote: 1. Note: Pre-dose = Baseline PET, PET1= 20-60 mins and PET2= 14-28 hrs PET 2. Unadjusted Geometric Means (95% CI) from GSK3008348 1000mcg arm only.	SAC

Pharmacodynamic Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.8	PP	Non-Standard PD_F4	Plot of Adjusted Medians and Adjusted Median Ratios of Standardised Uptake Values (SUV, g/mL) of [^{18}F]-FBA-A20FMDV2 Corrected for Air Volume.	Add different colours for GSK3008348 1000mcg and placebo patients Add footnote: 'The covariates: sex, age, baseline % predicted FVC and baseline % predicted DLCO were independently considered in the model but all were removed because the HPD CrI includes 0'.	SAC

15.10.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK	PK01	Summary of Plasma GSK3008348 Pharmacokinetic Concentration-Time Data (µg /mL)	By Dosing Period	SAC
PK Derived Parameters					
4.2.	PK	PK03	Summary Statistics of Derived Plasma GSK3008348 Pharmacokinetic Parameters	Parameters with units, By Dosing Period	IA SAC, SAC
4.3.	PK	PK05	Summary Statistics of Log-Transformed Derived Plasma GSK3008348 Pharmacokinetic Parameters	Parameters with units, By Dosing Period	SAC

15.10.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Plots					
4.1.	PK	PK16a	Individual GSK3008348 Plasma Concentration-Time Plot by Subject (Linear and Semi-Log)	By Dosing Period, both periods are on same plot i.e. 1 graph per subject with 2 curves (Period 1 and Period 2)	SAC
4.2.	PK	PK16a	Individual GSK3008348 Plasma Concentration-Time Plot (Linear and Semi-Log)	By Dosing Period. All Subjects on the same plot. For interim individual subject numbers will be scrambled so treatment allocation is not obvious	IA SAC, SAC
Mean / Median Plots					
4.3.	PK	PK17	Mean (+ SD) Plasma GSK3008348 Concentration-Time Plots (Linear and Semi-log)	By Dosing Period (Replace treatment by Dosing Period and the two Dosing Periods on same plot).	SAC
4.4.	PK	PK18	Median Plasma GSK3008348 Concentration-Time Plots Linear and Semi-log)	By Dosing Period (Replace treatment by Dosing Period in the plots)	SAC

15.10.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Participants	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	ITT	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3 Required for all studies except single dose studies.	SAC
4.	ITT	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3 Blinded studies only.	SAC
5.	ITT	TA1	Listing of Planned and Actual Treatments	IDSL Note: IDSL shell in development.	SAC
Protocol Deviations					
6.	All Participants	DV2	Listing of Important Protocol Deviations	ICH E3 Listing also includes analysis population exclusions.	SAC
7.	All Participants	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Populations Analysed					
8.	All Participants	SP3	Listing of Participants Excluded from Any Population	ICH E3 e.g., participants screened but not randomized, participants randomized but not treated, participants with deviations leading to exclusion from per protocol population (can be separate listing per population).	SAC
Demographic and Baseline Characteristics					
9.	ITT	DM2	Listing of Demographic Characteristics	ICH E3	SAC
10.	Enrolled	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
11.	ITT	CP_CM3	Listing of Concomitant Medications	IDSL Note: IDSL shell in development. Required for ClinPharm studies instead of a corresponding table. Not required for studies where a table is produced.	SAC
Exposure and Treatment Compliance					
12.	ITT	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
13.	ITT	AE8	Listing of All Adverse Events	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
14.	ITT	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
15.	ITT	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
16.	ITT	AE8	Listing of Fatal & Non-Fatal Serious Adverse Events	ICH E3 Fatal and Non-Fatal SAEs are combined into a single listing.	SAC
17.	ITT	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
Hepatobiliary (Liver)					
18.	ITT	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
19.	ITT	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC
All Laboratory					
20.	ITT	LB5	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	Display ALL labs for a subject who experienced a value Outside Normal Range.	SAC
21.	ITT	LB5	Listing of Laboratory Values of Potential Clinical Importance	IDSL	SAC
22.	ITT	UR2A	Listing of All Urinalysis Results.	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
23.	ITT	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	Display ALL ECGs for a subject who experienced a value of potential clinical importance.	SAC
24.	ITT	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
25.	ITT	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
26.	ITT	EG5	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
27.	ITT	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	Display ALL Vital Signs for a subject who experienced a value of potential clinical importance.	SAC
28.	ITT	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC
Immunogenicity					
29.	ITT	IMM1	Listing of Immunogenicity Results	IDSL	SAC

15.10.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Peripheral capillary oxygen saturation (SpO2)					
30.	ITT	Non-Standard SAFE_L1	Listings of Oxygen Saturation Monitoring (SpO2) Results	Sorted by subject id	SAC
Forced Expiratory Volume (FEV_1) and Forced Vital Capacity (FVC)					
31.	ITT	PFT8	Listings of Pulmonary Function Test Data	Sort by subject id and PFT test	SAC
Diffusing capacity of the lungs for carbon monoxide (DLCO)					
32.	ITT	PFT8	Listing of Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO)	Sort by subject id	SAC
Pharmacodynamic					
33.	ITT	Non-Standard SAFE_L2	Listing of [18F]-FBA-A20FMDV2 Administration		SAC
34.	PP	Non-Standard SAFE_L3	Listing of All PET Data	Sort by subjid	SAC
35.	ITT	Non-Standard SAFE_L3	Listing of All PET Data	Sort by subjid. This listing includes the extra subject with baseline PET data only and was not in the PP in listing 34.	SAC
Pharmacokinetic					
36.	ITT	PK07	Listing of Pharmacokinetic Concentration-Time Data.	Sort by subjid	SAC
37.	ITT	PK13	Listing of Derived Pharmacokinetic Parameters.	Sort by subjid	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
38.	ITT	Non-Standard SAFE_L4	Listing of the Final Output of the Statistical Analysis of Volume of Distribution (V_T, mL/cm^3) not Corrected for Air Volume of [^{18}F]-FBA-A20FMDV2 from the Bayesian Analysis Model Using PROC MCMC in SAS Assuming Non-Informative Prior Distributions.	A dump of the Proc MCMC plots from the final Bayesian analysis model, raw SAS outputs Scans will be labelled as 'Pre-dose, PET1 and PET2'	IA SAC, SAC
39.	ITT	Non-Standard SAFE_L4	Listing of the Final Output of the Statistical Analysis of Volume of Distribution (V_T, mL/cm^3) Corrected for Air Volume of [^{18}F]-FBA-A20FMDV2 from the Bayesian Analysis Model Using PROC MCMC in SAS Assuming Non-Informative Prior Distributions.	A dump of the Proc MCMC plots from the final Bayesian analysis model, raw SAS outputs Sort By endpoint as follows; Scans will be labelled as 'Pre-dose, PET1 and PET2'	SAC
40.	ITT	Non-Standard SAFE_L4	Listing of the Final Output of the Statistical Analysis of Standardised Uptake Values (SUV, g/mL) not Corrected for Air Volume of [^{18}F]-FBA-A20FMDV2 from the Bayesian Analysis Model Using PROC MCMC in SAS Assuming Non-Informative Prior Distributions.	A dump of the Proc MCMC plots from the final Bayesian analysis model, raw SAS outputs; Scans will be labelled as 'Pre-dose, PET1 and PET2'	SAC
41.	ITT	Non-Standard SAFE_L4	Listing of the Final Output of the Statistical Analysis of Standardised Uptake Values (SUV, g/mL) Corrected for Air Volume of [^{18}F]-FBA-A20FMDV2 from the Bayesian Analysis Model Using PROC MCMC in SAS Assuming Non-Informative Prior Distributions.	A dump of the Proc MCMC plots from the final Bayesian analysis model, raw SAS outputs; Scans will be labelled as 'Pre-dose, PET1 and PET2'	SAC

15.11. Appendix 13: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.