Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 201928: A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).
Compound Number	:	GSK2269557
Effective Date	:	09-JAN-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201928.
- This RAP is intended to describe the pharmacodynamic/biomarker, safety, pharmacokinetic and efficacy analyses required for the study.
- This version of the RAP includes amendments to the originally approved RAP.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

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PPD Statistician (Clinical Statistics)

RAP Team Review Confirmation:

Approver	Date	Approval Method
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Approver	Date	Approval Method
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
GlaxoSmithKline Document Number	**Date**	**Version**
2014N218070_00	2015-JUN-04	Original
2014N218070_01	2015-NOV-30	Amendment No. 1
Remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria and in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. It therefore is not valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.		
2014N218070_02	2016-JAN-26	Amendment No. 2
Increase the body mass index (BMI) range in the inclusion criteria from 18-32 kg/m^2 (inclusive) to 16- 35 kg/m^2 (inclusive). The original BMI range from 18-32 kg/m^2 is a typical range used in both healthy volunteer studies and general subject populations. The revised range is more appropriate for a COPD patient population.		
2014N218070_03	2016-NOV-16	Amendment No. 3
To remove photo toxicity from the protocol and to include minor administrative and clarification changes.		
2014N218070_04	2017-MAR-2	Amendment No. 4
Replace the administration of GSK2269557 via the DISKUS™ device (1000 µg) by a comparable dose administered via the ELLIPTA™ device (700 µg). GSK2269557 is no longer manufactured for use with the DISKUS device which will be replaced with ELLIPTA Device. To increase the number of patients to be recruited to obtain sufficient completers. Minor updates and clarifications.		

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

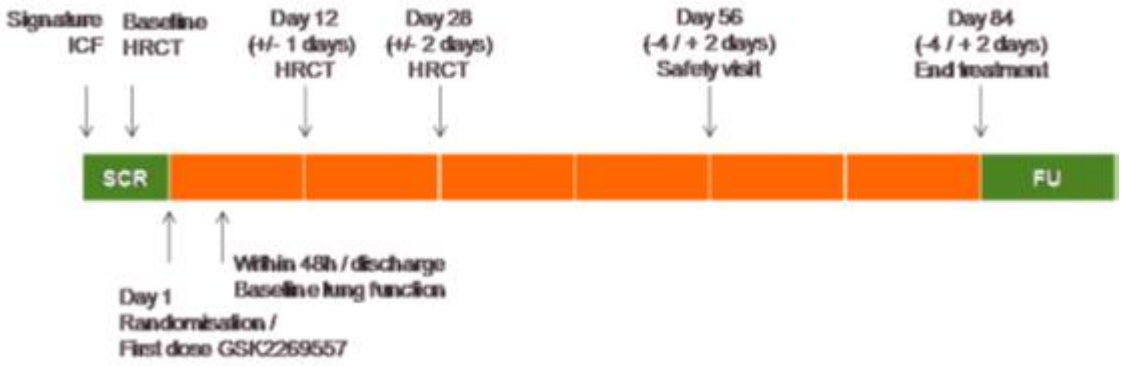
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Total lung capacity and lung lobar volumes included in HRCT secondary endpoint parameters	• Total lung capacity and lung lobar volumes dropped from HRCT secondary endpoint parameters included as an exploratory endpoint parameter instead	• The clinically relevant HRCT parameters are still to be decided. However, there was no clinical benefit seen in the comparison between GSK2269557 1000 mcg and Placebo in these parameters.

• Analysis population:
  • All Subject
  All randomised subjects who receive at least one dose of the study treatment.
  This population will be based on the
  treatment the subject actually received.
  • Pharmacokinetic
  Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.
	• Analysis population:
	  • All Subject
	  All randomised subjects who receive at least one dose of the study treatment.
	  This population will be based on the
	  treatment the subject actually received.
	  • Pharmacokinetic
	  Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.
	Note: The two subjects who were not compliant with inhaler instructions will be excluded from the outcome summaries if they received active treatment but will be included if they received placebo
		• 2 subjects were not compliant with inhaler instructions and may not have received the full dose in amendment 4. Therefore, these subjects will be excluded from the outcome summaries if they received active treatment but will be included if they received placebo. Sensitivity analyses may be conducted including these subjects.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline in siVaw, iVaw, iRaw, siRaw, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Haematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD.	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients. • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.	• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.
Exploratory Objectives	**Exploratory Endpoints**
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 qPCR.
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Multi-centre and Multi-Country • Randomised • Double-blind • Placebo-controlled • Parallel group
Dosing	• Once daily, in the morning for 84 days • Administered through the Diskus dry powder Inhaler
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Initially planned for approximately 30 subjects randomised to receive either 1000 μg GSK2269557 (Diskus) or matching Placebo in a 1:1 ratio as it was anticipated that 10 patients would drop-out. Twenty-eight subjects were randomised to this schedule, however, due to expiration date there was a protocol amendment following which additional subjects were subsequently randomised to receive either 700 μg GSK2269557 (Ellipta) or matching Placebo (Ellipta) in a 1:1 ratio. The protocol was updated such that approximately 45 subjects with an acute exacerbation of COPD would be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. • Subjects are assigned to treatment in accordance with the randomisation schedule generated by Clinical Statistics, using validated software.
Interim Analysis	• No formal interim analysis will be conducted

2.4. Statistical Analyses

2.4.1. Primary Analyses

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

Further details are provided in Section 7.1.

3. PLANNED ANALYSES

3.1. 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 Enrolled (APE)	• All subjects who were screened for eligibility	• Study Population

All Subjects	• Comprised of all subjects who were randomised.
	• This population will be based on the treatment the subject actually received.
	  ○ If participants receive >1 treatment, then they will be summarised according to the most frequently dosed treatment. In cases where the frequency is equal, the participant will be assigned the lowest dose strength of nemiralisib.
	  ○ If participants receive no treatment, then they will be summarised according to “No Treatment”
		• Study Population
		• Pharmacodynamics and Biomarker
		• Safety
		• Efficacy

Pharmacokinetic (PK)	• Subjects in the ‘All Subjects’ population for whom a pharmacokinetic sample was obtained and analysed.	• PK

Refer to Appendix 10: List of Data Displays which details the population used for each display.
Note: The two subjects who were not compliant with inhaler instructions will be excluded from the outcome summaries if they received active treatment but will be included if they received placebo

4.1. Protocol Deviations

During the course of the study it was noted that two subjects did not complete dosing instructions as required. The primary plan is if the subjects received active treatment they will be excluded from the study outcome summaries; if the subject received placebo treatment, they will be included in the study outcome summaries. It has not yet been identified if they received placebo or active treatment. A footnote will be applied to all relevant displays stating the rationale, subject number, treatment and if they were excluded, e.g. “Subjects X & Y did not complete dosing instructions as required; subject X received nemiralisib and was therefore excluded, subject Y received placebo and was therefore included.” The footnote may be tweaked for aesthetic purposes.

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.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan, refer to Appendix 1.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations 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.

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
This will be derived as subjects who did not receive any treatment		No Treatment	1
This will be derived as subjects in RandALL codes A or C		All Placebo	2
This will be derived as subjects in RandALL codes B or D		All NEMI	3
A	Placebo	Placebo Diskus	4
B	GSK2269557 1000 mcg	NEMI Diskus	5
C	Placebo via Ellipta	Placebo Ellipta	6
D	GSK2269557 700 mcg	NEMI Ellipta	7

NOTES:

1. The following footnote will be presented on displays which use the "Placebo Diskus", "NEMI Diskus", "Placebo Ellipta" or "NEMI Ellipta" treatment groups:
   NEMI Diskus =1000 mcg Nemiralisib administered via the Diskus device; NEMI Ellipta =700 mcg Nemiralisib administered via the Ellipta device
2. Order represents treatments being presented in TFL, as appropriate

Treatment groups "Placebo" and "Placebo via Ellipta" (RandAll NG codes A and C) will be combined into "All Placebo" treatment group. Similarly, treatment groups "GSK2269557 700 mcg" and "GSK2269557 1000 mcg" (RandAll NG codes B and D) will be combined into "All NEMI" treatment group.

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. All NEMI vs All Placebo

Notes:

- The "All Placebo" and "All NEMI" groups and "All NEMI vs All Placebo" treatment comparison will be presented for Pharmacodynamic and biomarker, efficacy and study population summaries unless otherwise specified.
- The "Placebo Diskus", "NEMI Diskus", "Placebo Ellipta" or "NEMI Ellipta" treatment groups will be presented for Pharmacokinetic and safety summaries unless otherwise specified.
- The "Placebo Diskus", "NEMI Diskus", "Placebo Ellipta" or "NEMI Ellipta" treatment groups will be presented for all listings

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 Assessments Considered as Baseline				Baseline Used in Data Display
	Screening	Day 1 (Pre-Treatment)	Day 2 Within 48H/discharge (On Treatment)	Day 12 (On Treatment)	
Safety					
Labs including Haematology	X	X			Day 1
ECG	X	X			Day 1
Vitals	X	X			Day 1
Efficacy					
HRCT Untrimmed	X				Screening
HRCT Scan Trimmed					
Screening&Day12	X				Screening
Screening&Day28	X				Screening
Day12&Day28				X	Day 12
FEV_1 and FVC		X	X		Day 1[1]
Daily PEF [2]		X			Day 1
					Mean of Days 1 to 3
					Maximum of Days 1 to 3
Pharmacodynamic					
Sputum and Blood	X				Screening
Genetic sample (PGx) [3]			X		

NOTES:

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- [1] Baseline will be investigated to ensure there is sufficient data and will be footnoted as appropriate
- [2] For PEF 3 different baselines will be calculated: Day 1, mean of Days 1 to 3 and Maximum of Days 1 to 3. TFLs will be footnoted with the relevant baseline.
- [3] Collected at any time after randomisation

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Examination of Covariates and Subgroups

5.3.1. Covariates and Other Strata

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

Category	Details
Covariates	Age, Sex, BMI, Country, Primary exacerbation severity

5.3.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Primary exacerbation severity	Moderate or Severe [1]
Country	Country

NOTES:
[1] Exacerbations are defined as severe if they require hospitalisation, otherwise they are defined as moderate

5.4. 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
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	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 "All Subjects" 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 10: List of Data Displays.

7. PHARMACODYNAMIC AND BIOMARKER ANALYSES

7.1. Primary Pharmacodynamic and Biomarker Analyses

7.1.1. Endpoint / Variables

Sputum RNA will be extracted and hybridised using a balanced batch design. An appropriate microarray platform will be determined at the time of hybridisation, to allow for improvements in technology. The quality of the data will be assessed and then normalised using appropriate methodologies and software.

Microarray mRNA data will be normalised using gcRMA or RMA in Array Studio v5.0 or later. After normalisation, the data will be quality assessed and any samples deemed as QC fails will be excluded from any further analysis. This quality assessment will involve looking for outlying signals in both the normalised expression data and the MAS5 QC metrics generated from each sample. If any samples are excluded, the remaining data will be re-normalised. The output from the normalisation will be log2 transformed mRNA intensity data (measured in arbitrary units).

Since the data will be log2 transformed prior to the analysis the treatment effects will be expressed as ratios after back transformation (2^). These ratios can be converted to fold change values as follows:

- If ratio ≥ 1 then fold change = ratio
- If ratio <1 then fold change = -1/ratio

Microarray data consists of expression values (log2-transformed) derived from individual probe sets designed against coding regions of individual genes. More than one probe set can exist per gene. This analysis will be conducted at the probe set level.

The mRNA data gives results from ~14000 genes encoded by ~54000 probe sets. To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA, we identified 258 gene to subset our data on, refer to Section 13.6.5. The gene names were converted to Affymetrix probe IDs, this resulted in 638 probes refer to Section 13.6.5.

To compare the expression value between treatments for each probe set, linear repeated measures mixed effects model will be fitted to each probe set, with log2 (intensity) as the response variable. Note: log2 (intensity) may also be referred to as mRNA intensities (logarithm base 2 scale). Alteration in previously identified immune cell mechanisms specifically related to neutrophil function will be determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment by the analysis of mRNA intensities (logarithm base 2 scale) subset by the 638 probes identified in Section 13.6.5.

7.1.2. Summary Measure

A repeated measures modelling analysis will be performed on the subset of 638 probes which have previously identified immune cell mechanisms specifically related to neutrophil function.

The model will be used to estimate the baseline adjusted fold changes for active treatment and placebo calculated for Day 12, Day 28 and Day 84 along with the corresponding 95% confidence intervals and unadjusted P-values. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals and unadjusted P-values.

7.1.3. Population of Interest

The primary pharmacodynamic analyses will be based on the "All Subjects" population, unless otherwise specified.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: 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.

7.1.4.1. Statistical Methodology Specification

Endpoint / Variables
• Alterations in the previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment. The response variable will be mRNA intensities (logarithm base 2 scale).
Model Specification
The mRNA data gives results from ~14000 genes encoded by ~54000 probe sets. A subset of 638 probe sets specifically relating to the cell mechanisms of neutrophil function is specified in Section 13.6.5 This subset will comprise the primary statistical analysis dataset.

Each probe set will be analysed separately.

The log2 transformed mRNA intensities will be analysed in a repeated measures model under a Frequentist framework. The model will include a Treatment, Visit and Treatment*Visit term. The Visit will consist of 4 levels: Screening (Baseline), Day 12, Day 28 and Day 84, and the Treatment will consist of three levels: Null (when Visit = Screening), All Placebo and All NEMI. An unstructured (UN) covariance structure will be fitted. The denominator degrees of freedom for use in significance testing will be computed using the Kenward Rogers approximation.

Back transformed baseline-adjusted ratios along with 95% CIs and two-sided unadjusted p-values will be calculated for each Visit for the All NEMI and All Placebo Treatments, i.e. Day 84, Day 28 and Day 12 in the All NEMI Treatment group vs Screening and Day 84, Day 28 and Day 12 in the All Placebo Treatment group vs Screening. Additionally, baseline adjusted ratios between All NEMI vs All Placebo will be calculated for Day 12, Day 28 and Day 84 along with 95% CI and two-sided unadjusted p-values, i.e. Day 84 in the All NEMI Treatment group vs Day 84 in the All Placebo Treatment group, similarly for Day 28 and Day 12. Other comparisons of interest may also be calculated such as means for each Visit and Treatment, i.e. Screening (Null Treatment), Day 12, 28 and 84 (All NEMI Treatment) Day 12, 28 and 84 (All Placebo Treatment).

To enable review by the study team, csv files will be created containing the output for all probe sets in scope for the primary statistical analysis will be generated sorted alphabetically by probe set ID. Separate csv files may be created containing only probe sets where the p-value for the comparisons is <0.05. Such probe sets will be ranked by fold change, with the expectation that, in general, a greater than a 1.5-fold change is scientifically meaningful. To comply with guidance regarding QC, csv files will be stored as a SAS dataset to ensure QC can be audited.

Following review by the study team of the results, a subset of probe sets may be identified and may be used for further reporting.

Model Checking & Diagnostics

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying ‘type=UN’ on the REPEATED line.
    - In the event that this model fails to converge, alternative correlation structures may be considered

Model Results Presentation

Output from the repeated measures modelling detailed above will be tabulated.

In particular, the estimated baseline adjusted fold changes, 95% CI, standard error (on the logarithm base 2 scale), unadjusted p-values at each time point and for the active treatment comparison with placebo. The probe set, gene/gene description will be included in the outputs.

7.2. Exploratory Pharmacodynamic and Biomarker Analyses

7.2.1. Endpoint / Variables

In addition to the primary analysis, there is an exploratory objective to establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. To address this

blood and sputum mRNA data, as described in Section 7.1,but analyses will be conducted on the complete mRNA data, i.e. the results from ~14000 genes encoded by ~54000 probe sets.

To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Endpoints may include, but not limited to, cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, total cell counts and PMNs differentials.

To explore the pharmacodynamic effects in blood of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Endpoints may include, but not limited to, total cell counts and PMNs differentials.

7.2.2. Summary Measure

To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. A repeated measures modelling analysis will be performed on the complete probe set. The model will be used to estimate the baseline adjusted fold changes for active treatment and placebo calculated for Day 12, Day 28 and Day 84 along with the corresponding 95% confidence intervals and unadjusted P-values. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals and unadjusted P-values.

To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Summary statistics of endpoints may include, but not limited to, cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, total cell counts and PMNs differentials.

To explore the pharmacodynamic effects in blood of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Summary statistics of endpoints may include, but not limited to, total cell counts and PMNs differentials.

7.2.3. Population of Interest

The exploratory pharmacodynamic analyses will be based on the “All Subjects” population, unless otherwise specified.

As previously discussed for the two subjects that did not follow inhalation instructions, if the subjects received active treatment they will be excluded from the study outcome summaries; if the subject received placebo treatment, they will be included in the study outcome summaries.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Refer to Section 7.1.4.1 for statistical methodology specification, however, for the exploratory analysis, the models will be fitted but on the complete dataset ~14000 genes encoded by ~54000 probe sets; sputum and blood data will be analysed separately. Note: only a subset of the results will be presented as it is not feasible to present all ~54,000 probe sets for the sputum and blood data. Biostatistics will await guidance following unblinded regarding which, if any, probe sets should be presented for the exploratory analysis and confirmation if a cut off criteria other than p-value<0.05 AND (fold change> 1.5 OR fold change< -1.5) should be used in determining which comparisons for the probe sets should be presented.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. For each endpoint, the values will be inspected to determine whether a data transformation is required. It is expected that: cytokines may require a transformed on the natural logarithm scale

8. EFFICACY ANALYSES

8.1. Secondary Efficacy Analyses (Not From HRCT Analyses)

8.1.1. Endpoint / Variables

To evaluate the effect of once daily repeat inhaled doses of nemiralisib on lung function parameters in subjects with acute exacerbation of COPD compared to placebo. Lung function parameters including:

- PEF
- FEV_1 and FVC at clinic prior to sputum induction
- reliever usage

8.1.2. Summary Measure

For PEF, summary statistics for the change from baseline PEF will be presented in tabular form, mean and 95% CIs of AM PEF readings will be plotted by study treatment vs. Study Day.

For FEV_1 (L) and FVC (L), a change from baseline statistical analysis will be conducted and presented via tables of predicted adjusted medians for each Treatment arm at each visit, and the difference between treatment arms at each visit.

For reliever use, bronchodilator use recorded in the diary will be summarised as the mean number of occasions of rescue use per day and the percentage of rescue-free days in four-week interval periods as described in Section 13.6.3, where a rescue-free day is defined as a 24-hour period in which the number of occasions bronchodilator taken is zero. Summary tables will display estimates for each 4-weekly period for mean number of occasions of rescue use per day and percentage of rescue-free days separately.

8.1.3. Population of Interest

The primary efficacy analyses will be based on the "All Subjects" population, unless otherwise specified.

8.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.1.4.1. Statistical Methodology Specification

NOTE: The description below describes the current thinking of how to analyse these endpoints. The proposed models will be assessed, and if not appropriate alternative models could be used.

Endpoint / Variables
• FEV1 (L), FVC(L)
Model Specification
• The data will be inspected during statistical analysis to determine whether a data transformation is required. It is likely no transformations will be required • The analysis will include all available values. If there are values which were recorded within 4h after the subject had taken relief medication, a sensitivity analysis may be done which excludes these values. • The endpoints (FEV_1 and FVC) will be analysed in separate models. The change from baseline in the endpoint will be analysed in a Bayesian repeated measures model, with a baseline by Visit covariate and Treatment by Visit class parameter. Note that the model will not include an intercept. The Treatment will have two levels: All NEMI and All Placebo, and the Visit will have two levels: Day 28 and Day 84. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e. covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior. • The change from baseline at each of the Visits will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in a tabular format. • The difference between the treatment arms, for the change from baseline will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular format. • The probabilities that the treatment difference is greater or less than 0 (depending on direction of the endpoint), in addition to other values appropriately selected based on the data, will also be computed for each Visit. These results will be presented in tabular format.

Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. For example, if data do not approximately follow a normal distribution then attempt will be made to find a suitable transformation. • A comprehensive investigation into a suitable model should be initiated. For example, additional covariates will be investigated • An unstructured covariance structure will be used. However, in the event that this model fails to converge, alternative correlation structures may be considered. • Models with a Bayesian Framework will use vague priors. If appropriate, conjugate priors will be used. For example, for a multivariate model, the prior for the variance covariance matrix will be an inverse Wishart distribution.
Model Results Presentation
• Output from the repeated measures modelling detailed above will be tabulated. In particular, the estimated change from baseline, 95% CI, standard error, and posterior probabilities at each time point and for the active treatment comparison with placebo.
Subgroup Analyses
• For FEV1, a subgroup analysis will be conducted by index exacerbation severity (refer to Section 5.3 Examination of Covariates and Subgroups). A similar model as described in Model specification will be fitted but will also include a Severity*Treatment*Visit term within the model. • The results of the subgroup analysis will be reported in a separate table.

8.2. Secondary Efficacy Analyses (From HRCT Analyses)

8.2.1. Endpoint / Variables

To evaluate the effect of once daily repeat inhaled doses of nemiralisib on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo. Ratio from baseline in siVaw, iVaw, iRaw, siRaw, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.

8.2.2. Summary Measure

Each HRCT scan will be conducted at two lung volumes: total lung capacity (TLC) and functional residual capacity (FRC); these will be referred to as scan conditions. The HRCT images will be processed to derive the HRCT parameters at FRC and TLC, however these conditions are not applicable for all parameters.

The HRCT scans will be conducted at Screening, Day 12 and Day 28. The 3 HRCT images will then be processed to derive the HRCT parameters at each scan; this data will be referred to as the untrimmed data. The untrimmed data measures all airways that are present in each scan.

However partially due to positioning of subjects whilst taking a scan, it can be that some airways are visible in some scans and not in other scans. For these reasons, some HRCT

imaging endpoints will be calculated to include only airways that are visible in both scans. Therefore, the scans were grouped into three scan trimming pairs where, within each scan trimming pair, the airways that were not present in both scans were removed/trimmed.

The three scan trimming pairs, and subsequent timepoints, are:

- The scan trimming pair SCRD28, which contains the Screening (SCRD28:SCR) and Day 28 (SCRD28:D28) timepoints, where only airways that were present in both screening and day 28 scans are accounted for.
- The scan trimming pair SCRD12, which contains the Screening (SCRD12:SCR) and Day 12 (SCRD12:D12) timepoints where only airways that were present in both screening and day 12 scan are accounted for.
- The scan trimming pair (D12D28), which contains the Day 12 (D12D28:D12) and Day 28 (D12D28:D28) timepoints, where only airways that were present in both day 12 and day 28 scans are accounted for.

These 6 HRCT images were then processed to derive the HRCT parameters at each of these scan-trimming pair time points; this data will be referred to as the scan trimmed data. The scan trimmed data considers only airways that were present in both scans within the scan trimming pair. This ensures the airway models are the same length although the cross-sectional area of the airway may vary. For example, the schematic below shows visible airways on Screening alone and Day 12 alone. It then shows the airways that are visible on both Screening & Day 12 scans, through removing/trimming airways that are not present in both scans.

Screening:  Day 12:  Scan Trimming Screening & Day 12: 

The HRCT scans can identify the 5 different lobes of the lungs and these lobes can then be categorized into and up to 5 regions depending on the endpoint. The 5 lobes are Right Upper Lobe (RUL), Left Upper Lobe (LUL), Right Middle Lobe (RML), Right Lower Lobe (RLL) and Left Lower Lobe (LLL). The 5 regions are Upper (comprising of RUL, RML and LUL), Lower (comprising of RLL and LLL), Central (the main bronchi between the lobes and the trachea), Distal (comprising of Upper and Lower) and Total (comprising of Distal and Central).

The endpoints for which the 5 regions apply include:

- Specific imaging airway volume (siVaw)
- Imaging airway volume (iVaw)
- Specific imaging airway resistance (siRaw)
- Imaging airway resistance (iRaw)
- Specific imaging airway wall volume (siVaww)
- Imaging airway wall volume (iVaww)

The endpoints for which only 3 regions (upper, lower & total) apply include:

- Imaging lobe volume (iVlobe)
- Percent predicted lobar volume (iVlobepred)
- Low attenuation score (LAS)
- Air trapping score (AT)
- Blood vessel density (BVD)

The endpoint for which only 2 regions (upper & lower) apply is:

- Internal airflow lobar distribution (IALD)

For the measures iVaw, iRaw and iVaww, standardization within a subject for the size of the lobar volume was conducted. These specific measures can be adjusted for the individual's lobar volume by correcting for the corresponding lobe/region. Note the central region is not applicable for lobar volumes, instead the corresponding region for the central, distal and total regions is the total lobar volume region. For example:

- To calculate siVaw, the lobes/regions of iVaw being divided by the corresponding lobes/regions of iVlobe to calculate the lobes/regions of siVaw, thus siVaw can be defined as a measure of volume in an individual's airways, corrected for the individual's lobar volume.
- To calculate siRaw, the lobes/regions of iRaw were multiplied by the corresponding lobes/regions of iVlobe.
- To calculate siVaww, the lobes/regions of iVaww were divided by the corresponding lobes/regions of iVlobe.

For such reasons, the table below shows the HRCT endpoints and the results that will be captured:

Table 2 HRCT Endpoints (and results that will be captured)

		Untrimmed			Scan Trimming, based on:		
Endpoints	**Units**	**Screening**	**Day 12**	**Day 28**	**Screening and Day 12 scans**	**Screening and Day 28 scans**	**Day 12 and Day 28 scans**
iVaw	mL	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
siVaw	mL/L	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
iRaw	KPa*s/L				x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
siRaw	KPa*s				x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
iVlobe	L	x	x	x			
Percent Predicted iVlobe	% of Predicted value	x	x	x			
IALD [3]	%	x	x	x			
LAS [1]	% of iVlobe	x	x	x			
AT [2]	% of iVlobe	x	x	x			
BVD [1]	% of iVlobe	x	x	x			
iVaww [1]	mL	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
siVaww [1]	mL/L	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
Trachea length	mm	x	x	x			
Trachea Diameter	mm	x	x	x			
Trachea Length/Diameter	mm/mm	x	x	x			

All these endpoints will be measured at TLC and FRC, except:

[1] These endpoints will only be measured at TLC

[2] This endpoint will be measured only at FRC

[3] The state (TLC/FRC) is not applicable

For the endpoints siVaw, iVaw, iRaw and siRaw appropriate transformations will be applied prior to summaries and statistical analyses, likely a log transformation. Summary statistics will be presented for absolute data and change from baseline. An attempt will be made to fit separate statistical models for each endpoint, scan trimming condition (Untrimmed or Scan Trimmed), lung volume (FRC or TLC) and Lobes (RUL, LUL, RML, RLL and LLL) or Regions (Upper, Lower, Central, Distal and Total) combination as appropriate. The primary plan for statistical analyses will be to fit separate statistical models for:

- siVaw
    - Untrimmed at FRC for all lobes, i.e. RUL, LUL, RML, RLL and LLL in one model.
    - Untrimmed at FRC for all regions, i.e. Upper, Lower, Central, Distal and Total in one model.
    - Scan Trimmed at FRC for Distal region only.
- siRaw
    - Scan Trimmed at FRC for Distal region only.

For untrimmed data, the ratio from baseline across the different Regions (accounting for the average baseline associated to the Region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). In addition, the placebo-adjusted ratio from baseline across the different Regions will be represented via adjusted posterior medians, as well as their associated 95% HPD-tailed credible intervals and posterior probabilities. These results will be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For scan trimmed data, the change from baseline across the different Regions (accounting for the average baseline associated to the Region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). In addition, the placebo-adjusted change from baseline across the different Regions will be represented via adjusted posterior medians, as well as their associated 95% HPD-tailed credible intervals and posterior probabilities. These results will be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For the tracheal endpoints, absolute data and change from baseline summary statistics will be provided for each lung volume (FRC or TLC) for trachea length, diameter and length/diameter.

8.2.3. Population of Interest

The primary efficacy analyses will be based on the “All Subjects” population, unless otherwise specified.

8.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.2.4.1. Statistical Methodology Specification

NOTE: The description below describes the current thinking of how to analyse these endpoints. The proposed models will be assessed, and if not appropriate alternative models could be used.

Endpoint / Variables
• Imaging Untrimmed endpoint siVaw at FRC
Model Specification
• The data will be inspected prior to analysis to determine whether a data transformation is required. It is likely that the data will approximately follow a log normal distribution; however, the most appropriate distribution should be used. • It is thought that the use of bronchodilators could affect the HRCT results. The database will contain information on whether relief medication was used in the 4 hours prior to each scan, and this information may be used in the sensitivity analyses of the HRCT results. • An attempt will be made to fit a statistical model for all Lobes (RUL, LUL, RML, RLL and LLL) and a separate statistical model for all Regions (Upper, Lower, Central, Distal and Total), i.e. two models; one for lobes, one for regions. However, should this model fail to converge or be deemed unsuitable potentially due to sample size, separate statistical models will be fitted for each Lobe/Region (RUL, LUL, RML, RLL, LLL, Upper, Lower, Central, Distal and Total), i.e. ten models in total, one for each lobe/region endpoint. • The log of (or other transformation as appropriate) the ratio from baseline will be analysed in a multivariate model), under a Bayesian framework. The model will include a Baseline*Region term and a Treatment*Visit*Region term, as well as any co-variates of interest. Note that the model will not include an intercept. The Visit will consist of two levels: Day 12 and Day 28, and the Treatment will consist of two levels: All NEMI and All Placebo. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e. covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior. • The change from baseline (accounting for the average baseline) across the different Visits will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). • The difference between the treatment arms, for the change from baseline across the different

Visits will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable) • The probabilities that the treatment ratio is greater than 1 (depending on direction of the endpoint), in addition to other values appropriately selected based on the data, will also be computed for each Visit. These results will be presented in tabular format
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. For example, if data do not approximately follow a normal distribution then attempt will be made to find a suitable transformation. Note: Should parameters require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arm, and then (ii) using these back transformed values, the ratio of the treatment arms (All NEMI/All Placebo) will be calculated for each posterior sample, and finally summarised accordingly • A comprehensive investigation into a suitable model should be initiated. For example, additional covariates will be investigated such as age, BMI, gender etc. Note: when investigating fitting separate statistical models for Lobes (RUL, LUL, RML, RLL and LLL) and Regions (Upper, Lower, Central, Distal and Total), i.e. two models; one for lobes, one for regions. If there are convergence issues an alternative structure of fitting separate statistical models for each Lobe (RUL, LUL, RML, RLL and LLL) and each Region (Upper, Lower, Central, Distal and Total), i.e. ten models; five for lobes, five for regions. a similar model as described in Model Specification should be tested but will include a baseline and a Treatment*Visit term instead of a Baseline*Region term and a Treatment*Visit*Region term, respectively. Note: It may also be prudent to investigate a model fitting baseline as a timepoint in which case the log of (or other transformation as appropriate) the absolute results will be analysed in a multivariate model, under a Bayesian framework. The model could include a Treatment*Visit*Region parameter, as well as any co-variates of interest. Note that this model would not include an intercept. The Visit would consist of three levels: Baseline, Day 12 and Day 28, and the Treatment would consist of three levels: Null (when Visit = Screening), NEMI and Placebo. With assumptions as described in Model Specification. • An unstructured covariance structure will be used. However, in the event that this model fails to converge, alternative correlation structures may be considered. • Models with a Bayesian Framework will use vague priors. If appropriate, conjugate priors will be used. For example, for a multivariate model, the prior for the variance covariance matrix will be an inverse Wishart distribution.
Model Results Presentation
• Output from the repeated measures modelling detailed above will be tabulated. In particular, the estimated ratio to baseline (or change from baseline if appropriate), 95% CI, standard error (on the appropriate scale, likely logarithm base e), and posterior probabilities at each time point and for the active treatment comparison with placebo. The scan trimming condition, lung volume and lobe or region description will be included in the outputs.
Sensitivity and Supportive Analyses
• It is thought that the use of bronchodilators could affect the HRCT results. The database will contain information on if relief medication was used in the 4 hours prior to each scan, and this

information may be used in the sensitivity analyses of the HRCT results including only those who did not take bronchodilator relief medication in the 4 hours prior to HRCT scan.

Endpoint / Variables

- Imaging Scan Trimmed endpoints siVaw and siRaw at FRC in the Distal Region only.

Model Specification

- It is likely that the data will approximately follow a log normal distribution; however, the most appropriate distribution should be used.
- Separate statistical models will be fitted for each endpoint, i.e. two models; one for siVaw (scan trimmed at FRC in Distal region), one for siRaw (scan trimmed at FRC in Distal region).
- The responses of interest are the change from baseline based on (i) Airways present on scans taken at Screening and Day 12, (ii) Airways present on scans taken at Screening and Day 28, and (iii) Airways present on scans taken at Day 12 and Day 28. The baselines for each of these endpoints are provided in the table below.

	(i) Screening & Day12 Scan trimming	**(ii) Screening & Day28 Scan trimming**	**(iii) Day 12 & Day 28 Scan trimming**
Screening Result	✓ (baseline)	✓ (baseline)	
Day 12 Result	✓ (post dose)		✓ (baseline)
Day 28 Result		✓ (post dose)	✓ (post dose)

- The modelling below assumes that the Scan trimming endpoints (Screening&Day12, Screening&Day28 and Day12&Day28) will be analysed in a single multivariate model. This is subject to sensitivity analysis.
- The log of (or other transformation as appropriate) the change from baseline (where baseline is defined in the table above) will be analysed in a multivariate model to account for the correlation between the multiple Scan Trimmings (Screening&Day12, Screening&Day28 and Day12&Day28), under a Bayesian framework. The model will have a separate intercept for each Scan Trimming combination (by fitting a class parameter Scan Trimming, and having no overall intercept), and will also include a baseline*Scan Trimming and a Treatment*Scan Trimming parameter. The Visit will consist of two levels: Day 12 and Day 28, the scan trimming will consist of three levels Screening&Day12, Screening&Day28 and Day12&Day28, and the Treatment will consist of two levels: All NEMI and All Placebo. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e. covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior.
- The change from baseline across the different Scan Trimming pairs (accounting for the average baseline) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be

presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable).

- The difference between the treatment arms, for the change from baseline across the different Scan Trimming pairs will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (if applicable). For parameters that require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arm, and then (ii) using these back transformed values, the ratio of the treatment arms (Active/Placebo) will be calculated for each posterior sample, and finally summarised accordingly.

  The probabilities that the treatment ratio is greater than 1 (for siVaw) and less than 1 (for siRaw), in addition to other values appropriately selected based on the data, will also be computed for each Visit. These results will be presented in tabular format.

Model Checking & Diagnostics

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data. For example if data do not approximately follow a normal distribution then an attempt will be made to find a suitable transformation.
  Note: Should parameters require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arm, and then (ii) using these back transformed values, the ratio of the treatment arms (All NEMI/All Placebo) will be calculated for each posterior sample, and finally summarised accordingly
- A comprehensive investigation into a suitable model should be initiated. For example, additional covariates will be investigated
- An unstructured covariance structure will be used. However, in the event that this model fails to converge, alternative correlation structures may be considered.
- Models with a Bayesian Framework will use vague priors. If appropriate, conjugate priors will be used. For example, for a multivariate model, the prior for the variance covariance matrix will be an inverse Wishart distribution.

Model Results Presentation

- Output from the repeated measures modelling detailed above will be tabulated. In particular, the estimated ratio to baseline (or change from baseline if appropriate), 95% CI, standard error (on the appropriate scale, likely logarithm base e), and posterior probabilities at each time point and for the active treatment comparison with placebo. The scan trimming condition, lung volume and lobe or region description will be included in the outputs.

Sensitivity and Supportive Analyses

- It is thought that the use of bronchodilators could affect the HRCT results. The database will contain information on if relief medication was used in the 4 hours prior to each scan, and this information may be used in the sensitivity analyses of the HRCT results including only those who did not take bronchodilator relief medication in the 4 hours prior to HRCT scan.

8.3. Exploratory Efficacy Analyses (From HRCT Analyses)

8.3.1. Endpoint / Variables

To assess the changes in other HRCT parameters such as low attenuation score after once daily repeat inhaled doses of nemiralisib administered to subjects with acute exacerbation of COPD, compared to placebo. Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.

8.3.2. Summary Measure

The structure of HRCT endpoints is as described in Section 8.2.2, exploratory endpoints include:

- iVlobe
- Percent Predicted iVlobe
- IALD
- LAS
- AT
- BVD
- iVaww
- siVaww

For all endpoints, the data will be inspected prior to analyses to determine whether a data transformation is required. Appropriate transformations will be applied prior to summaries and statistical analyses. It is likely a log transformation will be required for iVlobe, LAS, IALD, BVD iVaww and siVaww, and that no transformation will be required for Percent Predicted iVlobe and AT, however, the most appropriate distribution should be used

Summary statistics will be presented for absolute data and change from baseline. Separate statistical models will be fitted for each scan trimming condition (Untrimmed or Scan Trimmed), lung volume (FRC or TLC) and Regions (Upper, Lower, Central, Distal and Total) combination as appropriate, note: statistical analyses will only be conducted on:

- IALD for upper and lower regions only (within the same model)
- LAS at TLC for total region only
- AT at FRC for total region only
- BVD at TLC for total region only
- siVaww untrimmed data at TLC for distal region only

For the endpoints: LAS, AT and BVD, separate statistical models will be fitted for the Total region only. The change from baseline (accounting for the average baseline associated to the region) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). The difference between the treatment arms, for the change from baseline will be represented via adjusted medians, as

well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For the endpoint IALD, a statistical model will be fitted for both the Upper and Lower regions. The change from baseline across the different regions (accounting for the average baseline associated to the region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). The difference between the treatment arms, for the change from baseline across the different regions will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For the endpoint siVaww, a statistical model will be fitted for the distal region using untrimmed data. The change from baseline (accounting for the average baseline associated to the region) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). The difference between the treatment arms, for the change from baseline will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

8.3.3. Population of Interest

The secondary efficacy analyses will be based on the “All Subjects” population, unless otherwise specified.

8.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.3.4.1. Statistical Methodology Specification

For statistical analyses of IALD in the upper and lower regions refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note that it is likely only 1 statistical model would be fitted for the upper and lower regions only. If appropriate this could be adapted into two models; one for upper, one for lower. The probability that the treatment ratio is greater than 1 will be presented for the lower region and the probability that the treatment ratio is less than 1 will be presented for the upper region, in addition to other values appropriately selected based on the data.

For statistical analyses of LAS at TLC in the total region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note only 1 statistical model would be fitted for the Total regions only. The probability that the treatment ratio is less than 1 will be presented, in addition to other values appropriately selected based on the data.

For statistical analyses of AT at FRC in the total region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw however it is likely that no transformation will be required for this endpoint in which case the absolute change from baseline will be fitted and probabilities that the true treatment difference is less than 1, in addition to other values appropriately selected based on the data, will also be computed for each Visit. Note only 1 statistical model would be fitted for the Total regions only.

For statistical analyses of BVD at TLC in the total region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note only 1 statistical model would be fitted for the Total regions only.

For statistical analyses of siVaww at TLC in the distal region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note only 1 statistical model would be fitted for the Distal regions only. The probability that the treatment ratio is less than 1, in addition to other values appropriately selected based on the data will be presented.

8.4. Exploratory Efficacy Analyses (Not from HRCT Analyses)

8.4.1. Endpoint / Variables

Additional exploratory endpoints include the severity of index exacerbation, where exacerbations requiring hospitalisations are defined as severe and those not requiring hospitalisation are defined as moderate.

8.4.2. Summary Measure

For the severity of index exacerbation, a summary table detailing the number and percentage of subjects who had moderate or severe index exacerbations. Note: exacerbations requiring hospitalisations are defined as severe and those not requiring hospitalisation are defined as moderate.

If available, data on exacerbations occurring during the study will be summarised. This may include investigator defined exacerbations (including information on moderate or severe) and/or concomitant medication defined exacerbations. Concomitant medication defined exacerbations may be defined as treatment with systemic/oral corticosteroids and/or antibiotics where the exacerbation is deemed to have ended if no additional treatment with systemic/oral corticosteroids and/or antibiotics is required within < 7days from the end of treatment for the primary exacerbation.

8.4.3. Population of Interest

The secondary efficacy analyses will be based on the “All Subjects” population, unless otherwise specified.

8.4.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.4.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9. RELATIONSHIP BETWEEN THE PHARMACODYNAMIC AND BIOMARKER DATA AND THE HRCT DATA

9.1. Relationship between the mRNA data and the HRCT data

The relationship between a selection of the mRNA data and the HRCT data may be performed as an exploratory analysis. This may include scatter plots of individual participant data, linear regression lines, Pearson's correlation coefficient and 95% confidence intervals plots as appropriate. This data will be produced following SAC.

10. SAFETY ANALYSES

The safety analyses will be based on the "All Subjects" population, unless otherwise specified.

10.1. 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 10: List of Data Displays.

10.2. 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 10: List of Data Displays.

10.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

11. PHARMACOKINETIC ANALYSES

11.1. Secondary Pharmacokinetic Analyses

11.1.1. Endpoint / Variables

11.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic)

11.1.1.2. Derived Pharmacokinetic Parameters

No non-compartmental analysis will be conducted for this study as such there will be no derived pharmacokinetic parameters.

11.1.2. Summary Measure

The concentrations of the samples will be summarised.

11.1.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the “Pharmacokinetic” population, unless otherwise specified.

12. REFERENCES

Quanjer Ph.H, Tammeling G.J, Cotes J.E., Pedersen O.F, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows; *European Respiratory Journal* 1993 6: 5-40

13. APPENDICES

13.1. Appendix 1: Protocol Deviation Management

13.1.1. Important Protocol Deviations

Based on an assessment of the important protocol deviations listed in the PDMP, partial data exclusions or time-point exclusions may occur which may not remove a subject from the analysis population, but may exclude a portion of the subject's data.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

Screening and Follow Up Visits

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Full physical exam, including height and weight	X		
Brief physical examination, including weight		X	
Chest X-Ray	X		To be done before baseline HRCT to exclude significant pneumonia and other incidental serious underlying pathology.
Medical history (includes substance usage and Family history of premature CV disease)	X		Substances: Drugs, Alcohol, tobacco via history. No drug, alcohol screening is required.
Past and current medical conditions (including cardiovascular medical history and therapy history)	X		
Laboratory assessments (include Hematology and biochemistry)[1]	X	X	Historical values analysed by local lab to be used for eligibility assessment. Another sample must be collected and sent to central lab as soon as informed consent is obtained.
Hep B and Hep C screen[2]	X		
Urine pregnancy test (only WCBP)	X		Before conducting the HRCT. Done locally at the site.
12-lead ECG	X	X	Single assessment
Vital signs	X	X	Single assessment
HRCT (at TLC and FRC)	X		Within 48 h of diagnosis, if subject otherwise eligible. Includes electronic monitoring of breathing (if applicable). Baseline HRCT will be reviewed by the local site's radiologist to identify any significant occurring underlying medical conditions that require further clinical management or monitoring.

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Induced Sputum[3]	X[4]		To include sputum culture pre-first dose. Culture to be done by the local site laboratory.
Blood sample for mRNA Analysis	X[4]		Collected at any time on specified days
AE/SAE collection and review		X	
Concomitant medication review	X	X	

1. Due to the short screening window, central laboratory analysis results will not be available on time. Therefore, the local laboratory results should be used for eligibility assessment (to exclude severe subjects and underlying medical conditions). If local laboratory results are already available from diagnosis of current exacerbation, there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained. See Section 7.8.6 of Protocol Amendment 4 for further details.
2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required. Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor.
3. Induced sputum collection may be attempted on several occasions if an adequate sample is not produced at the first attempt.
4. To be collected at any time point before randomisation.

Treatment Period

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
ELLIPTA™ Inhaler Training	X						Training conducted by reviewing the Patient Information Leaflet with the subject (no device will be used). Additional training may be conducted at the discretion of the investigator
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
Diary Card dispense and review at clinic	X		X	X	X	X	Refer to SRM for details.

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

1. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2 of Protocol Amendment 4
2. Assessments do not need to be completed if screening assessments conducted within 48 hours
3. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
4. Informed consent for optional sub-studies (e.g. genetics research) must be obtained before collecting a sample. May be obtained at any visits.

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for Analyses

Population	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
Screening	NA	3 days prior to Visit 1 (Day 1)	Day 1	Screening
Safety, Efficacy, Study population and all other assessments	NA – Day of first dose	NA	NA	Visit 1
	If subject was hospitalised: Target = On discharge If subject wasn't hospitalised: Target = Within 48 hours of first dose administration	Target -1 day	Target +1 day	Visit 2
	Day 12	Target -2 day	Target +3 day	Visit 3
	Day 28	Target -4 day	Target +2 day	Visit 4
	Day 56	Target -7 day	Target +6 day	Visit 5
	Day 84	Target -8 day	Target +4 day	Visit 6
Follow-up	NA	1 week following last day of dose	4 weeks following the last day of dose	Follow-up

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

13.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the study treatment, unless otherwise specified

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

13.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is 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.

13.4.2. Treatment States for Adverse Events

Flag	Definition
Pre-Treatment	• If AE onset date is before the treatment start date. • AE Start Date < Study Treatment Start Date
Treatment Emergent (On-Treatment)	• 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.
Post-Treatment	• If AE onset date is after the treatment stop date. • AE Start Date > Study Treatment Stop Date
Onset Time Since 1st Dose (Days)	• If Treatment Start Date > AE Onset Date, then Onset Time = AE Onset Date - Treatment Start Date • If Treatment Start Date ≤ AE Onset Date, then Onset Time = AE Onset Date - Treatment Start Date +1 • Missing otherwise.
Duration (Days)	• AE Resolution Date – AE Onset Date + 1
Drug-related	• If relationship is marked 'YES' on [Inform/CRF OR value is missing].

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.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software (version 9.4) will be used.	
Reporting Area	
HARP Server	: UK1SALX00175.corpnet2.com
HARP Compound	: ARPROD/GSK2269557/mid201928 Note: the current planned reporting effort is final_01, this may be superseded.
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards and Integrated Data Standards Library	
Generation of RTF Files	
• RTF files will be generated for all tables	

13.5.2. 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 located in the modular appendices as ICH or non-ICH listings
• A project wide decision was made to present GSK2269557 as Nemiralisib (abbreviated to NEMI) refer to Section 5.1 for further details.

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.

• Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in summary 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. • All graphics will be done using the SGPLOT/SGPANEL/SG template procedures

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
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. Note: Use the separate NEMI DISKUS and NEMI ELLIPTA treatment groups
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.

13.6. Appendix 6: Derived and Transformed Data

13.6.1. 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 13.3.1) 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:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

13.6.2. Study Population

Treatment Compliance
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Counter Readings / (Actual Treatment Duration in Days * Frequency)** • Treatment compliance could be greater than 100% if there are events of overdose.
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly. • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Counter Readings x Study Drug Dose)**

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age at Screening where birth date will be imputed as follows: ○ Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Refer to IDSL standards for age range categories.
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2]**

13.6.3. Efficacy

HRCT

Endpoints provided by FluidDA

Y = Endpoints will be provided by FluidDA.

	Lobes & Regions										
	LLL	**LUL**	**RML**	**RUL**	**RLL**	**LL**	**UL**	**CENTRAL**	**DISTAL**	**TOTAL**	**TRACHEA**
iVaw	Y	Y	Y	Y	Y	C	C	Y	C	C	N/A
siVaw	C	C	C	C	C	C	C	C	C	C	N/A
iRaw	Y	Y	Y	Y	Y	C	C	Y	Y	Y	N/A
siRaw	C	C	C	C	C	C	C	C	C	C	N/A
iVlobe	Y	Y	Y	Y	Y	C	C	N/A	N/A	C	N/A
iVlobepred	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
LAS	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
IALD	C	C	C	C	C	C	C	N/A	N/A	N/A	N/A
AT	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
BVD	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
iVaww	Y	Y	Y	Y	Y	C	C	Y	C	C	N/A
siVaww	C	C	C	C	C	C	C	C	C	C	N/A
Diameter	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y
Length	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y
Length/Diameter	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	C

C = Endpoints will be Calculated by GSK (see Derived Data below)

Imaging Endpoints Calculated by GSK

iVaw LL = iVaw RLL + iVaw LLL
iVaw UL = iVaw RUL + iVaw RML + iVaw LUL
iVaw DISTAL = iVaw LL + iVaw UL
iVaw TOTAL = iVaw CENTRAL + iVaw DISTAL

iRaw LL = 1/ (1/iRaw RLL + 1/iRaw LLL)
iRaw UL = 1/ (1/iRaw RUL + 1/iRaw RML + 1/iRaw LUL)

iVlobe LL = iVlobe RLL + iVlobe LLL
iVlobe UL = iVlobe RUL + iVlobe RML + iVlobe LUL
iVlobe TOTAL = iVlobe LL + iVlobe UL

iVaww LL = iVaww RLL + iVaww LLL
iVaww UL = iVaww RUL + iVaww RML + iVaww LUL
iVaww DISTAL = iVaww LL + iVaww UL
iVaww TOTAL = iVaww CENTRAL + iVaww DISTAL

siVaw LLL = iVaw LLL / iVlobe LLL
siVaw LUL = iVaw LUL / iVlobe LUL
siVaw RML = iVaw RML / iVlobe RML
siVaw RUL = iVaw RUL / iVlobe RUL
siVaw RLL = iVaw RLL / iVlobe RLL
siVaw LL = iVaw LL / iVlobe LL
siVaw UL = iVaw UL / iVlobe UL
siVaw CENTRAL = iVaw CENTRAL / iVlobe TOTAL
siVaw DISTAL = iVaw DISTAL / iVlobe TOTAL
siVaw TOTAL = iVaw TOTAL / iVlobe TOTAL

siRaw LLL = iRaw LLL * iVlobe LLL
siRaw LUL = iRaw LUL * iVlobe LUL
siRaw RML = iRaw RML * iVlobe RML
siRaw RUL = iRaw RUL * iVlobe RUL
siRaw RLL = iRaw RLL * iVlobe RLL
siRaw LL = iRaw LL * iVlobe LL
siRaw UL = iRaw UL * iVlobe UL

siRaw CENTRAL = iRaw CENTRAL * iVlobe TOTAL siRaw DISTAL = iRaw DISTAL * iVlobe TOTAL siRaw TOTAL = iRaw TOTAL * iVlobe TOTAL
siVaww LLL = iVaww LLL / iVlobe LLL siVaww LUL = iVaww LUL / iVlobe LUL siVaww RML = iVaww RML / iVlobe RML siVaww RUL = iVaww RUL / iVlobe RUL siVaww RLL = iVaww RLL / iVlobe RLL siVaww LL = iVaww LL / iVlobe LL siVaww UL = iVaww UL / iVlobe UL siVaww CENTRAL = iVaww CENTRAL / iVlobe TOTAL siVaww DISTAL = iVaww DISTAL / iVlobe TOTAL siVaww TOTAL = iVaww TOTAL / iVlobe TOTAL
IALD LLL = 100 * (iVlobe LLL TLC - iVlobe LLL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD LUL = 100 * (iVlobe LUL TLC - iVlobe LUL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD RML = 100 * (iVlobe RML TLC - iVlobe RML FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD RUL = 100 * (iVlobe RUL TLC - iVlobe RUL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD RLL = 100 * (iVlobe RLL TLC - iVlobe RLL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD LL = IALD RLL + IALD LLL IALD UL = IALD RUL + IALD RML + IALD LUL

Lung Function Parameters

Lung Function Parameters Calculated by GSK

- FEV1 % Predicted (Men) = 4.30*Height – 0.029*Age – 2.49
- FEV1 % Predicted (Women) = 3.95*Height – 0.025*Age – 2.60

Formulas have been taken from Quanjer, 1993 Lung volumes and forced ventilator flows [accessed: 23rd July 2015] where height is measured in metres and age in years at screening.

Rescue Medication Endpoints

Number of occasions bronchodilator taken in the last 24 per hours 4-week period derived by GSK

- Number of occasions bronchodilator taken in the last 24 hours were collected in the daily diary
- The table below shows which daily diary records are used to calculate the daily diary endpoints for each analysis time period. Any diary data collected in the post-treatment phase of the study will not be slotted.

Daily Record		
Beginning Timepoint (day)	**Ending Timepoint (day)**	**Analysis Time Period**
1	28	Weeks 1 – 4
29	56	Weeks 5 – 8
57	84	Weeks 9 – 12

Note: There is no Day 0. Any records with actual day>84 will not be assigned to a time period. Any records with actual day<0 may be assigned to a Week -1 (Baseline) time period

Note: Daily diary records that were not assigned to a time period will not be used in calculation of daily diary endpoints.

- For a subject to be counted in any time period for a given endpoint they must have at least one diary entry recorded for that endpoint during that time period.
- Any daily diary data that were collected post-study treatment discontinuation will be excluded from analysis, including four weekly period data summaries.
- If a subject has more than one daily diary record for any given day, the worst-case response on that day for each endpoint will be used in the summaries and analyses. i.e.

the maximum number of occasions of bronchodilator use reported will be counted for the day in question and used to determine if it was a rescue-free day

- The mean number of occasions of rescue use per day and percentage of rescue-free days, will be calculated for each subject during the four weekly periods defined above.

13.6.4. Safety

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as:
  [1] If QTcB is machine read & QTcF is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value then do not derive.

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:

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Laboratory Values

- 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, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, 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.
  - Example 1: 2 Decimal Places = '< x' becomes x – 0.01
  - Example 2: 1 Decimal Places = '> x' becomes x + 0.1
  - Example 3: 0 Decimal Places = '< x' becomes x – 1

13.6.5. Pharmacodynamic and Biomarker

Biomarker Category	Analyte	Method	Lab	Matrix	Total samples
Inflammatory Cytokine	IL-8	MSD	Quest	Sputum	4
	IL-6	MSD	Quest	Sputum	4
	TNFα	MSD	Quest	Sputum	4
Microbiome	Bacterial DNA	16SRNA	GSK-RTP	Sputum	4
	Bacterial DNA	qPCR	GSK-RTP	Sputum	4
	Viral DNA	qPCR	GSK-RTP	Sputum	4
Transcriptomics	Human RNA	Affymetrix	Expression Analysis	Blood	4

NOTES:

- Sampling times: Screening, day 12, day 28 and day 84
- Inflammatory cytokine biomarkers are elevated in COPD patients. Expected to reduce with treatment.
- Microbiome biomarkers are drivers of exacerbations in COPD and are inhibited in preclinical disease studies
- PI3Kδ transcriptome analysis in FTIH study has 16 genes identified (sputum) showing a consistent response with dose – all are down regulated.

Pharmacodynamic and Biomarker

Pharmacodynamic

PMNs Differentials

- Percentage data may be arc-sine transformed especially if many of the percentage values are smaller than 20% or larger than 80%. The response variable, y, measured in radians, is $\sin^{-1}\text{sqrt}\{0.01*p\}$ where p is the differential percentage.
- If transformations are used then the results will be reported on the back-transformed scale, except where a transformed value:
  - exceeds 0.01*p/2 then the back-transformed value will be set equal to 100%
  - is less than 0 then the back-transformed value will be set equal to 0%.

Biomarkers

Inflammatory Cytokines

- In general, it is assumed that biomarker endpoints will require variance stabilising transformations, such as taking a loge transformation prior to analysis (and that summary statistics appropriate to loge normally distributed data will apply for all summaries). However, this assumption will be considered for each endpoint Individually prior to the generation of summary tables or statistical analysis, and if deemed more appropriate, a loge transformation will not be applied, or non-parametric methods may be employed.
- If transformations are used, then the results will be reported on the back-transformed scale unless otherwise stated.

RNA transcriptome

- Affymetrix microarray mRNA data will be normalised using RMA in ARRAY STUDIO v8.0 or later by the Statistical Consultancy Group (SCG) within GSK. After normalisation, the data will be quality assessed and any samples deemed as QC fails will be excluded from any further analysis. This quality assessment will involve looking for outlying signals in both the normalised expression data and the MAS5 QC metrics generated from each sample. If any samples are excluded, the remaining data will be re-normalised. The output from the normalization will be log2 transformed mRNA intensity data.
- Summary mRNA data will be reviewed and a decision made on which probe sets are to be included in the SI dataset.
- Treatment ratios from the statistical analyses of mRNA intensity data will be converted to fold changes as follows:
  - If ratio ≥ 1 then fold change = ratio
  - If ratio < 1 then fold change = -1/ratio

The primary pharmacodynamic endpoint is based on a subset of probe sets defined as those that have previously identified immune cell mechanisms specifically related to neutrophil function.

The gene list that meets this criterion based on PII115119 D14 vs D1 gene changes, PII115117 and Metacore neutrophil pathways identified in PII115119 study. This gene list identified 258 genes in total after filtering for redundancy and was agreed by the study team is presented in Table 3.

Table 3 Gene List that have previously identified immune cell mechanisms specifically related to neutrophil function

Gene	Source	Gene	Source
CD177	PII115119 - Neutrophil migration	ITGAL	Metacore: IL8 Neutrophil migration
CXCR1	PII115119 - Neutrophil migration	ADAM17	Metacore: Inhibition of neutrophil migration
CXCR2	PII115119 - Neutrophil migration	C5	Metacore: Inhibition of neutrophil migration
FPR2	PII115119 - Neutrophil migration	C5AR1	Metacore: Inhibition of neutrophil migration
LTB4R	PII115119 - Neutrophil migration	CCR5	Metacore: Inhibition of neutrophil migration
PAK1	PII115119 - Neutrophil migration	CD34	Metacore: Inhibition of neutrophil migration
PXN	PII115119 - Neutrophil migration	CALM1	Metacore: Inhibition of neutrophil migration
PREX1	PII115119 - Neutrophil migration	CALM2	Metacore: Inhibition of neutrophil migration
TLN1	PII115119 - Neutrophil migration	CALM3	Metacore: Inhibition of neutrophil migration
SSH2	PII115119 - Neutrophil migration	FPR1	Metacore: Inhibition of neutrophil migration
F2RL1	PII115119 - Neutrophil infection response	ICAM2	Metacore: Inhibition of neutrophil migration
TLR10	PII115119 - Neutrophil infection response	IL1B	Metacore: Inhibition of neutrophil migration
CEACAM3	PII115119 - Neutrophil infection response	IL1R1	Metacore: Inhibition of neutrophil migration
TREML2	PII115119 - Neutrophil infection response	ITPR1	Metacore: Inhibition of neutrophil migration
DEFB124	PII115119 - Neutrophil infection response	ITPR2	Metacore: Inhibition of neutrophil migration
CLEC4C	PII115119 - Neutrophil infection response	ITPR3	Metacore: Inhibition of neutrophil migration
IFITM1	PII115119 - Neutrophil infection response	SELL	Metacore: Inhibition of neutrophil migration
CR1	PII115119 - Neutrophil infection response	MSN	Metacore: Inhibition of neutrophil migration
PMAIP1	FTIH - GSK'557 response	NFKB1	Metacore: Inhibition of neutrophil migration
S100P	FTIH - GSK'557 response	NFKB2	Metacore: Inhibition of neutrophil migration
PTGS2	FTIH - GSK'557 response	REL	Metacore: Inhibition of neutrophil migration
CCL20	FTIH - GSK'557 response	RELA	Metacore: Inhibition of neutrophil migration
EGR3	FTIH - GSK'557 response	RELB	Metacore: Inhibition of neutrophil migration
H1F0	FTIH - GSK'557 response	PECAM1	Metacore: Inhibition of neutrophil migration
NCOA3	FTIH - GSK'557 response	PRKCA	Metacore: Inhibition of neutrophil migration
TARP	FTIH - GSK'557 response	PRKCB	Metacore: Inhibition of neutrophil migration
CEACAM1	FTIH - GSK'557 response	PRKCD	Metacore: Inhibition of neutrophil migration
TTPAL	FTIH - GSK'557 response	PRKCE	Metacore: Inhibition of neutrophil migration
VPS37B	FTIH - GSK'557 response	PRKCG	Metacore: Inhibition of neutrophil migration
SYAP1	FTIH - GSK'557 response	PRKCH	Metacore: Inhibition of neutrophil migration
SPTBN1	FTIH - GSK'557 response	PRKCI	Metacore: Inhibition of neutrophil migration

Gene	Source	Gene	Source
EGR1	FTIH - GSK'557 response	PRKCQ	Metacore: Inhibition of neutrophil migration
OSM	FTIH - GSK'557 response	PRKD1	Metacore: Inhibition of neutrophil migration
TBC1D22A	FTIH - GSK'557 response	PRKD2	Metacore: Inhibition of neutrophil migration
AKT1	Metacore: IL8 Neutrophil migration	PRKD3	Metacore: Inhibition of neutrophil migration
AKT2	Metacore: IL8 Neutrophil migration	PLCB2	Metacore: Inhibition of neutrophil migration
AKT3	Metacore: IL8 Neutrophil migration	PTAFR	Metacore: Inhibition of neutrophil migration
ACTA1	Metacore: IL8 Neutrophil migration	TLR2	Metacore: Inhibition of neutrophil migration
ACTA2	Metacore: IL8 Neutrophil migration	TLR4	Metacore: Inhibition of neutrophil migration
ACTB	Metacore: IL8 Neutrophil migration	TNFRSF1A	Metacore: Inhibition of neutrophil migration
ACTC1	Metacore: IL8 Neutrophil migration	TNFRSF1B	Metacore: Inhibition of neutrophil migration
ACTG1	Metacore: IL8 Neutrophil migration	TNF	Metacore: Inhibition of neutrophil migration
ACTG2	Metacore: IL8 Neutrophil migration	VAV1	Metacore: Inhibition of neutrophil migration
MYH1	Metacore: IL8 Neutrophil migration	EZR	Metacore: Inhibition of neutrophil migration
MYH10	Metacore: IL8 Neutrophil migration	VCL	Metacore: Inhibition of neutrophil migration
MYH11	Metacore: IL8 Neutrophil migration	ITGAM	Metacore: Inhibition of neutrophil migration
MYH13	Metacore: IL8 Neutrophil migration	ABL1	Metacore: Inhibition of neutrophil migration
MYH14	Metacore: IL8 Neutrophil migration	JUN	Metacore: Inhibition of neutrophil migration
MYH15	Metacore: IL8 Neutrophil migration	FOS	Metacore: Inhibition of neutrophil migration
MYH16	Metacore: IL8 Neutrophil migration	MAPK11	Metacore: Inhibition of neutrophil migration
MYH2	Metacore: IL8 Neutrophil migration	MAPK12	Metacore: Inhibition of neutrophil migration
MYH3	Metacore: IL8 Neutrophil migration	MAPK13	Metacore: Inhibition of neutrophil migration
MYH4	Metacore: IL8 Neutrophil migration	MAPK14	Metacore: Inhibition of neutrophil migration
MYH6	Metacore: IL8 Neutrophil migration	BDKRB1	Metacore: Neutrophil migration in Asthma
MYH7	Metacore: IL8 Neutrophil migration	CCL15	Metacore: Neutrophil migration in Asthma
MYH8	Metacore: IL8 Neutrophil migration	CCL2	Metacore: Neutrophil migration in Asthma
MYH9	Metacore: IL8 Neutrophil migration	CCL5	Metacore: Neutrophil migration in Asthma
MYL1	Metacore: IL8 Neutrophil migration	CCL7	Metacore: Neutrophil migration in Asthma
MYL12A	Metacore: IL8 Neutrophil migration	CCR1	Metacore: Neutrophil migration in Asthma
MYL12B	Metacore: IL8 Neutrophil migration	CCR2	Metacore: Neutrophil migration in Asthma
MYL2	Metacore: IL8 Neutrophil migration	CCR3	Metacore: Neutrophil migration in Asthma
MYL3	Metacore: IL8 Neutrophil migration	CXCL5	Metacore: Neutrophil migration in Asthma
MYL4	Metacore: IL8 Neutrophil migration	CXCL1	Metacore: Neutrophil migration in Asthma
MYL5	Metacore: IL8 Neutrophil migration	CXCL2	Metacore: Neutrophil migration in Asthma
MYL6	Metacore: IL8 Neutrophil migration	CXCL3	Metacore: Neutrophil migration in Asthma
MYL6B	Metacore: IL8 Neutrophil migration	HSPA14	Metacore: Neutrophil migration in Asthma
MYL7	Metacore: IL8 Neutrophil migration	HSPA1A	Metacore: Neutrophil migration in Asthma
MYL9	Metacore: IL8 Neutrophil migration	HSPA1B	Metacore: Neutrophil migration in Asthma
MYLPF	Metacore: IL8 Neutrophil migration	HSPA1L	Metacore: Neutrophil migration in Asthma
ACTN1	Metacore: IL8 Neutrophil migration	HSPA2	Metacore: Neutrophil migration in Asthma
ACTN2	Metacore: IL8 Neutrophil migration	HSPA4	Metacore: Neutrophil migration in Asthma
ACTN3	Metacore: IL8 Neutrophil migration	HSPA5	Metacore: Neutrophil migration in Asthma

Gene	Source	Gene	Source
ACTN4	Metacore: IL8 Neutrophil migration	HSPA6	Metacore: Neutrophil migration in Asthma
ACTR2	Metacore: IL8 Neutrophil migration	HSPA7	Metacore: Neutrophil migration in Asthma
ACTR3	Metacore: IL8 Neutrophil migration	HSPA8	Metacore: Neutrophil migration in Asthma
ACTR3B	Metacore: IL8 Neutrophil migration	HSPA9	Metacore: Neutrophil migration in Asthma
ARPC1A	Metacore: IL8 Neutrophil migration	MIF	Metacore: Neutrophil migration in Asthma
ARPC1B	Metacore: IL8 Neutrophil migration	CCL3	Metacore: Neutrophil migration in Asthma
ARPC2	Metacore: IL8 Neutrophil migration	PGF	Metacore: Neutrophil migration in Asthma
ARPC3	Metacore: IL8 Neutrophil migration	TAC1	Metacore: Neutrophil migration in Asthma
ARPC4	Metacore: IL8 Neutrophil migration	TACR1	Metacore: Neutrophil migration in Asthma
ARPC5	Metacore: IL8 Neutrophil migration	KLK1	Metacore: Neutrophil migration in Asthma
CFL1	Metacore: IL8 Neutrophil migration	KLK10	Metacore: Neutrophil migration in Asthma
CFL2	Metacore: IL8 Neutrophil migration	KLK11	Metacore: Neutrophil migration in Asthma
MAPK1	Metacore: IL8 Neutrophil migration	KLK12	Metacore: Neutrophil migration in Asthma
MAPK3	Metacore: IL8 Neutrophil migration	KLK13	Metacore: Neutrophil migration in Asthma
GNAI1	Metacore: IL8 Neutrophil migration	KLK14	Metacore: Neutrophil migration in Asthma
GNAI2	Metacore: IL8 Neutrophil migration	KLK15	Metacore: Neutrophil migration in Asthma
GNAI3	Metacore: IL8 Neutrophil migration	KLK2	Metacore: Neutrophil migration in Asthma
GNAO1	Metacore: IL8 Neutrophil migration	KLK3	Metacore: Neutrophil migration in Asthma
GNAZ	Metacore: IL8 Neutrophil migration	KLK4	Metacore: Neutrophil migration in Asthma
GNB1	Metacore: IL8 Neutrophil migration	KLK5	Metacore: Neutrophil migration in Asthma
GNB2	Metacore: IL8 Neutrophil migration	KLK6	Metacore: Neutrophil migration in Asthma
GNB3	Metacore: IL8 Neutrophil migration	KLK7	Metacore: Neutrophil migration in Asthma
GNB4	Metacore: IL8 Neutrophil migration	KLK8	Metacore: Neutrophil migration in Asthma
GNB5	Metacore: IL8 Neutrophil migration	KLK9	Metacore: Neutrophil migration in Asthma
GNG10	Metacore: IL8 Neutrophil migration	FLT1	Metacore: Neutrophil migration in Asthma
GNG11	Metacore: IL8 Neutrophil migration	RUNX1	Metacore: Transcription regulation of granulocytes
GNG12	Metacore: IL8 Neutrophil migration	CEBPA	Metacore: Transcription regulation of granulocytes
GNG13	Metacore: IL8 Neutrophil migration	CEBPE	Metacore: Transcription regulation of granulocytes
GNG2	Metacore: IL8 Neutrophil migration	ANPEP	Metacore: Transcription regulation of granulocytes
GNG3	Metacore: IL8 Neutrophil migration	PTPRC	Metacore: Transcription regulation of granulocytes
GNG4	Metacore: IL8 Neutrophil migration	E2F1	Metacore: Transcription regulation of granulocytes
GNG5	Metacore: IL8 Neutrophil migration	CSF3	Metacore: Transcription regulation of granulocytes
GNG7	Metacore: IL8 Neutrophil migration	CSF3R	Metacore: Transcription regulation of granulocytes
GNG8	Metacore: IL8 Neutrophil migration	GATA1	Metacore: Transcription regulation of granulocytes
GNGT1	Metacore: IL8 Neutrophil migration	JAK1	Metacore: Transcription regulation of granulocytes
GNGT2	Metacore: IL8 Neutrophil migration	JAK2	Metacore: Transcription regulation of granulocytes
ICAM1	Metacore: IL8 Neutrophil migration	LRG1	Metacore: Transcription regulation of granulocytes
CXCL8	Metacore: IL8 Neutrophil migration	LTF	Metacore: Transcription regulation of granulocytes
ITGB2	Metacore: IL8 Neutrophil migration	ELANE	Metacore: Transcription regulation of granulocytes
LIMK1	Metacore: IL8 Neutrophil migration	LYZ	Metacore: Transcription regulation of granulocytes
MYLK	Metacore: IL8 Neutrophil migration	MXD1	Metacore: Transcription regulation of granulocytes

Gene	Source	Gene	Source
MYLK2	Metacore: IL8 Neutrophil migration	MAX	Metacore: Transcription regulation of granulocytes
MYLK3	Metacore: IL8 Neutrophil migration	PRTN3	Metacore: Transcription regulation of granulocytes
PPP1CB	Metacore: IL8 Neutrophil migration	MPO	Metacore: Transcription regulation of granulocytes
PPP1R12A	Metacore: IL8 Neutrophil migration	SPI1	Metacore: Transcription regulation of granulocytes
PDPK1	Metacore: IL8 Neutrophil migration	RARA	Metacore: Transcription regulation of granulocytes
PIK3CG	Metacore: IL8 Neutrophil migration	RXRA	Metacore: Transcription regulation of granulocytes
PIK3R5	Metacore: IL8 Neutrophil migration	SOCS3	Metacore: Transcription regulation of granulocytes
PIP5K1A	Metacore: IL8 Neutrophil migration	STAT3	Metacore: Transcription regulation of granulocytes
PIP5K1B	Metacore: IL8 Neutrophil migration	STAT5A	Metacore: Transcription regulation of granulocytes
PIP5K1C	Metacore: IL8 Neutrophil migration	STAT5B	Metacore: Transcription regulation of granulocytes
PRKCZ	Metacore: IL8 Neutrophil migration	FES	Metacore: Transcription regulation of granulocytes
PLD1	Metacore: IL8 Neutrophil migration	MYB	Metacore: Transcription regulation of granulocytes
PLPP6	Metacore: IL8 Neutrophil migration	MYC	Metacore: Transcription regulation of granulocytes
RAC1	Metacore: IL8 Neutrophil migration	CYBB	Metacore: Transcription regulation of granulocytes
RAC2	Metacore: IL8 Neutrophil migration	NCF1	Metacore: Transcription regulation of granulocytes
TLN2	Metacore: IL8 Neutrophil migration	NCF2	Metacore: Transcription regulation of granulocytes

Gene names converted to Affymetrix probe ID, resulted in 638 probes in total, these are presented in Table 4.

Table 4 Probe Set that have previously identified immune cell mechanisms specifically related to neutrophil function

Gene	Probe ID	Gene	Probe ID
ABL1	202123_s_at	KLK7	239381_at
ACTA1	203872_at	KLK8	1552319_a_at
ACTA2	200974_at	KLK8	206125_s_at
ACTA2	215787_at	KLK9	233687_s_at
ACTA2	243140_at	LIMK1	204356_at
ACTB	200801_x_at	LIMK1	204357_s_at
ACTB	213867_x_at	LIMK1	208372_s_at
ACTB	224594_x_at	LRG1	228648_at
ACTB	AFFX-HSAC07/X00351_3_at	LTB4R	210128_s_at
ACTB	AFFX-HSAC07/X00351_5_at	LTB4R	216388_s_at
ACTB	AFFX-HSAC07/X00351_M_at	LTB4R	236172_at
ACTC1	205132_at	LTF	202018_s_at
ACTG1	201550_x_at	LYZ	1555745_a_at
ACTG1	211970_x_at	LYZ	213975_s_at
ACTG1	211983_x_at	MAPK1	1552263_at
ACTG1	211995_x_at	MAPK1	1552264_a_at
ACTG1	212363_x_at	MAPK1	208351_s_at
ACTG1	212988_x_at	MAPK1	212271_at
ACTG1	213214_x_at	MAPK1	224620_at
ACTG1	221607_x_at	MAPK1	224621_at
ACTG1	224585_x_at	MAPK1	229847_at
ACTG2	202274_at	MAPK11	206040_s_at
ACTG2	241148_at	MAPK11	211499_s_at

Gene	Probe ID	Gene	Probe ID
ACTN1	208636_at	MAPK11	211500_at
ACTN1	208637_x_at	MAPK12	1556340_at
ACTN1	211160_x_at	MAPK12	1556341_s_at
ACTN1	237401_at	MAPK12	206106_at
ACTN2	203861_s_at	MAPK13	210058_at
ACTN2	203862_s_at	MAPK13	210059_s_at
ACTN2	203863_at	MAPK14	202530_at
ACTN2	203864_s_at	MAPK14	210449_x_at
ACTN3	206891_at	MAPK14	211087_x_at
ACTN4	200601_at	MAPK14	211561_x_at
ACTR2	1554390_s_at	MAPK3	212046_x_at
ACTR2	1558015_s_at	MAX	208403_x_at
ACTR2	200727_s_at	MAX	209331_s_at
ACTR2	200728_at	MAX	209332_s_at
ACTR2	200729_s_at	MAX	210734_x_at
ACTR2	234210_x_at	MAX	214108_at
ACTR2	234212_at	MIF	217871_s_at
ACTR3	200996_at	MPO	203948_s_at
ACTR3	213101_s_at	MPO	203949_at
ACTR3	213102_at	MSN	200600_at
ACTR3	228603_at	MSN	233749_at
ACTR3	239170_at	MXD1	206877_at
ACTR3B	1555487_a_at	MXD1	226275_at
ACTR3B	218868_at	MXD1	228846_at
ADAM17	205745_x_at	MYB	204798_at
ADAM17	205746_s_at	MYB	215152_at
ADAM17	213532_at	MYC	202431_s_at
ADAM17	237897_at	MYH1	205951_at
AKT1	207163_s_at	MYH10	212372_at
AKT2	1560689_s_at	MYH10	213067_at
AKT2	203808_at	MYH11	1568760_at
AKT2	203809_s_at	MYH11	201495_x_at
AKT2	211453_s_at	MYH11	201496_x_at
AKT2	225471_s_at	MYH11	201497_x_at
AKT2	226156_at	MYH11	207961_x_at
AKT2	236664_at	MYH11	228133_s_at
AKT3	212607_at	MYH11	228134_at
AKT3	212609_s_at	MYH11	239307_at
AKT3	219393_s_at	MYH13	208208_at
AKT3	222880_at	MYH14	217545_at
AKT3	224229_s_at	MYH14	217660_at
AKT3	242876_at	MYH14	219946_x_at
AKT3	242879_x_at	MYH14	226988_s_at
ANPEP	202888_s_at	MYH14	232977_x_at
ANPEP	234458_at	MYH14	234290_x_at
ANPEP	234576_at	MYH15	215331_at
ARPC1A	200950_at	MYH16	1564072_at
ARPC1B	201954_at	MYH2	204631_at
ARPC2	207988_s_at	MYH3	205940_at
ARPC2	208679_s_at	MYH4	208148_at
ARPC2	213513_x_at	MYH6	214468_at
ARPC3	208736_at	MYH7	204737_s_at
ARPC4	211672_s_at	MYH7	216265_x_at
ARPC4	217817_at	MYH8	206717_at

Gene	Probe ID	Gene	Probe ID
ARPC4	217818_s_at	MYH8	34471_at
ARPC5	1555797_a_at	MYH9	211926_s_at
ARPC5	1569325_at	MYL1	209888_s_at
ARPC5	211963_s_at	MYL12A	1555976_s_at
ARPC5	237387_at	MYL12A	1555977_at
BDKRB1	207510_at	MYL12A	1555978_s_at
C5	205500_at	MYL12A	201318_s_at
C5AR1	220088_at	MYL12A	201319_at
CCL15	210390_s_at	MYL12B	221474_at
CCL2	216598_s_at	MYL2	209742_s_at
CCL20	205476_at	MYL3	205589_at
CCL3	205114_s_at	MYL4	210088_x_at
CCL5	1405_i_at	MYL4	210395_x_at
CCL5	1555759_a_at	MYL4	216054_x_at
CCL5	204655_at	MYL4	217274_x_at
CCL7	208075_s_at	MYL5	205145_s_at
CCR1	205098_at	MYL6	212082_s_at
CCR1	205099_s_at	MYL6	214002_at
CCR2	206978_at	MYL6B	204173_at
CCR2	207794_at	MYL7	219942_at
CCR3	208304_at	MYL9	201058_s_at
CCR5	206991_s_at	MYL9	244149_at
CD177	219669_at	MYLK	1563466_at
CD34	209543_s_at	MYLK	1568770_at
CEACAM1	206576_s_at	MYLK	1569956_at
CEACAM1	209498_at	MYLK	202555_s_at
CEACAM1	210610_at	MYLK	224823_at
CEACAM1	211883_x_at	MYLK2	231792_at
CEACAM1	211889_x_at	MYLK3	1562411_at
CEACAM3	208052_x_at	MYLK3	1568925_at
CEACAM3	210789_x_at	MYLK3	1568926_x_at
CEACAM3	217209_at	MYLK3	217623_at
CEBPA	204039_at	MYLK3	238834_at
CEBPE	214523_at	MYLPF	205163_at
CFL1	1555730_a_at	NCF1	204961_s_at
CFL1	200021_at	NCF1	214084_x_at
CFL1	230870_at	NCF2	209949_at
CFL1	236792_at	NCOA3	1562439_at
CFL2	224352_s_at	NCOA3	207700_s_at
CFL2	224663_s_at	NCOA3	209060_x_at
CFL2	233496_s_at	NCOA3	209061_at
CLEC4C	1552552_s_at	NCOA3	209062_x_at
CLEC4C	1555687_a_at	NCOA3	211352_s_at
CR1	206244_at	NFKB1	209239_at
CR1	208488_s_at	NFKB2	207535_s_at
CR1	217484_at	NFKB2	209636_at
CR1	217552_x_at	NFKB2	211524_at
CR1	244313_at	OSM	214637_at
CSF3	207442_at	OSM	230170_at
CSF3R	1553297_a_at	PAK1	1565772_at
CSF3R	203591_s_at	PAK1	209615_s_at
CXCL1	204470_at	PAK1	226507_at
CXCL2	1569203_at	PAK1	230100_x_at
CXCL2	209774_x_at	PDPK1	204524_at

Gene	Probe ID	Gene	Probe ID
CXCL2	230101_at	PDPK1	221244_s_at
CXCL3	207850_at	PDPK1	224986_s_at
CXCL5	207852_at	PDPK1	244629_s_at
CXCL5	214974_x_at	PDPK1	244630_at
CXCL5	215101_s_at	PDPK1	32029_at
CXCL8	202859_x_at	PECAM1	1558397_at
CXCL8	211506_s_at	PECAM1	1559921_at
CXCR1	207094_at	PECAM1	208981_at
CXCR2	207008_at	PECAM1	208982_at
CYBB	203922_s_at	PECAM1	208983_s_at
CYBB	203923_s_at	PGF	209652_s_at
CYBB	217431_x_at	PGF	215179_x_at
CYBB	233538_s_at	PIK3CG	206369_s_at
DEFB124	1568375_at	PIK3CG	206370_at
DEFB124	1568377_x_at	PIK3CG	239294_at
E2F1	2028_s_at	PIK3R5	220566_at
E2F1	204947_at	PIK3R5	227553_at
EGR1	201693_s_at	PIK3R5	227645_at
EGR1	201694_s_at	PIP5K1A	207391_s_at
EGR1	227404_s_at	PIP5K1A	210256_s_at
EGR3	206115_at	PIP5K1A	211205_x_at
ELANE	206871_at	PIP5K1B	205632_s_at
EZR	208621_s_at	PIP5K1B	217477_at
EZR	208622_s_at	PIP5K1C	212518_at
EZR	208623_s_at	PLCB2	204046_at
EZR	217230_at	PLCB2	210388_at
EZR	217234_s_at	PLD1	1557126_a_at
FES	205418_at	PLD1	177_at
FLT1	204406_at	PLD1	205203_at
FLT1	210287_s_at	PLD1	215723_s_at
FLT1	222033_s_at	PLD1	215724_at
FLT1	226497_s_at	PLD1	226636_at
FLT1	226498_at	PLD1	232530_at
FLT1	232809_s_at	PLPP6	227385_at
FOS	209189_at	PMAIP1	204285_s_at
FPR1	205118_at	PMAIP1	204286_s_at
FPR1	205119_s_at	PPP1CB	201407_s_at
FPR2	210772_at	PPP1CB	201408_at
FPR2	210773_s_at	PPP1CB	201409_s_at
GATA1	1555590_a_at	PPP1CB	228222_at
GATA1	210446_at	PPP1R12A	201602_s_at
GNAI1	209576_at	PPP1R12A	201603_at
GNAI1	227692_at	PPP1R12A	201604_s_at
GNAI2	201040_at	PREX1	224909_s_at
GNAI2	215996_at	PREX1	224925_at
GNAI2	217271_at	PRKCA	1560074_at
GNAI3	201179_s_at	PRKCA	206923_at
GNAI3	201180_s_at	PRKCA	213093_at
GNAI3	201181_at	PRKCA	215194_at
GNAO1	204762_s_at	PRKCA	215195_at
GNAO1	204763_s_at	PRKCB	207957_s_at
GNAO1	215912_at	PRKCB	209685_s_at
GNAO1	231951_at	PRKCB	227817_at
GNAZ	204993_at	PRKCB	227824_at

Gene	Probe ID	Gene	Probe ID
GNB1	200744_s_at	PRKCB	228795_at
GNB1	200745_s_at	PRKCB	230437_s_at
GNB1	200746_s_at	PRKCD	202545_at
GNB2	200852_x_at	PRKCE	206248_at
GNB3	206047_at	PRKCE	226101_at
GNB4	223487_x_at	PRKCE	234089_at
GNB4	223488_s_at	PRKCE	236459_at
GNB4	225710_at	PRKCE	239011_at
GNB5	1554346_at	PRKCG	206270_at
GNB5	204000_at	PRKCG	236195_x_at
GNB5	207124_s_at	PRKCH	206099_at
GNB5	211871_x_at	PRKCH	218764_at
GNB5	242404_at	PRKCH	230124_at
GNG10	201921_at	PRKCI	209677_at
GNG11	204115_at	PRKCI	209678_s_at
GNG11	239942_at	PRKCI	213518_at
GNG12	1555240_s_at	PRKCQ	210038_at
GNG12	212294_at	PRKCQ	210039_s_at
GNG12	222834_s_at	PRKCZ	1569748_at
GNG13	220806_x_at	PRKCZ	202178_at
GNG2	1555766_a_at	PRKD1	205880_at
GNG2	223943_s_at	PRKD1	217705_at
GNG2	224964_s_at	PRKD2	209282_at
GNG2	224965_at	PRKD2	241669_x_at
GNG3	222005_s_at	PRKD2	38269_at
GNG4	1555765_a_at	PRKD3	1554910_at
GNG4	1555867_at	PRKD3	211084_x_at
GNG4	1566513_a_at	PRKD3	218236_s_at
GNG4	205184_at	PRKD3	222565_s_at
GNG5	207157_s_at	PRKD3	242549_at
GNG7	206896_s_at	PRTN3	207341_at
GNG7	214227_at	PTAFR	206278_at
GNG7	228831_s_at	PTAFR	211661_x_at
GNG7	232043_at	PTAFR	227184_at
GNG8	233416_at	PTGS2	1554997_a_at
GNG8	234284_at	PTGS2	204748_at
GNGT1	207166_at	PTPRC	1552480_s_at
GNGT2	235139_at	PTPRC	1569830_at
H1F0	208886_at	PTPRC	207238_s_at
HSPA14	219212_at	PTPRC	212587_s_at
HSPA14	226887_at	PTPRC	212588_at
HSPA14	227650_at	PXN	201087_at
HSPA1L	210189_at	PXN	211823_s_at
HSPA1L	233694_at	RAC1	1567457_at
HSPA2	211538_s_at	RAC1	1567458_s_at
HSPA4	208814_at	RAC1	208640_at
HSPA4	208815_x_at	RAC1	208641_s_at
HSPA4	211015_s_at	RAC2	207419_s_at
HSPA4	211016_x_at	RAC2	213603_s_at
HSPA5	211936_at	RARA	1565358_at
HSPA5	230031_at	RARA	203749_s_at
HSPA6	117_at	RARA	203750_s_at
HSPA6	213418_at	RARA	211605_s_at
HSPA8	208687_x_at	RARA	216300_x_at

Gene	Probe ID	Gene	Probe ID
HSPA8	210338_s_at	REL	206035_at
HSPA8	221891_x_at	REL	206036_s_at
HSPA8	224187_x_at	REL	228812_at
HSPA9	200690_at	REL	235242_at
HSPA9	200691_s_at	REL	239486_at
HSPA9	200692_s_at	RELA	201783_s_at
HSPA9	232200_at	RELA	209878_s_at
ICAM1	202637_s_at	RELA	230202_at
ICAM1	202638_s_at	RELB	205205_at
ICAM1	215485_s_at	RXRA	202426_s_at
ICAM2	204683_at	RXRA	202449_s_at
ICAM2	213620_s_at	S100P	204351_at
IFITM1	201601_x_at	SELL	204563_at
IFITM1	214022_s_at	SOCS3	206359_at
IL1B	205067_at	SOCS3	206360_s_at
IL1B	39402_at	SOCS3	214105_at
IL1R1	202948_at	SOCS3	227697_at
IL1R1	215561_s_at	SPI1	205312_at
ITGAL	1554240_a_at	SPTBN1	200671_s_at
ITGAL	213475_s_at	SPTBN1	200672_x_at
ITGAM	205785_at	SPTBN1	212071_s_at
ITGAM	205786_s_at	SPTBN1	213914_s_at
ITGB2	1555349_a_at	SPTBN1	214856_at
ITGB2	202803_s_at	SPTBN1	215918_s_at
ITGB2	236988_x_at	SPTBN1	226342_at
ITPR1	1562373_at	SPTBN1	226765_at
ITPR1	203710_at	SPTBN1	228246_s_at
ITPR1	211323_s_at	SPTBN1	230540_at
ITPR1	216944_s_at	SPTBN1	242220_at
ITPR1	240052_at	SSH2	1554114_s_at
ITPR2	202660_at	SSH2	1555423_at
ITPR2	202661_at	SSH2	1555425_x_at
ITPR2	202662_s_at	SSH2	1560306_at
ITPR2	211360_s_at	SSH2	226080_at
ITPR3	201187_s_at	STAT3	208991_at
ITPR3	201188_s_at	STAT3	208992_s_at
ITPR3	201189_s_at	STAT3	225289_at
ITPR3	239542_at	STAT3	243213_at
JAK1	1552610_a_at	STAT5A	203010_at
JAK1	1552611_a_at	STAT5B	1555086_at
JAK1	201648_at	STAT5B	1555088_x_at
JAK1	239695_at	STAT5B	205026_at
JAK1	240613_at	STAT5B	212549_at
JAK2	1562031_at	STAT5B	212550_at
JAK2	205841_at	SYAP1	225154_at
JAK2	205842_s_at	TAC1	206552_s_at
JUN	201464_x_at	TACR1	208048_at
JUN	201465_s_at	TACR1	208049_s_at
JUN	201466_s_at	TACR1	210637_at
JUN	213281_at	TACR1	230908_at
KLK1	216699_s_at	TARP	211144_x_at
KLK10	209792_s_at	TARP	216920_s_at
KLK10	215808_at	TARP	217381_s_at
KLK11	205470_s_at	TBC1D22A	209650_s_at

Gene	Probe ID	Gene	Probe ID
KLK12	220782_x_at	TBC1D22A	210144_at
KLK12	233586_s_at	TBC1D22A	33778_at
KLK12	234316_x_at	TLN1	203254_s_at
KLK13	205783_at	TLN1	232763_at
KLK13	216670_at	TLN1	236132_at
KLK13	217315_s_at	TLN2	212701_at
KLK14	220573_at	TLN2	212703_at
KLK15	221462_x_at	TLN2	232625_at
KLK15	233477_at	TLR10	223750_s_at
KLK15	234495_at	TLR10	223751_x_at
KLK15	234966_at	TLR2	204924_at
KLK2	1555545_at	TLR4	1552798_a_at
KLK2	209854_s_at	TLR4	221060_s_at
KLK2	209855_s_at	TLR4	224341_x_at
KLK2	210339_s_at	TLR4	232068_s_at
KLK3	204582_s_at	TNF	1563357_at
KLK3	204583_x_at	TNF	207113_s_at
KLK3	231629_x_at	TNFRSF1A	207643_s_at
KLK4	1555697_at	TNFRSF1B	203508_at
KLK4	1555737_a_at	TREML2	219748_at
KLK4	224062_x_at	TTPAL	219633_at
KLK4	231782_s_at	TTPAL	228031_at
KLK4	233854_x_at	VAV1	206219_s_at
KLK5	222242_s_at	VCL	200930_s_at
KLK6	204733_at	VCL	200931_s_at
KLK7	205778_at	VPS37B	221704_s_at

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as Subject whom have completed their final visit (day 84). • Withdrawn subjects will not be replaced in the study. • 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.

13.7.2. 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 by the use of 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.
PD	• Any values below the Lower Limit of Quantification (LLQ) will be assigned a value of ½ LLQ for display purposes in Figures and for computation of summary statistics. Any values above the Upper Limit of Quantification (ULQ) will be assigned to the ULQ for display purposes in Figures and for computation of summary statistics. Where biomarker concentrations are from an assay of an increased dilution factor the LLQ and ULQ will be multiplied by this factor. Note: Values sent to biostatistics are raw and have not taken into account dilution factor. LLQ and ULQ need to be taken into account prior to dilution factor and then imputed. Then Dilution factor needs to be applied. E.g. if raw value is 10 and dilution factor is 1:2 and ULD is 15, then this value is valid, but the final value should be 20. • If the number of LLQ (and/or ULQ) values is large for an individual biomarker then an alternative analysis method, such as TOBIT analysis, may be required. "Large" is hard to define prospectively and may depend upon the dataset in question. Any such methodology will be documented in the statistical contributions to the study report. • Imputed values will be used in tables and figures, unless the proportion of imputed values at a given time point is large, in which case the summary statistics may not be presented for that time point and/or alternative actions will be taken and documented in the study report. • Where values are imputed, the number of such imputations will be included as a summary statistic in the relevant summary tables.
HRCT	• No missing data imputation methods will be used. • Note that for the HRCT data, there may be instances such that measurements from a particular Lobe cannot be distinguished between another Lobe, for example the iVlobe may be measured from both the LLL and LUL lobes. In such a case, the Lobe will be denoted as LLL + LUL. Therefore, for the statistical analysis purpose, since analysis is

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>performed on a lobar level, the LLL and LUL Lobes will be set to missing and will therefore not be included in the analysis. Below is a table of all possible scenarios, where the data is set to missing and not used in the statistical analysis:
<table>
<tr><th colspan="5">Lobes</th><th rowspan="2">Label</th></tr>
<tr><th>RUL</th><th>RML</th><th>RLL</th><th>LUL</th><th>LLL</th></tr>
<tr><td>x</td><td>x</td><td></td><td></td><td></td><td>RUL + RML</td></tr>
<tr><td></td><td>x</td><td>x</td><td></td><td></td><td>RML + RLL</td></tr>
<tr><td>x</td><td></td><td>x</td><td></td><td></td><td>RUL + RLL</td></tr>
<tr><td>x</td><td>x</td><td>x</td><td></td><td></td><td>RUL + RML + RLL</td></tr>
<tr><td></td><td></td><td></td><td>x</td><td>x</td><td>LUL + LLL</td></tr>
</table>
</td></tr>
</table>

13.7.2.1. 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: ○ Missing Start Day: First of the month will be used unless this 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.

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
Haemoglobin	g/L	Male		180
		Female		180
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
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 U/L	High	≥1.5xULN T. Bilirubin + ≥ 2x ULN ALT

13.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 500 [1]
Absolute PR Interval	msec	< 110 [1]	> 220 [2]
Absolute QRS Interval	msec	< 75 [1]	> 110 [2]

NOTES:
[1] An upper limit of 450 would represent standard ECG values of PCI for HV studies, this has been extended to 500 as often with exacerbations the treatment can result in a short term prolongation of QTc up to 500.
[2] Represent standard ECG values of PCI for HV studies

13.8.3. 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

13.9. Appendix 9: Abbreviations & Trade Marks

13.9.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
AT	Air Trapping Score (% of iVlobe)
BVD	Blood Vessel Density (% of iVlobe)
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CENTRAL	Central lung region
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CT	Computed tomography
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
Diameter	Diameter
DISTAL	Distal lung region
DLco	Diffusion capacity
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
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
FRI	Functional respiratory imaging
FRC	Functional residual capacity
GSK	GlaxoSmithKline
GUI	Guidance
HRCT	High Resolution Computed Tomography
IA	Interim Analysis
IALD	Internal Airflow Lobar Distribution
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IL-8	Interleukin 8
IL-6	Interleukin 6

Abbreviation	Description
IMMS	International Modules Management System
IP	Investigational Product
iRaw	Imaging Airway Resistance
ITT	Intent-To-Treat
iVlobe	Lobar Volume
iVlobepred	Percent Predicted Lobar Volume
iVaw	Imaging Airway Volume
iVaww	Airway Wall Volume
LAS	Low Attenuation Score (% of iVlobe)
Length	Length
LL	Lung, lower lobes
LLL	Lung, left lower lobe
LOC	Last Observation Carries Forward
LUL	Lung, left upper lobe
LUL+LLL	Lung, left upper and lower lobe
MMP9	Matrix metallopeptidase 9
MMRC	Modified Medical Research Council
MMRM	Mixed Model Repeated Measures
NQ	Non-quantifiable
OTU	Operational Taxonomic Unit
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PEF	peak expiratory flow
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
qPCR	Quantitative polymerase chain reaction
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RLL	Lung, right lower lobe
RML	Lung, right middle lobe
RML+RLL	Lung, right middle and lower lobe
RUL	Lung, right upper lobe
RUL+RLL	Lung, right upper and lower lobe
RUL+RML	Lung, right upper and middle lobe
RUL+RML+RLL	Lung, right upper, middle and lower lobe
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
sGaw	Specific conductance
siRaw	Specific Imaging Airway Resistance

Abbreviation	Description
siVaw	Specific Imaging Airway Volume
siVaww	Specific Airway Wall Volume
SoC	Standard of Care
SOP	Standard Operation Procedure
sRaw	Specific Resistance
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TLC	Total lung capacity
TNFα	Tumor necrosis factor alpha
TOTAL	Total lung region
TRACHEA	Trachea
UL	Lung, upper lobes

13.9.2. Trademarks

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RAMOS NG
RANDALL NG

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13.10. Appendix 10: List of Data Displays

13.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.17	N/A
Efficacy	2.1 to 2.68	2.1
Safety	3.1 to 3.20	N/A
Pharmacokinetic	4.1 to 4.4	4.1
Pharmacodynamic and / or Biomarker	6.1 to 6.21	6.1
Section	**Listings**	
ICH Listings	1 to 34	
Other Listings	35 to 49	

13.10.2. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

13.10.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Subjects	ES1	Summary of Subject Disposition	ICH E3, FDAAA, EudraCT	SAC
1.2.	All Subjects	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.3.	APE	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.4.	All Subjects	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.5.	All Subjects	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.6.	APE	SP1	Summary of Study Populations	IDSL	SAC
1.7.	All Subjects	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
Demographic and Baseline Characteristics					
1.8.	All Subjects	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.9.	APE	DM11	Summary of Age Ranges	EudraCT	SAC
1.10.	All Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.11.	All Subjects	DM6	Summary of Race and Racial Combinations Details		SAC
1.12.	All Subjects	PII116678/final/ Table 2.109	Summary of Index Exacerbation Severity		

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
1.13.	All Subjects	MH1	Summary of Current Medical Conditions	ICH E3	SAC
1.14.	All Subjects	MH1	Summary of Past Medical Conditions	ICH E3	SAC
1.15.	All Subjects	CM1	Summary of Prior Medications	ICH E3	SAC
1.16.	All Subjects	CM1	Summary of Concomitant Medications	ICH E3	SAC
Exposure and Treatment Compliance					
1.17.	All Subjects	EX1	Summary of Exposure to Study Treatment	ICH E3 Include Daily Dose, Cumulative does and Days on study drug per template.	SAC
Family History of Cardiovascular Risk Factors					
1.18.	All Subjects	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC

13.10.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HRCT Imaging Endpoints					
2.1.	All Subjects	PII116678/ final/ Table 2.1	Summary of iVaw (mL) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.2.	All Subjects	PII116678/ final/ Table 2.2	Summary of iVaw (mL) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC
2.3.	All Subjects	PII116678/ final/ Table 2.3	Summary of iVaw (mL) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC
2.4.	All Subjects	PII116678/ final/ Table 2.4	Summary of iVaw (mL) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.5.	All Subjects	PII116678/ final/ Table 2.9	Summary of siVaw (mL/L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.6.	All Subjects	PII116678/ final/ Table 2.10	Summary of siVaw (mL/L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC
2.7.	All Subjects	PII116678/final/ Table 2.11	Summary of siVaw (mL/L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC
2.8.	All Subjects	PII116678/final/ Table 2.12	Summary of siVaw (mL/L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC
2.9.	All Subjects	PII116678/final/ Table 2.17	Summary of iRaw (kPa*s/L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.10.	All Subjects	PII116678/final/ Table 2.18	Summary of iRaw (kPa*s/L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.11.	All Subjects	PII116678/final/ Table 2.19	Summary of iRaw (kPa*s/L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used	SAC
2.12.	All Subjects	PII116678/final/ Table 2.20	Summary of iRaw (kPa*s/L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.13.	All Subjects	PII116678/final/ Table 2.25	Summary of siRaw (kPa*s) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.14.	All Subjects	PII116678/final/ Table 2.26	Summary of siRaw (kPa*s) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.15.	All Subjects	PII116678/final/ Table 2.27	Summary of siRaw (kPa*s) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used	SAC
2.16.	All Subjects	PII116678/final/ Table 2.28	Summary of siRaw (kPa*s) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.17.	All Subjects	PII116678/final/ Table 2.33	Summary of iVlobe (L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.18.	All Subjects	PII116678/final/ Table 2.34	Summary of iVlobe (L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.19.	All Subjects	PII116678/final/ Table 2.35	Summary of iVlobe (L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.20.	All Subjects	PII116678/final/ Table 2.36	Summary of iVlobe (L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.21.	All Subjects	PII116678/final/ Table 2.41	Summary of Percent Predicted iVlobe (%) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Note in HARP to output (%) it may be necessary to input (%%)	SAC
2.22.	All Subjects	PII116678/final/ Table 2.42	Summary of Percent Predicted iVlobe (%) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline Note in HARP to output (%) it may be necessary to input (%%)	SAC
2.23.	All Subjects	PII116678/final/ Table 2.43	Summary of Percent Predicted iVlobe (%) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Note in HARP to output (%) it may be necessary to input (%%)	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.24.	All Subjects	PII116678/final/ Table 2.44	Summary of Percent Predicted iVlobe (%) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline Note in HARP to output (%) it may be necessary to input (%%)	SAC
2.25.	All Subjects	PII116678/final/ Table 2.49	Summary of LAS (% of iVlobe) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.26.	All Subjects	PII116678/final/ Table 2.50	Summary of LAS (% of iVlobe) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.27.	All Subjects	PII116678/final/ Table 2.51	Summary of LAS (% of iVlobe) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.28.	All Subjects	PII116678/final/ Table 2.52	Summary of LAS (% of iVlobe) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.29.	All Subjects	PII116678/final/ Table 2.55	Summary of IALD (%) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.30.	All Subjects	PII116678/final/ Table 2.56	Summary of IALD (%) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.31.	All Subjects	PII116678/final/ Table 2.57	Summary of IALD (%) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central, Distal and Total do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.32.	All Subjects	PII116678/final/ Table 2.58	Summary of IALD (%) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central, Distal and Total do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.33.	All Subjects	PII116678/final/ Table 2.61	Summary of AT (% of iVlobe) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.34.	All Subjects	PII116678/final/ Table 2.62	Summary of AT (% of iVlobe) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.35.	All Subjects	PII116678/final/ Table 2.63	Summary of AT (% of iVlobe) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.36.	All Subjects	PII116678/final/ Table 2.64	Summary of AT (% of iVlobe) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.37.	All Subjects	PII116678/final/ Table 2.67	Summary of BVD (% of iVlobe) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.38.	All Subjects	PII116678/final/ Table 2.68	Summary of BVD (% of iVlobe) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.39.	All Subjects	PII116678/final/ Table 2.69	Summary of BVD (% of iVlobe) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.40.	All Subjects	PII116678/final/ Table 2.70	Summary of BVD (% of iVlobe) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.41.	All Subjects	PII116678/final/ Table 2.73	Summary of iVaww (mL) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.42.	All Subjects	PII116678/final/ Table 2.74	Summary of iVaww (mL) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.43.	All Subjects	PII116678/final/ Table 2.75	Summary of iVaww (mL) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC
2.44.	All Subjects	PII116678/final/ Table 2.76	Summary of iVaww (mL) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC
2.45.	All Subjects	PII116678/final/ Table 2.79	Summary of siVaww (mL/L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.46.	All Subjects	PII116678/final/ Table 2.80	Summary of siVaww (mL/L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC
2.47.	All Subjects	PII116678/final/ Table 2.81	Summary of siVaww (mL/L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.48.	All Subjects	PII116678/final/ Table 2.82	Summary of siVaww (mL/L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC
2.49.	All Subjects	PII116678/final/ Table 2.85	Summary of Trachea Length (mm), Diameter (mm) and Length /Diameter (mm/mm) (Absolute)	Footnote any transformations used	SAC
2.50.	All Subjects	PII116678/final/ Table 2.86	Summary of Trachea Length (mm), Diameter (mm) and Length /Diameter (mm/mm) (Change from Baseline)	Footnote any transformations used Footnote baseline	SAC
2.51.	All Subjects	PII116678/final/ Table 2.14	Summary of Statistical Analysis for siVaw (mL/L), for Individual Lobes at FRC using Untrimmed Data	Ensure no overlapping information across pages for each Lobe Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.52.	All Subjects	PII116678/final/ Table 2.16	Summary of Statistical Analysis for siVaw (mL/L), for Individual Regions at FRC using Untrimmed Data	Ensure no overlapping information across pages for each Lobe Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.53.	All Subjects	Refer to: PII116678/final/ Table 2.16 Note: there will be less regions	Summary of Statistical Analysis for siVaw (mL/L), for Distal Region at FRC using Scan Trimmed Data	Ensure no overlapping information across pages for each Lobe Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.54.	All Subjects	Refer to: PII116678/final/ Table 2.29 Note: there will be less regions	Summary of Statistical Analysis for siRaw (kPa*s), for Distal Region at FRC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.55.	All Subjects	Refer to: PII116678/final/ Table 2.54 Note: there will be less regions	Summary of Statistical Analysis for LAS (% of iVlobe), for Total Region at TLC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.56.	All Subjects	Refer to: PII116678/final/ Table 2.60 Note: there will be less regions	Summary of Statistical Analysis for IALD (%), for Upper and Lower Regions	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.57.	All Subjects	Refer to: PII116678/final/ Table 2.66 Note: there will be less regions	Summary of Statistical Analysis for AT (% of iVlobe), for Total Region at FRC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.58.	All Subjects	Refer to: PII116678/final/ Table 2.72 Note: there will be less regions	Summary of Statistical Analysis for BVD (% of iVlobe), for Total Region at TLC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.59.	All Subjects	Refer to: PII116678/final/ Table 2.84 Note: there will be less regions	Summary of Statistical Analysis for siVaww (mL/L), for Distal Region at TLC using Untrimmed Data	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
Lung Function					
2.60.	All Subjects	PII115119/ Part_A /Table 3.18	Summary of FEV1 (L) and FVC (L) (Absolute Values)	Summaries by Visit Footnote any transformations used	SAC
2.61.	All Subjects	PII115119/ Part_A /Table 3.19	Summary of FEV1 (L) and FVC (L) (Change from Baseline)	Summaries by Visit Footnote any transformations used Footnote Baseline	SAC
2.62.	All Subjects	PII116678/ final /Table 2.88	Summary of Statistical Analysis for FEV1 (L) (Change from Baseline)	Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.63.	All Subjects	PII116678/ postcsr_2017_01 /Table 2.1	Sub Group Analysis: by Index Exacerbation Severity Summary of Statistical Analysis for FEV1 (L) (Change from Baseline)	Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.64.	All Subjects	PII116678/ final /Table 2.88	Summary of Statistical Analysis for FVC (L) (Change from Baseline)	Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
Relief Medication					
2.65.	All Subjects	Refer to programming notes	Summary of Rescue Medication Free Days	Use the standard tu_sumstatsinrows to summarise Rescue Medication Free days by time period and treatment. Include columns for time period, treatment, N, n, mean, 95% CI, SD, median, min and max	SAC
2.66.	All Subjects	Refer to programming notes	Summary of Mean Number of Occasions of Rescue Use per Day	Use the standard tu_sumstatsinrows to summarise Mean Number of Occasions of Rescue Use per Day by time period and treatment. Include columns for timeperiod, treatment, N, n, mean, 95% CI, SD, median, min and max	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exacerbations					
2.67.	All Subjects	Refer to PII116678/ final /Table 2.97 And programming notes	Summary of Investigator Defined Exacerbations	Update rows to be consistent with data i.e. include 6, 7, etc exacerbations as appropriate	SAC
2.68.	All Subjects	Refer to PII116678/ final /Table 2.116 And programming notes	Summary of Investigator Reported Exacerbations Requiring Concomitant Medication Treatment	Update rows to be consistent with data i.e. include 6, 7, etc exacerbations as appropriate	SAC

13.10.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Lung Function					
2.1.	All Subjects	Refer to PII116678/final/ Table 2.2 but update the number of plots based on the data as appropriate	Summary of PEF (morning)	X-axis to contain each Day, with Means and confidence intervals, grouped by Treatment. Include baseline as a subheading per example shell	SAC

13.10.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	All Subjects	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
3.2.	All Subjects	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency	ICH E3	SAC
3.3.	All Subjects	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3 Include flag for serious	SAC
3.4.	All Subjects	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT	SAC
Serious and Other Significant Adverse Events					
3.5.	All Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.6.	All Subjects	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL	SAC
Laboratory: Chemistry					
3.7.	All Subjects	LB1	Summary of Chemistry	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.8.	All Subjects	LB15	Summary of Worst Case Emergent Laboratory Chemistry Results Post-Baseline Relative to Baseline		SAC
Laboratory: Hematology					
3.9.	All Subjects	LB1	Summary of Hematology	ICH E3	SAC
3.10.	All Subjects	LB15	Summary of Worst Case Emergent Laboratory Hematology Results Post-Baseline Relative to Baseline		SAC
Laboratory: Hepatobiliary (Liver)					
3.11.	All Subjects	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC
3.12.	All Subjects	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.13.	All Subjects	EG1	Summary of ECG Findings	IDSL	SAC
3.14.	All Subjects	EG2	Summary of ECG Values by Visit		SAC
3.15.	All Subjects	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
Vital Signs					
3.16.	All Subjects	VS1	Summary of Vital Signs		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.17.	All Subjects	VS1	Summary of Change from Baseline in Vital Signs	ICH E3 Includes Baseline Values	SAC
3.18.	All Subjects	VS7	Summary of Worst Case Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		SAC

13.10.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma Concentration					
4.1.	PK	PK01 PII116678/final/Table 4.1	Summary of Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL)	All visits/timepoints, include a column for visit. Summarise PK data on original scale. Produce 95% CIs Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Excluding the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.2.	PK	PK01 PII116678/final/Table 4.2	Summary of Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL) Including All PK Concentrations Analysed	All visits/timepoints, include a column for visit. Summarise PK data on original scale. Produce 95% CIs Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Including the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC
4.3.	PK	PII116678/final/Table 4.3	Summary of Log-Transformed Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL)	All visits/timepoints, include a column for visit and planned time. Summarise PK data on original scale. Produce n, No. imputed, geometric mean and corresponding 95% Cis SD Logs and %CVb Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Excluding the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.4.	PK	PII116678/final/Table 4.4	Summary of Log-Transformed Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL) Including All PK Concentrations Analysed	All visits/timepoints, include a column for visit and planned time. Summarise PK data on original scale. Produce n, No. imputed, geometric mean and corresponding 95% Cis SD Logs and %CVb Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Including the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC

13.10.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma Concentration					
4.1.	PK	Refer to PII116678/ final/ Figure 4.1 But include additional timepoints per programming notes	Box and Whisker Plot of Plasma Concentration	Two figures to be created: 1st: Plasma Concentration at Day 1 (5 min and 24 hours post-dose) and Day 12 2nd: Plasma Concentration at Day 12, Day 28, Day 56 and Day 84 Note: Use the separate NEMI Diskus and NEMI ELLIPTA	SAC

13.10.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MRNa					
6.1.	All Subjects	PII115119/ Part A/ Listing 40	Summary of Statistical Analysis of mRNA Transcriptome in Induced Sputum (Selected Probe Sets Related to Neutrophil Function)	Summarise ratio, 95% CI and p-values. Sort alphabetically on probe set ID	SAC
6.2.	All Subjects	PII115119/ Part A/ Listing 40	Summary of Statistical Analysis of mRNA Transcriptome in Blood (All Probe Sets)	Biostatistics will await guidance following unblinded regarding which, if any, probe sets should be presented for the exploratory analysis and confirmation if a cut off criteria other than p-value<0.05 AND (fold change> 1.5 OR fold change< -1.5) should be used in determining which comparisons for the probe sets should be presented. Summarise ratio, 95% CI and p-values.	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.3.	All Subjects	PII115119/ Part A/ Listing 40	Summary of Additional Statistical Analysis of mRNA Transcriptome in Induced Sputum (All Probe Sets)	Biostatistics will await guidance following unblinded regarding which, if any, probe sets should be presented for the exploratory analysis and confirmation if a cut off criteria other than p-value<0.05 AND (fold change> 1.5 OR fold change< -1.5) should be used in determining which comparisons for the probe sets should be presented. Summarise ratio, 95% CI and p-values.	SAC
Cell Count Data and PMN Differentials					
6.4.	All Subjects	PII115119/ Part A/Table 5.7	Summary Statistics (Absolute): Total Cell Count Data in Sputum by Treatment and Time.	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.5.	All Subjects	PII115119/ Part A/Table 5.8	Summary Statistics (Change from Baseline): Total Cell Count Data in Sputum by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.6.	All Subjects	PII115119/ Part A/Table 5.9	Summary Statistics (Absolute): PMNs Differentials in Sputum by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.7.	All Subjects	PII115119/ Part A/Table 5.10	Summary Statistics (Change from Baseline): PMNs Differentials in Sputum by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.8.	All Subjects	PII115119/ Part A/Table 5.11	Summary Statistics (Absolute): Total Cell Count Data in Blood by Treatment and Time.	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.9.	All Subjects	PII115119/ Part A/Table 5.12	Summary Statistics (Change from Baseline): Total Cell Count Data in Blood by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.10.	All Subjects	PII115119/ Part A/Table 5.13	Summary Statistics (Absolute): PMNs Differentials in Blood by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.11.	All Subjects	PII115119/ Part A/Table 5.14	Summary Statistics (Change from Baseline): PMNs Differentials in Blood by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
Inflammatory Biomarkers					
6.12.	All Subjects	PII115119/ Part A/Table 5.17	Summary Statistics (Absolute): Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for this Table (6.12) and a log transformation will be required for Table 6.14. However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.13.	All Subjects	PII115119/ Part A/Table 5.18	Summary Statistics (Change from Baseline): Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for this Table (6.13) and a log transformation will be required for Table 6.15. However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.14.	All Subjects	PII115119/ Part A/Table 5.19	Summary Statistics (Log-Transformed Absolute) Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for Table 6.12 and a log transformation will be required for this Table (6.14). However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.15.	All Subjects	PII115119/ Part A/Table 5.20	Summary Statistics (Log-Transformed Change from Baseline) Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for Table 6.13 and a log transformation will be required for this Table (6.15). However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
Microbiome (16S rRNA) and qPCR					
6.16.	All Subjects	PD4 and Refer to programming notes	Summary Statistics (Absolute): Microbiome (16S rRNA) Relative Abundance by Treatment and Time	If Data available Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.17.	All Subjects	PD4 and Refer to programming notes	Summary Statistics (Percentage Change from Baseline): Microbiome (16S rRNA) Relative Abundance by Treatment and Time	If Data available. Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.18.	All Subjects	PII115119/ Part A/Table 5.24	Summary Statistics (Absolute): qPCR delta Ct by Treatment and Time	If Data available. Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.19.	All Subjects	PII115119/ Part A/Table 5.25	Summary Statistics (Log-Transformed Absolute): qPCR fold change by Treatment and Time	If Data available. Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
Bacterial Culture					
6.20.	All Subjects	PII115119/ Part A/Table 5.26	Frequency Table of Bacterial Culture (Presence) by Treatment and Time		SAC

13.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	APE	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	All Subjects	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	All Subjects	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4.	All Subjects	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC
5.	All Subjects	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
6.	All Subjects	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
7.	All Subjects	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
8.	APE	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
9.	All Subjects	DM2	Listing of Demographic Characteristics	ICH E3	SAC
10.	All Subjects	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
11.	All Subjects	CM3	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
12.	All Subjects	EX3	Listing of Exposure Data	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
13.	All Subjects	AE8	Listing of All Adverse Events	ICH E3	SAC
14.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
15.	All Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
16.	All Subjects	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC
17.	All Subjects	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
18.	All Subjects	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
19.	All Subjects	AE8	Listing of Adverse Events Leading to Withdrawal from Study or Permanent Discontinuation of Study Treatment	ICH E3	SAC
Hepatobiliary (Liver)					
20.	All Subjects	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
21.	All Subjects	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC
22.	All Subjects	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC
23.	All Subjects	LIVER7	Listing of Liver Biopsy Details		SAC
24.	All Subjects	LIVER8	Listing of Liver Imaging Details		SAC
All Laboratory					
25.	All Subjects	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
26.	All Subjects	LB5	Listing of Laboratory Values of Potential Clinical Importance		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
27.	All Subjects	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
ECG					
28.	All Subjects	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
29.	All Subjects	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
30.	All Subjects	CP_EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
31.	All Subjects	EG5	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
32.	All Subjects	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
33.	All Subjects	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC

13.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demography and Baseline Characteristics					
34.	All Subjects	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC
35.	All Subjects	Refer to Programming notes	COPD Disease duration and Exacerbation Duration	Include investigator ID, subject ID, country, treatment group, COPD Disease Duration (in years and months) and Exacerbation History (number requiring oral/systemic corticosteroids and/or antibiotics and number requiring hospitalisation) as columns	SAC
36.	All Subjects	PREG1a	Listing of Subjects Who Became Pregnant During the Study	Also indicate if the female partners of subjects became pregnant during the study	SAC
Labs					
37.	All Subjects	LB13	Listing of Laboratory Reference Ranges		SAC
38.	All Subjects	CP_LB5	Listing of Laboratory Values Outside Normal Reference Range		SAC
PK					
39.	PK	PK07	Listing of Individual Subjects Plasma Concentrations at all time points		SAC
PD/Biomarkers					
40.	All Subjects	PII115119/ Part A/Listing 25	Listing of Sputum Collection	Include sample ID if available	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
41.	All Subjects	PII115119/ Part A/Listing 26	Listing of Blood Collection for RNA		SAC
42.	All Subjects	PII115119/ Part A/Listing 31	Listing of Cell Count Data		SAC
43.	All Subjects	PII115119/ Part A/Listing 32	Listing of PMNs Differentials		SAC
44.	All Subjects	PII115119/ Part A/Listing 34	Listing of Individual Subject Inflammatory Cytokine Biomarker Data		SAC
45.	All Subjects	PII115119/ Part A/Listing 35	Listing of Microbiome (16S rRNA) Biomarker Data		SAC
46.	All Subjects	PII115119/ Part A/Listing 36	Listing of qPCR Data		SAC
47.	All Subjects	PII115119/ Part A/Listing 37	Listing of Bacterial Culture Data		SAC
Compliance and Drug Accountability					
48.	All Subjects	Example Shell POP_L1	Listing of Overall Compliance	Adaptation of IDSL Shell COMP2	SAC
49.	All Subjects	POP_L2	Listing of Drug Accountability Data	Adaptation of IDSL Shell COMP3A	SAC
Patient Profiles					
50.	All Subjects	CVEND1	Patient Profile for Congestive Heart Failure	Listing for subject with Myocardial infarction/unstable angina	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
51.	All Subjects	Refer to IDSL Library Arrythmias Statistical Display Standards	Patient Profile for Arrythmias	Listing for subject with Arrhythmias	SAC
52.	All Subjects	Refer to IDSL Library Cerebrovascular Events, Stroke And Transient Ischemic Attack Statistical Display Standards	Patient Profile for Cerebrovascular Events, Stroke and Transient Ischemic Attack	Listing for subject with Cerebrovascular events/stroke and transient ischemic attack	SAC

13.11. Appendix 11: Example Mock Shells for Data Displays

Available Upon Request

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 201928: A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).
Compound Number	:	GSK2269557
Effective Date	:	26-JUN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201928.
- This RAP is intended to describe the pharmacodynamic/biomarker, safety, pharmacokinetic and efficacy analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver
PPD Statistician (Clinical Statistics)

RAP Team Approvals:

Approver	Date	Approval Method
PPD Study Accountable Person (Clinical Development)	11-JUN-2018	Email
PPD Study Manager (Clinical Development)	14-JUN-2018	Email
PPD Head (Respiratory HUB)	20-JUN-2018	Email
PPD Medical Director (Safety Lead)	19-JUN-2018	Email
PPD Data Quality Lead (Data Management)	11-JUN-2018	Email
PPD Clinical Pharmacokineticist (PK)	15-JUN-2018	Email
PPD Director (Human Translational Models and Biomarkers)	11-JUN-2018	Email
PPD Senior Director (Target Sciences Computational Biology)	19-JUN-2018	Email
PPD Principal Programmer (Clinical Programming)	11-JUN-2018	Email

Notes:
[1] Approval of the gene list

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Director (Clinical Statistics)	20-JUN-2018	email
PPD Manager (Clinical Programming)	26-JUN-2018	email

CONFIDENTIAL

201928

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
GlaxoSmithKline Document Number	**Date**	**Version**
2014N218070_00	2015-JUN-04	Original
2014N218070_01	2015-NOV-30	Amendment No. 1
Remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria and in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. It therefore is not valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.		
2014N218070_02	2016-JAN-26	Amendment No. 2
Increase the body mass index (BMI) range in the inclusion criteria from 18-32 kg/m^2 (inclusive) to 16- 35 kg/m^2 (inclusive). The original BMI range from 18-32 kg/m^2 is a typical range used in both healthy volunteer studies and general subject populations. The revised range is more appropriate for a COPD patient population.		
2014N218070_03	2016-NOV-16	Amendment No. 3
To remove photo toxicity from the protocol and to include minor administrative and clarification changes.		
2014N218070_04	2017-MAR-2	Amendment No. 4
Replace the administration of GSK2269557 via the DISKUS™ device (1000 µg) by a comparable dose administered via the ELLIPTA™ device (700 µg). GSK2269557 is no longer manufactured for use with the DISKUS device which will be replaced with ELLIPTA Device. To increase the number of patients to be recruited to obtain sufficient completers. Minor updates and clarifications.		

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Total lung capacity and lung lobar volumes included in HRCT secondary endpoint parameters	• Total lung capacity and lung lobar volumes dropped from HRCT secondary endpoint parameters included as an exploratory endpoint parameter instead	• The clinically relevant HRCT parameters are still to be decided. However, there was no clinical benefit seen in the comparison between GSK2269557 1000 mcg and Placebo in these parameters.

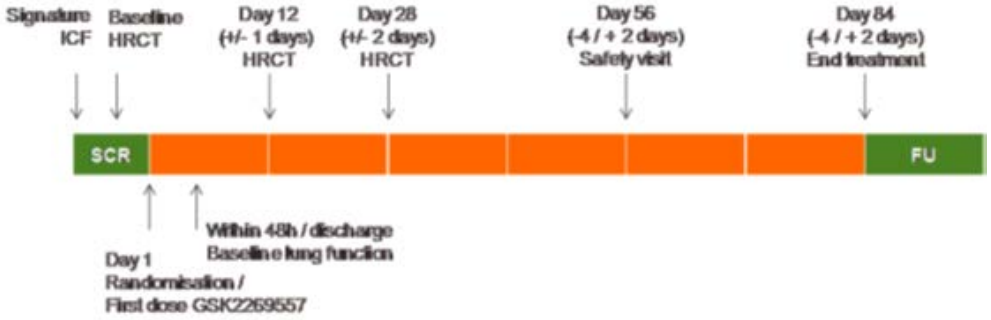
• Analysis population:
  • All Subject
  All randomised subjects who receive at least one dose of the study treatment.
  This population will be based on the
  treatment the subject actually received.
  • Pharmacokinetic
  Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.
	• Analysis population:
	  • All Subject
	  All randomised subjects who receive at least one dose of the study treatment.
	  This population will be based on the
	  treatment the subject actually received.
	  • Pharmacokinetic
	  Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.
	Note: The two subjects who were not compliant with inhaler instructions will be excluded from the outcome summaries if they received active treatment but will be included if they received placebo
		• 2 subjects were not compliant with inhaler instructions and may not have received the full dose in amendment 4. Therefore, these subjects will be excluded from the outcome summaries if they received active treatment but will be included if they received placebo. Sensitivity analyses may be conducted including these subjects.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline in siVaw, iVaw, iRaw, siRaw, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Haematology, clinical chemistry • Vital signs • 12-lead ECG

Objectives	Endpoints
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD.	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients. • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.	• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.
Exploratory Objectives	**Exploratory Endpoints**
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 qPCR.
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Multi-centre and Multi-Country • Randomised • Double-blind • Placebo-controlled • Parallel group
Dosing	• Once daily, in the morning for 84 days • Administered through the Diskus dry powder Inhaler
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Initially planned for approximately 30 subjects randomised to receive either 1000 μg GSK2269557 (Diskus) or matching Placebo in a 1:1 ratio as it was anticipated that 10 patients would drop-out. Twenty-eight subjects were randomised to this schedule, however, due to expiration date there was a protocol amendment following which additional subjects were subsequently randomised to receive either 700 μg GSK2269557 (Ellipta) or matching Placebo (Ellipta) in a 1:1 ratio. The protocol was updated such that approximately 45 subjects with an acute exacerbation of COPD would be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. • Subjects are assigned to treatment in accordance with the randomisation schedule generated by Clinical Statistics, using validated software.
Interim Analysis	• No formal interim analysis will be conducted

2.4. Statistical Analyses

2.4.1. Primary Analyses

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at

Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

Further details are provided in Section 7.1.

3. PLANNED ANALYSES

3.1. 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 Enrolled (APE)	• All subjects who were screened for eligibility	• Study Population

All Subject	• Comprised of all subjects who were randomised.
	• This population will be based on the treatment the subject actually received.
	  ○ If participants receive >1 treatment, then they will be summarised according to the most frequently dosed treatment. In cases where the frequency is equal, the participant will be assigned the lowest dose strength of nemiralisib.
	  ○ If participants receive no treatment, then they will be summarised according to "No Treatment"
		• Study Population
		• Pharmacodynamics and Biomarker
		• Safety
		• Efficacy

Pharmacokinetic (PK)	• Subjects in the 'All Subject' population for whom a pharmacokinetic sample was obtained and analysed.	• PK

Refer to Appendix 10: List of Data Displays which details the population used for each display.
Note: The two subjects who were not compliant with inhaler instructions will be excluded from the outcome summaries if they received active treatment but will be included if they received placebo

4.1. Protocol Deviations

During the course of the study it was noted that two subjects did not complete dosing instructions as required. The primary plan is if the subjects received active treatment they will be excluded from the study outcome summaries; if the subject received placebo treatment, they will be included in the study outcome summaries. It has not yet been identified if they received placebo or active treatment. A footnote will be applied to all relevant displays stating the rationale, subject number, treatment and if they were excluded, e.g. "Subjects X & Y did not complete dosing instructions as required; subject X received nemiralisib and was therefore excluded, subject Y received placebo and was therefore included." The footnote may be tweaked for aesthetic purposes.

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.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan, refer to Appendix 1.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations 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.

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
This will be derived as subjects who did not receive any treatment		No Treatment	1
This will be derived as subjects in RandALL codes A or C		All Placebo	2
This will be derived as subjects in RandALL codes B or D		All NEMI	3
A	Placebo	Placebo Diskus	4
B	GSK2269557 1000 mcg	NEMI Diskus	5
C	Placebo via Ellipta	Placebo Ellipta	6
D	GSK2269557 700 mcg	NEMI Ellipta	7

NOTES:

1. The following footnote will be presented on displays which use the "Placebo Diskus", "NEMI Diskus", "Placebo Ellipta" or "NEMI Ellipta" treatment groups:
   NEMI Diskus =1000 mcg Nemiralisib administered via the Diskus device; NEMI Ellipta =700 mcg Nemiralisib administered via the Ellipta device
2. Order represents treatments being presented in TFL, as appropriate

Treatment groups "Placebo" and "Placebo via Ellipta" (RandAll NG codes A and C) will be combined into "All Placebo" treatment group. Similarly, treatment groups "GSK2269557 700 mcg" and "GSK2269557 1000 mcg" (RandAll NG codes B and D) will be combined into "All NEMI" treatment group.

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. All NEMI vs All Placebo

Notes:

- The "All Placebo" and "All NEMI" groups and "All NEMI vs All Placebo" treatment comparison will be presented for Pharmacodynamic and biomarker, efficacy and study population summaries unless otherwise specified.
- The "Placebo Diskus", "NEMI Diskus", "Placebo Ellipta" or "NEMI Ellipta" treatment groups will be presented for Pharmacokinetic and safety summaries unless otherwise specified.
- The "Placebo Diskus", "NEMI Diskus", "Placebo Ellipta" or "NEMI Ellipta" treatment groups will be presented for all listings

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 Assessments Considered as Baseline				Baseline Used in Data Display
	Screening	Day 1 (Pre-Treatment)	Day 2 Within 48H/discharge (On Treatment)	Day 12 (On Treatment)	
Safety					
Labs including Haematology	X	X			Day 1
ECG	X	X			Day 1
Vitals	X	X			Day 1
Efficacy					
HRCT Untrimmed	X				Screening
HRCT Scan Trimmed					
Screening&Day12	X				Screening
Screening&Day28	X				Screening
Day12&Day28				X	Day 12
FEV_1 and FVC		X	X		Day 1[1]
Daily PEF [2]		X			Day 1
					Mean of Days 1 to 3
					Maximum of Days 1 to 3
Pharmacodynamic					
Sputum and Blood	X				Screening
Genetic sample (PGx) [3]			X		

NOTES:

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- [1] Baseline will be investigated to ensure there is sufficient data and will be footnoted as appropriate
- [2] For PEF 3 different baselines will be calculated: Day 1, mean of Days 1 to 3 and Maximum of Days 1 to 3. TFLs will be footnoted with the relevant baseline.
- [3] Collected at any time after randomisation

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Examination of Covariates and Subgroups

5.3.1. Covariates and Other Strata

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

Category	Details
Covariates	Age, Sex, BMI, Country, Primary exacerbation severity

5.3.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Primary exacerbation severity	Moderate or Severe [1]
Country	Country

NOTES:

[1] Exacerbations are defined as severe if they require hospitalisation, otherwise they are defined as moderate

5.4. 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
13.3	Appendix 3: Assessment Windows
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	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 "All Subject" 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 10: List of Data Displays.

7. PHARMACODYNAMIC AND BIOMARKER ANALYSES

7.1. Primary Pharmacodynamic and Biomarker Analyses

7.1.1. Endpoint / Variables

Sputum RNA will be extracted and hybridised using a balanced batch design. An appropriate microarray platform will be determined at the time of hybridisation, to allow for improvements in technology. The quality of the data will be assessed and then normalised using appropriate methodologies and software.

Microarray mRNA data will be normalised using gcRMA or RMA in Array Studio v5.0 or later. After normalisation, the data will be quality assessed and any samples deemed as QC fails will be excluded from any further analysis. This quality assessment will involve looking for outlying signals in both the normalised expression data and the MAS5 QC metrics generated from each sample. If any samples are excluded, the remaining data will be re-normalised. The output from the normalisation will be log2 transformed mRNA intensity data (measured in arbitrary units).

Since the data will be log2 transformed prior to the analysis the treatment effects will be expressed as ratios after back transformation (2^). These ratios can be converted from treatment ratios to fold change values as follows:

- If ratio ≥ 0 then fold change = ratio
- If ratio <0 then fold change = -1/ratio

Microarray data consists of expression values (log2-transformed) derived from individual probe sets designed against coding regions of individual genes. More than one probe set can exist per gene. This analysis will be conducted at the probe set level.

The mRNA data gives results from ~14000 genes encoded by ~54000 probe sets. To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA, we identified 258 gene to subset our data on, refer to Section 13.6.5. The gene names were converted to Affymetrix probe IDs, this resulted in 638 probes refer to Section 13.6.5.

To compare the expression value between treatments for each probe set, linear repeated measures mixed effects model will be fitted to each probe set, with log2 (intensity) as the response variable. Note: log2 (intensity) may also be referred to as mRNA intensities (logarithm base 2 scale). Alteration in previously identified immune cell mechanisms specifically related to neutrophil function will be determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment by the analysis of mRNA intensities (logarithm base 2 scale) subset by the 638 probes identified in Section 13.6.5.

7.1.2. Summary Measure

A repeated measures modelling analysis will be performed on the subset of 638 probes which have previously identified immune cell mechanisms specifically related to neutrophil function.

The model will be used to estimate the baseline adjusted fold changes for active treatment and placebo calculated for Day 12, Day 28 and Day 84 along with the corresponding 95% confidence intervals and unadjusted P-values. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals and unadjusted P-values.

7.1.3. Population of Interest

The primary pharmacodynamic analyses will be based on the "All Subject" population, unless otherwise specified.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: 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.

7.1.4.1. Statistical Methodology Specification

Endpoint / Variables
• Alterations in the previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment. The response variable will be mRNA intensities (logarithm base 2 scale).
Model Specification
The mRNA data gives results from ~14000 genes encoded by ~54000 probe sets. A subset of 638 probe sets specifically relating to the cell mechanisms of neutrophil function is specified in Section 13.6.5 This subset will comprise the primary statistical analysis dataset. The repeated measures modeling analysis will be performed for each probe set separately. To estimate differences in mRNA intensities between treatment groups, a repeated measures model will be fitted to mRNA intensities at Screening, Day 12, Day 28 and Day 84. The Screening time point will be considered Baseline. The model will include terms for treatment group (All Placebo or All NEMI), time and a treatment group by time interaction. An unstructured (UN) covariance structure will be fitted, however, in the event that this structure results in a model failing to converge then attempts will be made to fit a model that converges i.e. alternative covariance structures may be considered. The denominator degrees of freedom for use in significance testing

will be computed using the Kenward Rogers approximation.

Back transformed baseline-adjusted means along with 95% CIs will be calculated for each treatment group and time-point. Additionally, baseline adjusted fold changes between All NEMI and All Placebo will be calculated for Day 12, Day 28 and Day 84 as well as the ratio between the baseline adjusted fold changes for All NEMI vs. All Placebo at day 12, 28 and 84, along with 95% CI and two-sided unadjusted p-values. Additionally, the fold change between All NEMI vs. All Placebo at day 84 may be investigate along with 95% CI and two-sided unadjusted p-values and other comparisons of interest.

To enable review by the study team a spreadsheet will be created containing the output for all probe sets in scope for the primary statistical analysis will be generated and ranked by p-value for the comparison All NEMI vs. All Placebo at day 12, 28 and 84 in separate tabs. A separate spreadsheet will be created containing only probe sets where the p-value for the comparison All NEMI vs. All Placebo is <0.05, with day 12, 28 and 84 in separate tabs. Such probe sets will be ranked by fold change, with the expectation that, in general, a greater than a 1.5-fold change is scientifically meaningful. To comply with guidance regarding QC, each tab will be stored as a SAS dataset to ensure QC can be audited.

Following review by the study team of the results, a subset of probe sets will be identified and may be used for further reporting.

Model Checking & Diagnostics

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.
  - In the event that this model fails to converge, alternative correlation structures may be considered

Model Results Presentation

The subset of probe sets where the p-value for the comparison All NEMI vs. All Placebo at day 12, 28 and 84, is <0.05 will be reported as described below:

Output from the repeated measures modelling detailed above will be tabulated. In particular, the estimated baseline adjusted fold changes, 95% CI, standard error (on the logarithm base 2 scale), unadjusted p-values at each time point and for the active treatment comparison with placebo. The probe set, gene/gene description will be included in the outputs.

7.2. Exploratory Pharmacodynamic and Biomarker Analyses

7.2.1. Endpoint / Variables

In addition to the primary analysis, there is an exploratory objective to establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. To address this blood and sputum mRNA data, as described in Section 7.1,but analyses will be conducted

on the complete mRNA data, i.e. the results from ~14000 genes encoded by ~54000 probe sets.

To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Endpoints may include, but not limited to, cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, total cell counts and PMNs differentials.

To explore the pharmacodynamic effects in blood of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Endpoints may include, but not limited to, total cell counts and PMNs differentials.

7.2.2. Summary Measure

To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. A repeated measures modelling analysis will be performed on the complete probe set. The model will be used to estimate the baseline adjusted fold changes for active treatment and placebo calculated for Day 12, Day 28 and Day 84 along with the corresponding 95% confidence intervals and unadjusted P-values. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals and unadjusted P-values.

To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Summary statistics of endpoints may include, but not limited to, cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, total cell counts and PMNs differentials.

To explore the pharmacodynamic effects in blood of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo. Summary statistics of endpoints may include, but not limited to, total cell counts and PMNs differentials.

7.2.3. Population of Interest

The exploratory pharmacodynamic analyses will be based on the “All Subjects” population, unless otherwise specified.

As previously discussed for the two subjects that did not follow inhalation instructions, if the subjects received active treatment they will be excluded from the study outcome summaries; if the subject received placebo treatment, they will be included in the study outcome summaries.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Refer to Section 7.1.4.1 for statistical methodology specification, however, for the exploratory analysis, the models will be fitted but on the complete dataset ~14000 genes encoded by ~54000 probe sets; sputum and blood data will be analysed separately.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. For each endpoint, the values will be inspected to determine whether a data transformation is required. It is expected that: cytokines may require a transformed on the natural logarithm scale

8. EFFICACY ANALYSES

8.1. Secondary Efficacy Analyses (Not From HRCT Analyses)

8.1.1. Endpoint / Variables

To evaluate the effect of once daily repeat inhaled doses of nemiralisib on lung function parameters in subjects with acute exacerbation of COPD compared to placebo. Lung function parameters including:

- PEF
- FEV_1 and FVC at clinic prior to sputum induction
- reliever usage

8.1.2. Summary Measure

For PEF, summary statistics for the change from baseline PEF will be presented in tabular form, mean and 95% CIs of AM PEF readings will be plotted by study treatment vs. Study Day.

For FEV_1 (mL) and FVC (mL), a change from baseline statistical analysis will be conducted and presented via tables of predicted adjusted medians for each Treatment arm at each visit, and the difference between treatment arms at each visit.

For reliever use, bronchodilator use recorded in the diary will be summarised as the mean number of occasions of rescue use per day and the percentage of rescue-free days in four-week interval periods as described in Section 13.6.3, where a rescue-free day is defined as a 24-hour period in which the number of occasions bronchodilator taken is zero. Summary tables will display estimates for each 4-weekly period for mean number of occasions of rescue use per day and percentage of rescue-free days separately.

8.1.3. Population of Interest

The primary efficacy analyses will be based on the "All Subjects" population, unless otherwise specified.

8.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.1.4.1. Statistical Methodology Specification

NOTE: The description below describes the current thinking of how to analyse these endpoints. The proposed models will be assessed, and if not appropriate alternative models could be used.

Endpoint / Variables
• FEV1 (ml), FVC(ml)
Model Specification
• The data will be inspected during statistical analysis to determine whether a data transformation is required. It is likely no transformations will be required • The analysis will include all available values. If there are values which were recorded within 4h after the subject had taken relief medication, a sensitivity analysis may be done which excludes these values. • The endpoints (FEV_1 and FVC) will be analysed in separate models. The change from baseline in the endpoint will be analysed in a Bayesian repeated measures model, with a baseline by Visit covariate and Treatment by Visit class parameter. Note that the model will not include an intercept. The Treatment will have two levels: All NEMI and All Placebo, and the Visit will have two levels: Day 28 and Day 84. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e. covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior. • The change from baseline at each of the Visits will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in a tabular format. • The difference between the treatment arms, for the change from baseline will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular format. • The probabilities that the treatment difference is greater or less than 0 (depending on direction of the endpoint), in addition to other values appropriately selected based on the data, will also be computed for each Visit. These results will be presented in tabular format.
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. For example, if data do not approximately follow a normal distribution then attempt will be made to find a suitable transformation. • A comprehensive investigation into a suitable model should be initiated. For example, additional covariates will be investigated • An unstructured covariance structure will be used. However, in the event that this model fails to converge, alternative correlation structures may be considered. • Models with a Bayesian Framework will use vague priors. If appropriate, conjugate priors will be used. For example, for a multivariate model, the prior for the variance covariance matrix will be an inverse Wishart distribution.
Model Results Presentation
• Output from the repeated measures modelling detailed above will be tabulated. In particular, the estimated change from baseline, 95% CI, standard error, and posterior probabilities at each time point and for the active treatment comparison with placebo.

Subgroup Analyses
• For FEV1, a subgroup analysis will be conducted by index exacerbation severity (refer to Section 5.3 Examination of Covariates and Subgroups). A similar model as described in Model specification will be fitted but will also include a Severity*Treatment*Visit term within the model. • The results of the subgroup analysis will be reported in a separate table.

8.2. Secondary Efficacy Analyses (From HRCT Analyses)

8.2.1. Endpoint / Variables

To evaluate the effect of once daily repeat inhaled doses of nemiralisib on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo. Ratio from baseline in siVaw, iVaw, iRaw, siRaw, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.

8.2.2. Summary Measure

Each HRCT scan will be conducted at two lung volumes: total lung capacity (TLC) and functional residual capacity (FRC); these will be referred to as scan conditions. The HRCT images will be processed to derive the HRCT parameters at FRC and TLC, however these conditions are not applicable for all parameters.

The HRCT scans will be conducted at Screening, Day 12 and Day 28. The 3 HRCT images will then be processed to derive the HRCT parameters at each scan; this data will be referred to as the untrimmed data. The untrimmed data measures all airways that are present in each scan.

However partially due to positioning of subjects whilst taking a scan, it can be that some airways are visible in some scans and not in other scans. For these reasons, some HRCT imaging endpoints will be calculated to include only airways that are visible in both scans. Therefore, the scans were grouped into three scan trimming pairs where, within each scan trimming pair, the airways that were not present in both scans were removed/trimmed.

The three scan trimming pairs, and subsequent timepoints, are:

- The scan trimming pair SCRD28, which contains the Screening (SCRD28:SCR) and Day 28 (SCRD28:D28) timepoints, where only airways that were present in both screening and day 28 scans are accounted for.
- The scan trimming pair SCRD12, which contains the Screening (SCRD12:SCR) and Day 12 (SCRD12:D12) timepoints where only airways that were present in both screening and day 12 scan are accounted for.
- The scan trimming pair (D12D28), which contains the Day 12 (D12D28:D12) and Day 28 (D12D28:D28) timepoints, where only airways that were present in both day 12 and day 28 scans are accounted for.

These 6 HRCT images were then processed to derive the HRCT parameters at each of these scan-trimming pair time points; this data will be referred to as the scan trimmed

data. The scan trimmed data considers only airways that were present in both scans within the scan trimming pair. This ensures the airway models are the same length although the cross-sectional area of the airway may vary. For example, the schematic below shows visible airways on Screening alone and Day 12 alone. It then shows the airways that are visible on both Screening & Day 12 scans, through removing/trimming airways that are not present in both scans.

Screening:  Day 12:  Scan Trimming Screening & Day 12: 

The HRCT scans can identify the 5 different lobes of the lungs and these lobes can then be categorized into and up to 5 regions depending on the endpoint. The 5 lobes are Right Upper Lobe (RUL), Left Upper Lobe (LUL), Right Middle Lobe (RML), Right Lower Lobe (RLL) and Left Lower Lobe (LLL). The 5 regions are Upper (comprising of RUL, RML and LUL), Lower (comprising of RLL and LLL), Central (the main bronchi between the lobes and the trachea), Distal (comprising of Upper and Lower) and Total (comprising of Distal and Central).

The endpoints for which the 5 regions apply include:

- Specific imaging airway volume (siVaw)
- Imaging airway volume (iVaw)
- Specific imaging airway resistance (siRaw)
- Imaging airway resistance (iRaw)
- Specific imaging airway wall volume (siVaww)
- Imaging airway wall volume (iVaww)

The endpoints for which only 3 regions (upper, lower & total) apply include:

- Imaging lobe volume (iVlobe)
- Percent predicted lobar volume (iVlobepred)
- Low attenuation score (LAS)
- Air trapping score (AT)
- Blood vessel density (BVD)

The endpoint for which only 2 regions (upper & lower) apply is:

- Internal airflow lobar distribution (IALD)

For the measures iVaw, iRaw and iVaww, standardization within a subject for the size of the lobar volume was conducted. These specific measures can be adjusted for the individual's lobar volume by correcting for the corresponding lobe/region. Note the central region is not applicable for lobar volumes, instead the corresponding region for the central, distal and total regions is the total lobar volume region. For example:

- To calculate siVaw, the lobes/regions of iVaw being divided by the corresponding lobes/regions of iVlobe to calculate the lobes/regions of siVaw, thus siVaw can be

defined as a measure of volume in an individual's airways, corrected for the individual's lobar volume.

- To calculate siRaw, the lobes/regions of iRaw were multiplied by the corresponding lobes/regions of iVlobe.
- To calculate siVaww, the lobes/regions of iVaww were divided by the corresponding lobes/regions of iVlobe.

For such reasons, the table below shows the HRCT endpoints and the results that will be captured:

Table 2 HRCT Endpoints (and results that will be captured)

		Untrimmed			Scan Trimming, based on:		
Endpoints	**Units**	**Screening**	**Day 12**	**Day 28**	**Screening and Day 12 scans**	**Screening and Day 28 scans**	**Day 12 and Day 28 scans**
iVaw	mL	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
siVaw	mL/L	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
iRaw	KPa*s/L				x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
siRaw	KPa*s				x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
iVlobe	L	x	x	x			
Percent Predicted iVlobe	% of Predicted value	x	x	x			
IALD [3]	%	x	x	x			
LAS [1]	% of iVlobe	x	x	x			
AT [2]	% of iVlobe	x	x	x			
BVD [1]	% of iVlobe	x	x	x			
iVaww [1]	mL	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)
siVaww [1]	mL/L	x	x	x	x (Screening) x (Day 12)	x (Screening) x (Day 28)	x (Day 12) x (Day 28)

		Untrimmed			Scan Trimming, based on:		
Endpoints	**Units**	**Screening**	**Day 12**	**Day 28**	**Screening and Day 12 scans**	**Screening and Day 28 scans**	**Day 12 and Day 28 scans**
Trachea length	mm	x	x	x			
Trachea Diameter	mm	x	x	x			
Trachea Length/Diameter	mm/mm	x	x	x			

All these endpoints will be measured at TLC and FRC, except:
[1] These endpoints will only be measured at TLC
[2] This endpoint will be measured only at FRC
[3] The state (TLC/FRC) is not applicable

For the endpoints siVaw, iVaw, iRaw and siRaw appropriate transformations will be applied prior to summaries and statistical analyses, likely a log transformation. Summary statistics will be presented for absolute data and change from baseline. An attempt will be made to fit separate statistical models for each endpoint, scan trimming condition (Untrimmed or Scan Trimmed), lung volume (FRC or TLC) and Lobes (RUL, LUL, RML, RLL and LLL) or Regions (Upper, Lower, Central, Distal and Total) combination as appropriate. The primary plan for statistical analyses will be to fit separate statistical models for:

- siVaw
  - Untrimmed at FRC for all lobes, i.e. RUL, LUL, RML, RLL and LLL in one model.
  - Untrimmed at FRC for all regions, i.e. Upper, Lower, Central, Distal and Total in one model.
  - Scan Trimmed at FRC for Distal region only.
- siRaw
  - Scan Trimmed at FRC for Distal region only.

For untrimmed data, the ratio from baseline across the different Regions (accounting for the average baseline associated to the Region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). In addition, the placebo-adjusted ratio from baseline across the different Regions will be represented via adjusted posterior medians, as well as their associated 95% HPD-tailed credible intervals and posterior probabilities. These results will be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For scan trimmed data, the change from baseline across the different Regions (accounting for the average baseline associated to the Region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated

95% HPD-tailed credible intervals. These results will be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). In addition, the placebo-adjusted change from baseline across the different Regions will be represented via adjusted posterior medians, as well as their associated 95% HPD-tailed credible intervals and posterior probabilities. These results will be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For the tracheal endpoints, absolute data and change from baseline summary statistics will be provided for each lung volume (FRC or TLC) for trachea length, diameter and length/diameter.

8.2.3. Population of Interest

The primary efficacy analyses will be based on the "All Subjects" population, unless otherwise specified.

8.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.2.4.1. Statistical Methodology Specification

NOTE: The description below describes the current thinking of how to analyse these endpoints. The proposed models will be assessed, and if not appropriate alternative models could be used.

Endpoint / Variables
• Imaging Untrimmed endpoint siVaw at FRC
Model Specification
• The data will be inspected prior to analysis to determine whether a data transformation is required. It is likely that the data will approximately follow a log normal distribution; however, the most appropriate distribution should be used. • It is thought that the use of bronchodilators could affect the HRCT results. The database will contain information on whether relief medication was used in the 4 hours prior to each scan, and this information may be used in the sensitivity analyses of the HRCT results. • An attempt will be made to fit a statistical model for all Lobes (RUL, LUL, RML, RLL and LLL) and a separate statistical model for all Regions (Upper, Lower, Central, Distal and Total), i.e. two models; one for lobes, one for regions. However, should this model fail to converge or be deemed unsuitable potentially due to sample size, separate statistical models will be fitted for each Lobe/Region (RUL, LUL, RML, RLL, LLL, Upper, Lower, Central, Distal and Total), i.e. ten models in total, one for each lobe/region endpoint.

- The log of (or other transformation as appropriate) the ratio from baseline will be analysed in a multivariate model), under a Bayesian framework. The model will include a Baseline*Region term and a Treatment*Visit*Region term, as well as any co-variates of interest. Note that the model will not include an intercept. The Visit will consist of two levels: Day 12 and Day 28, and the Treatment will consist of two levels: All NEMI and All Placebo. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e. covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior.
- The change from baseline (accounting for the average baseline) across the different Visits will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable).
- The difference between the treatment arms, for the change from baseline across the different Visits will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable)
- The probabilities that the treatment ratio is greater than 1 (depending on direction of the endpoint), in addition to other values appropriately selected based on the data, will also be computed for each Visit. These results will be presented in tabular format

Model Checking & Diagnostics

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data. For example, if data do not approximately follow a normal distribution then attempt will be made to find a suitable transformation.
  Note: Should parameters require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arm, and then (ii) using these back transformed values, the ratio of the treatment arms (All NEMI/All Placebo) will be calculated for each posterior sample, and finally summarised accordingly
- A comprehensive investigation into a suitable model should be initiated. For example, additional covariates will be investigated such as age, BMI, gender etc.
  Note: when investigating fitting separate statistical models for Lobes (RUL, LUL, RML, RLL and LLL) and Regions (Upper, Lower, Central, Distal and Total), i.e. two models; one for lobes, one for regions. If there are convergence issues an alternative structure of fitting separate statistical models for each Lobe (RUL, LUL, RML, RLL and LLL) and each Region (Upper, Lower, Central, Distal and Total), i.e. ten models; five for lobes, five for regions. a similar model as described in Model Specification should be tested but will include a baseline and a Treatment*Visit term instead of a Baseline*Region term and a Treatment*Visit*Region term, respectively.
  Note: It may also be prudent to investigate a model fitting baseline as a timepoint in which case the log of (or other transformation as appropriate) the absolute results will be analysed in a multivariate model, under a Bayesian framework. The model could include a Treatment*Visit*Region parameter, as well as any co-variates of interest. Note that this model would not include an intercept. The Visit would consist of three levels: Baseline, Day 12 and Day 28, and the Treatment would consist of three levels: Null (when Visit = Screening), NEMI

and Placebo. With assumptions as described in Model Specification.

- An unstructured covariance structure will be used. However, in the event that this model fails to converge, alternative correlation structures may be considered.
- Models with a Bayesian Framework will use vague priors. If appropriate, conjugate priors will be used. For example, for a multivariate model, the prior for the variance covariance matrix will be an inverse Wishart distribution.

Model Results Presentation

- Output from the repeated measures modelling detailed above will be tabulated. In particular, the estimated ratio to baseline (or change from baseline if appropriate), 95% CI, standard error (on the appropriate scale, likely logarithm base e), and posterior probabilities at each time point and for the active treatment comparison with placebo. The scan trimming condition, lung volume and lobe or region description will be included in the outputs.

Sensitivity and Supportive Analyses

- It is thought that the use of bronchodilators could affect the HRCT results. The database will contain information on if relief medication was used in the 4 hours prior to each scan, and this information may be used in the sensitivity analyses of the HRCT results including only those who did not take bronchodilator relief medication in the 4 hours prior to HRCT scan.

Endpoint / Variables

- Imaging Scan Trimmed endpoints siVaw and siRaw at FRC in the Distal Region only.

Model Specification

- It is likely that the data will approximately follow a log normal distribution; however, the most appropriate distribution should be used.
- Separate statistical models will be fitted for each endpoint, i.e. two models; one for siVaw (scan trimmed at FRC in Distal region), one for siRaw (scan trimmed at FRC in Distal region).
- The responses of interest are the change from baseline based on (i) Airways present on scans taken at Screening and Day 12, (ii) Airways present on scans taken at Screening and Day 28, and (iii) Airways present on scans taken at Day 12 and Day 28. The baselines for each of these endpoints are provided in the table below.

	(i) Screening & Day12 Scan trimming	**(ii) Screening & Day28 Scan trimming**	**(iii) Day 12 & Day 28 Scan trimming**
Screening Result	✓ (baseline)	✓ (baseline)	
Day 12 Result	✓ (post dose)		✓ (baseline)
Day 28 Result		✓ (post dose)	✓ (post dose)

- The modelling below assumes that the Scan trimming endpoints (Screening&Day12, Screening&Day28 and Day12&Day28) will be analysed in a single multivariate model. This is subject to sensitivity analysis.

- The log of (or other transformation as appropriate) the change from baseline (where baseline is defined in the table above) will be analysed in a multivariate model to account for the correlation between the multiple Scan Trimmings (Screening&Day12, Screening&Day28 and Day12&Day28), under a Bayesian framework. The model will have a separate intercept for each Scan Trimming combination (by fitting a class parameter Scan Trimming, and having no overall intercept), and will also include a baseline*Scan Trimming and a Treatment*Scan Trimming parameter. The Visit will consist of two levels: Day 12 and Day 28, the scan trimming will consist of three levels Screening&Day12, Screening&Day28 and Day12&Day28, and the Treatment will consist of two levels: All NEMI and All Placebo. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e. covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior.
- The change from baseline across the different Scan Trimming pairs (accounting for the average baseline) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable).
- The difference between the treatment arms, for the change from baseline across the different Scan Trimming pairs will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (if applicable). For parameters that require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arm, and then (ii) using these back transformed values, the ratio of the treatment arms (Active/Placebo) will be calculated for each posterior sample, and finally summarised accordingly.

  The probabilities that the treatment ratio is greater than 1 (for siVaw) and less than 1 (for siRaw), in addition to other values appropriately selected based on the data, will also be computed for each Visit. These results will be presented in tabular format.

Model Checking & Diagnostics

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data. For example if data do not approximately follow a normal distribution then an attempt will be made to find a suitable transformation.
  Note: Should parameters require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arm, and then (ii) using these back transformed values, the ratio of the treatment arms (All NEMI/All Placebo) will be calculated for each posterior sample, and finally summarised accordingly
- A comprehensive investigation into a suitable model should be initiated. For example, additional covariates will be investigated
- An unstructured covariance structure will be used. However, in the event that this model fails to converge, alternative correlation structures may be considered.
- Models with a Bayesian Framework will use vague priors. If appropriate, conjugate priors will be used. For example, for a multivariate model, the prior for the variance covariance matrix will be an inverse Wishart distribution.

Model Results Presentation
• Output from the repeated measures modelling detailed above will be tabulated. In particular, the estimated ratio to baseline (or change from baseline if appropriate), 95% CI, standard error (on the appropriate scale, likely logarithm base e), and posterior probabilities at each time point and for the active treatment comparison with placebo. The scan trimming condition, lung volume and lobe or region description will be included in the outputs.
Sensitivity and Supportive Analyses
• It is thought that the use of bronchodilators could affect the HRCT results. The database will contain information on if relief medication was used in the 4 hours prior to each scan, and this information may be used in the sensitivity analyses of the HRCT results including only those who did not take bronchodilator relief medication in the 4 hours prior to HRCT scan.

8.3. Exploratory Efficacy Analyses (From HRCT Analyses)

8.3.1. Endpoint / Variables

To assess the changes in other HRCT parameters such as low attenuation score after once daily repeat inhaled doses of nemiralisib administered to subjects with acute exacerbation of COPD, compared to placebo. Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.

8.3.2. Summary Measure

The structure of HRCT endpoints is as described in Section 8.2.2, exploratory endpoints include:

- iVlobe
- Percent Predicted iVlobe
- IALD
- LAS
- AT
- BVD
- iVaww
- siVaww

For all endpoints, the data will be inspected prior to analyses to determine whether a data transformation is required. Appropriate transformations will be applied prior to summaries and statistical analyses. It is likely a log transformation will be required for iVlobe, LAS, IALD, BVD iVaww and siVaww, and that no transformation will be required for Percent Predicted iVlobe and AT, however, the most appropriate distribution should be used

Summary statistics will be presented for absolute data and change from baseline. Separate statistical models will be fitted for each scan trimming condition (Untrimmed or Scan Trimmed), lung volume (FRC or TLC) and Regions (Upper, Lower, Central, Distal

and Total) combination as appropriate, note: statistical analyses will only be conducted on:

- IALD for upper and lower regions only (within the same model)
- LAS at TLC for total region only
- AT at FRC for total region only
- BVD at TLC for total region only
- siVaww untrimmed data at TLC for distal region only

For the endpoints: LAS, AT and BVD, separate statistical models will be fitted for the Total region only. The change from baseline (accounting for the average baseline associated to the region) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). The difference between the treatment arms, for the change from baseline will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For the endpoint IALD, a statistical model will be fitted for both the Upper and Lower regions. The change from baseline across the different regions (accounting for the average baseline associated to the region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). The difference between the treatment arms, for the change from baseline across the different regions will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

For the endpoint siVaww, a statistical model will be fitted for the distal region using untrimmed data. The change from baseline (accounting for the average baseline associated to the region) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented within tabular form, and will be presented after the data have been appropriately back transformed (if applicable). The difference between the treatment arms, for the change from baseline will be represented via adjusted medians, as well as their associated 95% HPD-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios (or median differences if applicable).

8.3.3. Population of Interest

The secondary efficacy analyses will be based on the “All Subjects” population, unless otherwise specified.

8.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.3.4.1. Statistical Methodology Specification

For statistical analyses of IALD in the upper and lower regions refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note that it is likely only 1 statistical model would be fitted for the upper and lower regions only. If appropriate this could be adapted into two models; one for upper, one for lower. The probability that the treatment ratio is greater than 1 will be presented for the lower region and the probability that the treatment ratio is less than 1 will be presented for the upper region, in addition to other values appropriately selected based on the data.

For statistical analyses of LAS at TLC in the total region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note only 1 statistical model would be fitted for the Total regions only. The probability that the treatment ratio is less than 1 will be presented, in addition to other values appropriately selected based on the data.

For statistical analyses of AT at FRC in the total region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw however it is likely that no transformation will be required for this endpoint in which case the absolute change from baseline will be fitted and probabilities that the true treatment difference is less than 1, in addition to other values appropriately selected based on the data, will also be computed for each Visit. Note only 1 statistical model would be fitted for the Total regions only.

For statistical analyses of BVD at TLC in the total region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note only 1 statistical model would be fitted for the Total regions only.

For statistical analyses of siVaww at TLC in the distal region only, refer to Section 8.2.4.1 for the analysis of untrimmed siVaw but note only 1 statistical model would be fitted for the Distal regions only. The probability that the treatment ratio is less than 1, in addition to other values appropriately selected based on the data will be presented.

8.4. Exploratory Efficacy Analyses (Not from HRCT Analyses)

8.4.1. Endpoint / Variables

Additional exploratory endpoints include the severity of index exacerbation, where exacerbations requiring hospitalisations are defined as severe and those not requiring hospitalisation are defined as moderate.

8.4.2. Summary Measure

For the severity of index exacerbation, a summary table detailing the number and percentage of subjects who had moderate or severe index exacerbations. Note:

exacerbations requiring hospitalisations are defined as severe and those not requiring hospitalisation are defined as moderate.

If available, data on exacerbations occurring during the study will be summarised. This may include investigator defined exacerbations (including information on moderate or severe) and concomitant medication defined exacerbations. Concomitant medication defined exacerbations will be defined as treatment with systemic/oral corticosteroids and/or antibiotics where the exacerbation is deemed to have ended if no additional treatment with systemic/oral corticosteroids and/or antibiotics is required within < 7days from the end of treatment for the primary exacerbation.

8.4.3. Population of Interest

The secondary efficacy analyses will be based on the "All Subjects" population, unless otherwise specified.

8.4.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.4.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9. RELATIONSHIP BETWEEN THE PHARMACODYNAMIC AND BIOMARKER DATA AND THE HRCT DATA

9.1. Relationship between the mRNA data and the HRCT data

The relationship between a selection of the mRNA data and the HRCT data may be performed as an exploratory analysis. This may include scatter plots of individual participant data, linear regression lines, Pearson's correlation coefficient and 95% confidence intervals plots as appropriate. This data will be produced following SAC.

10. SAFETY ANALYSES

The safety analyses will be based on the "All Subjects" population, unless otherwise specified.

10.1. 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 10: List of Data Displays.

10.2. 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 10: List of Data Displays.

10.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

11. PHARMACOKINETIC ANALYSES

11.1. Secondary Pharmacokinetic Analyses

11.1.1. Endpoint / Variables

11.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic)

11.1.1.2. Derived Pharmacokinetic Parameters

No non-compartmental analysis will be conducted for this study as such there will be no derived pharmacokinetic parameters.

11.1.2. Summary Measure

The concentrations of the samples will be summarised.

11.1.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the “Pharmacokinetic” population, unless otherwise specified.

12. REFERENCES

Quanjer Ph.H, Tammeling G.J, Cotes J.E., Pedersen O.F, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows; *European Respiratory Journal* 1993 6: 5-40

13. APPENDICES

13.1. Appendix 1: Protocol Deviation Management

13.1.1. Important Protocol Deviations

Based on an assessment of the important protocol deviations listed in the PDMP, partial data exclusions or time-point exclusions may occur which may not remove a subject from the analysis population, but may exclude a portion of the subject's data.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

Screening and Follow Up Visits

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Full physical exam, including height and weight	X		
Brief physical examination, including weight		X	
Chest X-Ray	X		To be done before baseline HRCT to exclude significant pneumonia and other incidental serious underlying pathology.
Medical history (includes substance usage and Family history of premature CV disease)	X		Substances: Drugs, Alcohol, tobacco via history. No drug, alcohol screening is required.
Past and current medical conditions (including cardiovascular medical history and therapy history)	X		
Laboratory assessments (include Hematology and biochemistry)[1]	X	X	Historical values analysed by local lab to be used for eligibility assessment. Another sample must be collected and sent to central lab as soon as informed consent is obtained.
Hep B and Hep C screen[2]	X		
Urine pregnancy test (only WCBP)	X		Before conducting the HRCT. Done locally at the site.
12-lead ECG	X	X	Single assessment
Vital signs	X	X	Single assessment
HRCT (at TLC and FRC)	X		Within 48 h of diagnosis, if subject otherwise eligible. Includes electronic monitoring of breathing (if applicable). Baseline HRCT will be reviewed by the local site's radiologist to identify any significant occurring underlying medical conditions that require further clinical management or monitoring.

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Induced Sputum[3]	X[4]		To include sputum culture pre-first dose. Culture to be done by the local site laboratory.
Blood sample for mRNA Analysis	X[4]		Collected at any time on specified days
AE/SAE collection and review		X	
Concomitant medication review	X	X	

1. Due to the short screening window, central laboratory analysis results will not be available on time. Therefore, the local laboratory results should be used for eligibility assessment (to exclude severe subjects and underlying medical conditions). If local laboratory results are already available from diagnosis of current exacerbation, there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained. See Section 7.8.6 of Protocol Amendment 4 for further details.
2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required. Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor.
3. Induced sputum collection may be attempted on several occasions if an adequate sample is not produced at the first attempt.
4. To be collected at any time point before randomisation.

Treatment Period

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
ELLIPTA™ Inhaler Training	X						Training conducted by reviewing the Patient Information Leaflet with the subject (no device will be used). Additional training may be conducted at the discretion of the investigator
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
Diary Card dispense and review at clinic	X		X	X	X	X	Refer to SRM for details.

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

1. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2 of Protocol Amendment 4
2. Assessments do not need to be completed if screening assessments conducted within 48 hours
3. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
4. Informed consent for optional sub-studies (e.g. genetics research) must be obtained before collecting a sample. May be obtained at any visits.

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for Analyses

Population	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
Screening	NA	3 days prior to Visit 1 (Day 1)	Day 1	Screening
Safety, Efficacy, Study population and all other assessments	NA – Day of first dose	NA	NA	Visit 1
	If subject was hospitalised: Target = On discharge If subject wasn't hospitalised: Target = Within 48 hours of first dose administration	Target -1 day	Target +1 day	Visit 2
	Day 12	Target -2 day	Target +2 day	Visit 3
	Day 28	Target -2 day	Target +2 day	Visit 4
	Day 56	Target -4 day	Target +2 day	Visit 5
	Day 84	Target -4 day	Target +2 day	Visit 6
Follow-up	NA	1 week following last day of dose	2 weeks following the last day of dose	Follow-up

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

13.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the study treatment, unless otherwise specified

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

13.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is 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.

13.4.2. Treatment States for Adverse Events

Flag	Definition
Pre-Treatment	• If AE onset date is before the treatment start date. • AE Start Date < Study Treatment Start Date
Treatment Emergent (On-Treatment)	• 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.
Post-Treatment	• If AE onset date is after the treatment stop date. • AE Start Date > Study Treatment Stop Date
Onset Time Since 1st Dose (Days)	• If Treatment Start Date > AE Onset Date, then Onset Time = AE Onset Date - Treatment Start Date • If Treatment Start Date ≤ AE Onset Date, then Onset Time = AE Onset Date - Treatment Start Date +1 • Missing otherwise.
Duration (Days)	• AE Resolution Date – AE Onset Date + 1
Drug-related	• If relationship is marked 'YES' on [Inform/CRF OR value is missing].

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.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software (version 9.4) will be used.	
Reporting Area	
HARP Server	: UK1SALX00175.corpnet2.com
HARP Compound	: ARPROD/GSK2269557/mid201928 Note: the current planned reporting effort is final_01, this may be superseded.
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards and Integrated Data Standards Library	
Generation of RTF Files	
• RTF files will be generated for all tables	

13.5.2. 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 located in the modular appendices as ICH or non-ICH listings
• A project wide decision was made to present GSK2269557 as Nemiralisib (abbreviated to NEMI) refer to Section 5.1 for further details.

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.

• Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in summary 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. • All graphics will be done using the SGPLOT/SGPANEL/SG template procedures	

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
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. Note: Use the separate NEMI DISKUS and NEMI ELLIPTA treatment groups
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.

13.6. Appendix 6: Derived and Transformed Data

13.6.1. 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 13.3.1) 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:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

13.6.2. Study Population

Treatment Compliance
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)** • Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) at each visit will be calculated. • Planned Treatment Duration is defined as 84 days.
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2]**

13.6.3. Efficacy

HRCT

Endpoints provided by FluidDA

Y = Endpoints will be provided by FluidDA.

	Lobes & Regions										
	LLL	**LUL**	**RML**	**RUL**	**RLL**	**LL**	**UL**	**CENTRAL**	**DISTAL**	**TOTAL**	**TRACHEA**
iVaw	Y	Y	Y	Y	Y	C	C	Y	C	C	N/A
siVaw	C	C	C	C	C	C	C	C	C	C	N/A
iRaw	Y	Y	Y	Y	Y	C	C	Y	Y	Y	N/A
siRaw	C	C	C	C	C	C	C	C	C	C	N/A
iVlobe	Y	Y	Y	Y	Y	C	C	N/A	N/A	C	N/A
iVlobepred	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
LAS	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
IALD	C	C	C	C	C	C	C	N/A	N/A	N/A	N/A
AT	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
BVD	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	N/A
iVaww	Y	Y	Y	Y	Y	C	C	Y	C	C	N/A
siVaww	C	C	C	C	C	C	C	C	C	C	N/A
Diameter	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y
Length	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y
Length/Diameter	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	C

C = Endpoints will be Calculated by GSK (see Derived Data below)

Imaging Endpoints Calculated by GSK

iVaw LL = iVaw RLL + iVaw LLL
iVaw UL = iVaw RUL + iVaw RML + iVaw LUL
iVaw DISTAL = iVaw LL + iVaw UL
iVaw TOTAL = iVaw CENTRAL + iVaw DISTAL

iRaw LL = 1/ (1/iRaw RLL + 1/iRaw LLL)
iRaw UL = 1/ (1/iRaw RUL + 1/iRaw RML + 1/iRaw LUL)

iVlobe LL = iVlobe RLL + iVlobe LLL
iVlobe UL = iVlobe RUL + iVlobe RML + iVlobe LUL
iVlobe TOTAL = iVlobe LL + iVlobe UL

iVaww LL = iVaww RLL + iVaww LLL
iVaww UL = iVaww RUL + iVaww RML + iVaww LUL
iVaww DISTAL = iVaww LL + iVaww UL
iVaww TOTAL = iVaww CENTRAL + iVaww DISTAL

siVaw LLL = iVaw LLL / iVlobe LLL
siVaw LUL = iVaw LUL / iVlobe LUL
siVaw RML = iVaw RML / iVlobe RML
siVaw RUL = iVaw RUL / iVlobe RUL
siVaw RLL = iVaw RLL / iVlobe RLL
siVaw LL = iVaw LL / iVlobe LL
siVaw UL = iVaw UL / iVlobe UL
siVaw CENTRAL = iVaw CENTRAL / iVlobe TOTAL
siVaw DISTAL = iVaw DISTAL / iVlobe TOTAL
siVaw TOTAL = iVaw TOTAL / iVlobe TOTAL

siRaw LLL = iRaw LLL * iVlobe LLL
siRaw LUL = iRaw LUL * iVlobe LUL
siRaw RML = iRaw RML * iVlobe RML
siRaw RUL = iRaw RUL * iVlobe RUL
siRaw RLL = iRaw RLL * iVlobe RLL
siRaw LL = iRaw LL * iVlobe LL
siRaw UL = iRaw UL * iVlobe UL

HRCT
siRaw CENTRAL = iRaw CENTRAL * iVlobe TOTAL siRaw DISTAL = iRaw DISTAL * iVlobe TOTAL siRaw TOTAL = iRaw TOTAL * iVlobe TOTAL
siVaww LLL = iVaww LLL / iVlobe LLL siVaww LUL = iVaww LUL / iVlobe LUL siVaww RML = iVaww RML / iVlobe RML siVaww RUL = iVaww RUL / iVlobe RUL siVaww RLL = iVaww RLL / iVlobe RLL siVaww LL = iVaww LL / iVlobe LL siVaww UL = iVaww UL / iVlobe UL siVaww CENTRAL = iVaww CENTRAL / iVlobe TOTAL siVaww DISTAL = iVaww DISTAL / iVlobe TOTAL siVaww TOTAL = iVaww TOTAL / iVlobe TOTAL
IALD LLL = 100 * (iVlobe LLL TLC - iVlobe LLL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD LUL = 100 * (iVlobe LUL TLC - iVlobe LUL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD RML = 100 * (iVlobe RML TLC - iVlobe RML FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD RUL = 100 * (iVlobe RUL TLC - iVlobe RUL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD RLL = 100 * (iVlobe RLL TLC - iVlobe RLL FRC) / (iVlobe TOTAL TLC - iVlobe TOTAL FRC) IALD LL = IALD RLL + IALD LLL IALD UL = IALD RUL + IALD RML + IALD LUL

Lung Function Parameters
Lung Function Parameters Calculated by GSK
• FEV1 % Predicted (Men) = 4.30*Height – 0.029*Age – 2.49 • FEV1 % Predicted (Women) = 3.95*Height – 0.025*Age – 2.60 Formulas have been taken from Quanjer, 1993 Lung volumes and forced ventilator flows [accessed: 23rd July 2015] where height is measured in metres and age in years at screening.

Rescue Medication Endpoints
Number of occasions bronchodilator taken in the last 24 per hours 4-week period derived by GSK

- Number of occasions bronchodilator taken in the last 24 hours were collected in the daily diary
- The table below shows which daily diary records are used to calculate the daily diary endpoints for each analysis time period. Any diary data collected in the post-treatment phase of the study will not be slotted.

Daily Record		
Beginning Timepoint (day)	Ending Timepoint (day)	Analysis Time Period
1	28	Weeks 1 – 4
29	56	Weeks 5 – 8
57	84	Weeks 9 – 12

Note: There is no Day 0. Any records with actual day>84 will not be assigned to a time period. Any records with actual day<0 may be assigned to a Week -1 (Baseline) time period

Note: Daily diary records that were not assigned to a time period will not be used in calculation of daily diary endpoints.

- For a subject to be counted in any time period for a given endpoint they must have at least one diary entry recorded for that endpoint during that time period.
- Any daily diary data that were collected post-study treatment discontinuation will be excluded from analysis, including four weekly period data summaries.
- If a subject has more than one daily diary record for any given day, the worst-case

Rescue Medication Endpoints
response on that day for each endpoint will be used in the summaries and analyses. i.e. the maximum number of occasions of bronchodilator use reported will be counted for the day in question and used to determine if it was a rescue-free day • The mean number of occasions of rescue use per day and percentage of rescue-free days, will be calculated for each subject during the four weekly periods defined above.

13.6.4. Safety

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as:
  [1] If QTcB is machine read & QTcF is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value then do not derive.

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:

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

13.6.5. Pharmacodynamic and Biomarker

Biomarker Category	Analyte	Method	Lab	Matrix	Total samples
Inflammatory Cytokine	IL-8	MSD	Quest	Sputum	4
	IL-6	MSD	Quest	Sputum	4
	TNFα	MSD	Quest	Sputum	4
Microbiome	Bacterial DNA	16SRNA	GSK-RTP	Sputum	4
	Bacterial DNA	qPCR	GSK-RTP	Sputum	4
	Viral DNA	qPCR	GSK-RTP	Sputum	4
Transcriptomics	Human RNA	Affymetrix	Expression Analysis	Blood	4

NOTES:

- Sampling times: Screening, day 12, day 28 and day 84
- Inflammatory cytokine biomarkers are elevated in COPD patients. Expected to reduce with treatment.
- Microbiome biomarkers are drivers of exacerbations in COPD and are inhibited in preclinical disease studies
- PI3Kδ transcriptome analysis in FTIH study has 16 genes identified (sputum) showing a consistent response with dose – all are down regulated.

Pharmacodynamic and Biomarker
Pharmacodynamic
PMNs Differentials

• Percentage data may be arc-sine transformed especially if many of the percentage values are smaller than 20% or larger than 80%. The response variable, y, measured in radians, is $\sin^{-1}\text{sqrt}\{0.01*p\}$ where p is the differential percentage.
• If transformations are used then the results will be reported on the back-transformed scale, except where a transformed value:
  ○ exceeds 0.01*p/2 then the back-transformed value will be set equal to 100%
  ○ is less than 0 then the back-transformed value will be set equal to 0%.

Biomarkers
Inflammatory Cytokines
• In general, it is assumed that biomarker endpoints will require variance stabilising transformations, such as taking a loge transformation prior to analysis (and that summary statistics appropriate to loge normally distributed data will apply for all summaries). However, this assumption will be considered for each endpoint Individually prior to the generation of summary tables or statistical analysis, and if deemed more appropriate, a loge transformation will not be applied, or non-parametric methods may be employed. • If transformations are used, then the results will be reported on the back-transformed scale unless otherwise stated.
RNA transcriptome

• Affymetrix microarray mRNA data will be normalised using RMA in ARRAY STUDIO v8.0 or later by the Statistical Consultancy Group (SCG) within GSK. After normalisation, the data will be quality assessed and any samples deemed as QC fails will be excluded from any further analysis. This quality assessment will involve looking for outlying signals in both the normalised expression data and the MAS5 QC metrics generated from each sample. If any samples are excluded, the remaining data will be re-normalised. The output from the normalization will be log2 transformed mRNA intensity data.
• Summary mRNA data will be reviewed and a decision made on which probe sets are to be included in the SI dataset.
• Treatment ratios from the statistical analyses of mRNA intensity data will be converted to fold changes as follows:
  ○ If ratio ≥ 1 then fold change = ratio
  ○ If ratio < 1 then fold change = -1/ratio

The primary pharmacodynamic endpoint is based on a subset of probe sets defined as those that have previously identified immune cell mechanisms specifically related to neutrophil function.

The gene list that meets this criterion based on PII115119 D14 vs D1 gene changes, PII115117 and Metacore neutrophil pathways identified in PII115119 study. This gene list identified 258 genes in total after filtering for redundancy and was agreed by the study team is presented in Table 3.

Table 3 Gene List that have previously identified immune cell mechanisms specifically related to neutrophil function

Gene	Source	Gene	Source
CD177	PII115119 - Neutrophil migration	ITGAL	Metacore: IL8 Neutrophil migration
CXCR1	PII115119 - Neutrophil migration	ADAM17	Metacore: Inhibition of neutrophil migration
CXCR2	PII115119 - Neutrophil migration	C5	Metacore: Inhibition of neutrophil migration
FPR2	PII115119 - Neutrophil migration	C5AR1	Metacore: Inhibition of neutrophil migration
LTB4R	PII115119 - Neutrophil migration	CCR5	Metacore: Inhibition of neutrophil migration
PAK1	PII115119 - Neutrophil migration	CD34	Metacore: Inhibition of neutrophil migration
PXN	PII115119 - Neutrophil migration	CALM1	Metacore: Inhibition of neutrophil migration
PREX1	PII115119 - Neutrophil migration	CALM2	Metacore: Inhibition of neutrophil migration
TLN1	PII115119 - Neutrophil migration	CALM3	Metacore: Inhibition of neutrophil migration
SSH2	PII115119 - Neutrophil migration	FPR1	Metacore: Inhibition of neutrophil migration
F2RL1	PII115119 - Neutrophil infection response	ICAM2	Metacore: Inhibition of neutrophil migration
TLR10	PII115119 - Neutrophil infection response	IL1B	Metacore: Inhibition of neutrophil migration
CEACAM3	PII115119 - Neutrophil infection response	IL1R1	Metacore: Inhibition of neutrophil migration
TREML2	PII115119 - Neutrophil infection response	ITPR1	Metacore: Inhibition of neutrophil migration
DEFB124	PII115119 - Neutrophil infection response	ITPR2	Metacore: Inhibition of neutrophil migration
CLEC4C	PII115119 - Neutrophil infection response	ITPR3	Metacore: Inhibition of neutrophil migration
IFITM1	PII115119 - Neutrophil infection response	SELL	Metacore: Inhibition of neutrophil migration
CR1	PII115119 - Neutrophil infection response	MSN	Metacore: Inhibition of neutrophil migration
PMAIP1	FTIH - GSK'557 response	NFKB1	Metacore: Inhibition of neutrophil migration
S100P	FTIH - GSK'557 response	NFKB2	Metacore: Inhibition of neutrophil migration
PTGS2	FTIH - GSK'557 response	REL	Metacore: Inhibition of neutrophil migration
CCL20	FTIH - GSK'557 response	RELA	Metacore: Inhibition of neutrophil migration
EGR3	FTIH - GSK'557 response	RELB	Metacore: Inhibition of neutrophil migration
H1F0	FTIH - GSK'557 response	PECAM1	Metacore: Inhibition of neutrophil migration
NCOA3	FTIH - GSK'557 response	PRKCA	Metacore: Inhibition of neutrophil migration
TARP	FTIH - GSK'557 response	PRKCB	Metacore: Inhibition of neutrophil migration
CEACAM1	FTIH - GSK'557 response	PRKCD	Metacore: Inhibition of neutrophil migration
TTPAL	FTIH - GSK'557 response	PRKCE	Metacore: Inhibition of neutrophil migration
VPS37B	FTIH - GSK'557 response	PRKCG	Metacore: Inhibition of neutrophil migration
SYAP1	FTIH - GSK'557 response	PRKCH	Metacore: Inhibition of neutrophil migration
SPTBN1	FTIH - GSK'557 response	PRKCI	Metacore: Inhibition of neutrophil migration
EGR1	FTIH - GSK'557 response	PRKCQ	Metacore: Inhibition of neutrophil migration
OSM	FTIH - GSK'557 response	PRKD1	Metacore: Inhibition of neutrophil migration
TBC1D22A	FTIH - GSK'557 response	PRKD2	Metacore: Inhibition of neutrophil migration
AKT1	Metacore: IL8 Neutrophil migration	PRKD3	Metacore: Inhibition of neutrophil migration
AKT2	Metacore: IL8 Neutrophil migration	PLCB2	Metacore: Inhibition of neutrophil migration
AKT3	Metacore: IL8 Neutrophil migration	PTAFR	Metacore: Inhibition of neutrophil migration
ACTA1	Metacore: IL8 Neutrophil migration	TLR2	Metacore: Inhibition of neutrophil migration
ACTA2	Metacore: IL8 Neutrophil migration	TLR4	Metacore: Inhibition of neutrophil migration

Gene	Source	Gene	Source
ACTB	Metacore: IL8 Neutrophil migration	TNFRSF1A	Metacore: Inhibition of neutrophil migration
ACTC1	Metacore: IL8 Neutrophil migration	TNFRSF1B	Metacore: Inhibition of neutrophil migration
ACTG1	Metacore: IL8 Neutrophil migration	TNF	Metacore: Inhibition of neutrophil migration
ACTG2	Metacore: IL8 Neutrophil migration	VAV1	Metacore: Inhibition of neutrophil migration
MYH1	Metacore: IL8 Neutrophil migration	EZR	Metacore: Inhibition of neutrophil migration
MYH10	Metacore: IL8 Neutrophil migration	VCL	Metacore: Inhibition of neutrophil migration
MYH11	Metacore: IL8 Neutrophil migration	ITGAM	Metacore: Inhibition of neutrophil migration
MYH13	Metacore: IL8 Neutrophil migration	ABL1	Metacore: Inhibition of neutrophil migration
MYH14	Metacore: IL8 Neutrophil migration	JUN	Metacore: Inhibition of neutrophil migration
MYH15	Metacore: IL8 Neutrophil migration	FOS	Metacore: Inhibition of neutrophil migration
MYH16	Metacore: IL8 Neutrophil migration	MAPK11	Metacore: Inhibition of neutrophil migration
MYH2	Metacore: IL8 Neutrophil migration	MAPK12	Metacore: Inhibition of neutrophil migration
MYH3	Metacore: IL8 Neutrophil migration	MAPK13	Metacore: Inhibition of neutrophil migration
MYH4	Metacore: IL8 Neutrophil migration	MAPK14	Metacore: Inhibition of neutrophil migration
MYH6	Metacore: IL8 Neutrophil migration	BDKRB1	Metacore: Neutrophil migration in Asthma
MYH7	Metacore: IL8 Neutrophil migration	CCL15	Metacore: Neutrophil migration in Asthma
MYH8	Metacore: IL8 Neutrophil migration	CCL2	Metacore: Neutrophil migration in Asthma
MYH9	Metacore: IL8 Neutrophil migration	CCL5	Metacore: Neutrophil migration in Asthma
MYL1	Metacore: IL8 Neutrophil migration	CCL7	Metacore: Neutrophil migration in Asthma
MYL12A	Metacore: IL8 Neutrophil migration	CCR1	Metacore: Neutrophil migration in Asthma
MYL12B	Metacore: IL8 Neutrophil migration	CCR2	Metacore: Neutrophil migration in Asthma
MYL2	Metacore: IL8 Neutrophil migration	CCR3	Metacore: Neutrophil migration in Asthma
MYL3	Metacore: IL8 Neutrophil migration	CXCL5	Metacore: Neutrophil migration in Asthma
MYL4	Metacore: IL8 Neutrophil migration	CXCL1	Metacore: Neutrophil migration in Asthma
MYL5	Metacore: IL8 Neutrophil migration	CXCL2	Metacore: Neutrophil migration in Asthma
MYL6	Metacore: IL8 Neutrophil migration	CXCL3	Metacore: Neutrophil migration in Asthma
MYL6B	Metacore: IL8 Neutrophil migration	HSPA14	Metacore: Neutrophil migration in Asthma
MYL7	Metacore: IL8 Neutrophil migration	HSPA1A	Metacore: Neutrophil migration in Asthma
MYL9	Metacore: IL8 Neutrophil migration	HSPA1B	Metacore: Neutrophil migration in Asthma
MYLPF	Metacore: IL8 Neutrophil migration	HSPA1L	Metacore: Neutrophil migration in Asthma
ACTN1	Metacore: IL8 Neutrophil migration	HSPA2	Metacore: Neutrophil migration in Asthma
ACTN2	Metacore: IL8 Neutrophil migration	HSPA4	Metacore: Neutrophil migration in Asthma
ACTN3	Metacore: IL8 Neutrophil migration	HSPA5	Metacore: Neutrophil migration in Asthma
ACTN4	Metacore: IL8 Neutrophil migration	HSPA6	Metacore: Neutrophil migration in Asthma
ACTR2	Metacore: IL8 Neutrophil migration	HSPA7	Metacore: Neutrophil migration in Asthma
ACTR3	Metacore: IL8 Neutrophil migration	HSPA8	Metacore: Neutrophil migration in Asthma
ACTR3B	Metacore: IL8 Neutrophil migration	HSPA9	Metacore: Neutrophil migration in Asthma
ARPC1A	Metacore: IL8 Neutrophil migration	MIF	Metacore: Neutrophil migration in Asthma
ARPC1B	Metacore: IL8 Neutrophil migration	CCL3	Metacore: Neutrophil migration in Asthma
ARPC2	Metacore: IL8 Neutrophil migration	PGF	Metacore: Neutrophil migration in Asthma
ARPC3	Metacore: IL8 Neutrophil migration	TAC1	Metacore: Neutrophil migration in Asthma

Gene	Source	Gene	Source
ARPC4	Metacore: IL8 Neutrophil migration	TACR1	Metacore: Neutrophil migration in Asthma
ARPC5	Metacore: IL8 Neutrophil migration	KLK1	Metacore: Neutrophil migration in Asthma
CFL1	Metacore: IL8 Neutrophil migration	KLK10	Metacore: Neutrophil migration in Asthma
CFL2	Metacore: IL8 Neutrophil migration	KLK11	Metacore: Neutrophil migration in Asthma
MAPK1	Metacore: IL8 Neutrophil migration	KLK12	Metacore: Neutrophil migration in Asthma
MAPK3	Metacore: IL8 Neutrophil migration	KLK13	Metacore: Neutrophil migration in Asthma
GNAI1	Metacore: IL8 Neutrophil migration	KLK14	Metacore: Neutrophil migration in Asthma
GNAI2	Metacore: IL8 Neutrophil migration	KLK15	Metacore: Neutrophil migration in Asthma
GNAI3	Metacore: IL8 Neutrophil migration	KLK2	Metacore: Neutrophil migration in Asthma
GNAO1	Metacore: IL8 Neutrophil migration	KLK3	Metacore: Neutrophil migration in Asthma
GNAZ	Metacore: IL8 Neutrophil migration	KLK4	Metacore: Neutrophil migration in Asthma
GNB1	Metacore: IL8 Neutrophil migration	KLK5	Metacore: Neutrophil migration in Asthma
GNB2	Metacore: IL8 Neutrophil migration	KLK6	Metacore: Neutrophil migration in Asthma
GNB3	Metacore: IL8 Neutrophil migration	KLK7	Metacore: Neutrophil migration in Asthma
GNB4	Metacore: IL8 Neutrophil migration	KLK8	Metacore: Neutrophil migration in Asthma
GNB5	Metacore: IL8 Neutrophil migration	KLK9	Metacore: Neutrophil migration in Asthma
GNG10	Metacore: IL8 Neutrophil migration	FLT1	Metacore: Neutrophil migration in Asthma
GNG11	Metacore: IL8 Neutrophil migration	RUNX1	Metacore: Transcription regulation of granulocytes
GNG12	Metacore: IL8 Neutrophil migration	CEBPA	Metacore: Transcription regulation of granulocytes
GNG13	Metacore: IL8 Neutrophil migration	CEBPE	Metacore: Transcription regulation of granulocytes
GNG2	Metacore: IL8 Neutrophil migration	ANPEP	Metacore: Transcription regulation of granulocytes
GNG3	Metacore: IL8 Neutrophil migration	PTPRC	Metacore: Transcription regulation of granulocytes
GNG4	Metacore: IL8 Neutrophil migration	E2F1	Metacore: Transcription regulation of granulocytes
GNG5	Metacore: IL8 Neutrophil migration	CSF3	Metacore: Transcription regulation of granulocytes
GNG7	Metacore: IL8 Neutrophil migration	CSF3R	Metacore: Transcription regulation of granulocytes
GNG8	Metacore: IL8 Neutrophil migration	GATA1	Metacore: Transcription regulation of granulocytes
GNGT1	Metacore: IL8 Neutrophil migration	JAK1	Metacore: Transcription regulation of granulocytes
GNGT2	Metacore: IL8 Neutrophil migration	JAK2	Metacore: Transcription regulation of granulocytes
ICAM1	Metacore: IL8 Neutrophil migration	LRG1	Metacore: Transcription regulation of granulocytes
CXCL8	Metacore: IL8 Neutrophil migration	LTF	Metacore: Transcription regulation of granulocytes
ITGB2	Metacore: IL8 Neutrophil migration	ELANE	Metacore: Transcription regulation of granulocytes
LIMK1	Metacore: IL8 Neutrophil migration	LYZ	Metacore: Transcription regulation of granulocytes
MYLK	Metacore: IL8 Neutrophil migration	MXD1	Metacore: Transcription regulation of granulocytes
MYLK2	Metacore: IL8 Neutrophil migration	MAX	Metacore: Transcription regulation of granulocytes
MYLK3	Metacore: IL8 Neutrophil migration	PRTN3	Metacore: Transcription regulation of granulocytes
PPP1CB	Metacore: IL8 Neutrophil migration	MPO	Metacore: Transcription regulation of granulocytes
PPP1R12A	Metacore: IL8 Neutrophil migration	SPI1	Metacore: Transcription regulation of granulocytes
PDPK1	Metacore: IL8 Neutrophil migration	RARA	Metacore: Transcription regulation of granulocytes
PIK3CG	Metacore: IL8 Neutrophil migration	RXRA	Metacore: Transcription regulation of granulocytes
PIK3R5	Metacore: IL8 Neutrophil migration	SOCS3	Metacore: Transcription regulation of granulocytes
PIP5K1A	Metacore: IL8 Neutrophil migration	STAT3	Metacore: Transcription regulation of granulocytes

Gene	Source	Gene	Source
PIP5K1B	Metacore: IL8 Neutrophil migration	STAT5A	Metacore: Transcription regulation of granulocytes
PIP5K1C	Metacore: IL8 Neutrophil migration	STAT5B	Metacore: Transcription regulation of granulocytes
PRKCZ	Metacore: IL8 Neutrophil migration	FES	Metacore: Transcription regulation of granulocytes
PLD1	Metacore: IL8 Neutrophil migration	MYB	Metacore: Transcription regulation of granulocytes
PLPP6	Metacore: IL8 Neutrophil migration	MYC	Metacore: Transcription regulation of granulocytes
RAC1	Metacore: IL8 Neutrophil migration	CYBB	Metacore: Transcription regulation of granulocytes
RAC2	Metacore: IL8 Neutrophil migration	NCF1	Metacore: Transcription regulation of granulocytes
TLN2	Metacore: IL8 Neutrophil migration	NCF2	Metacore: Transcription regulation of granulocytes

Gene names converted to Affymetrix probe ID, resulted in 638 probes in total, these are presented in Table 4.

Table 4 Probe Set that have previously identified immune cell mechanisms specifically related to neutrophil function

Gene	Probe ID	Gene	Probe ID
ABL1	202123_s_at	KLK7	239381_at
ACTA1	203872_at	KLK8	1552319_a_at
ACTA2	200974_at	KLK8	206125_s_at
ACTA2	215787_at	KLK9	233687_s_at
ACTA2	243140_at	LIMK1	204356_at
ACTB	200801_x_at	LIMK1	204357_s_at
ACTB	213867_x_at	LIMK1	208372_s_at
ACTB	224594_x_at	LRG1	228648_at
ACTB	AFFX-HSAC07/X00351_3_at	LTB4R	210128_s_at
ACTB	AFFX-HSAC07/X00351_5_at	LTB4R	216388_s_at
ACTB	AFFX-HSAC07/X00351_M_at	LTB4R	236172_at
ACTC1	205132_at	LTF	202018_s_at
ACTG1	201550_x_at	LYZ	1555745_a_at
ACTG1	211970_x_at	LYZ	213975_s_at
ACTG1	211983_x_at	MAPK1	1552263_at
ACTG1	211995_x_at	MAPK1	1552264_a_at
ACTG1	212363_x_at	MAPK1	208351_s_at
ACTG1	212988_x_at	MAPK1	212271_at
ACTG1	213214_x_at	MAPK1	224620_at
ACTG1	221607_x_at	MAPK1	224621_at
ACTG1	224585_x_at	MAPK1	229847_at
ACTG2	202274_at	MAPK11	206040_s_at
ACTG2	241148_at	MAPK11	211499_s_at
ACTN1	208636_at	MAPK11	211500_at
ACTN1	208637_x_at	MAPK12	1556340_at
ACTN1	211160_x_at	MAPK12	1556341_s_at
ACTN1	237401_at	MAPK12	206106_at
ACTN2	203861_s_at	MAPK13	210058_at
ACTN2	203862_s_at	MAPK13	210059_s_at
ACTN2	203863_at	MAPK14	202530_at
ACTN2	203864_s_at	MAPK14	210449_x_at
ACTN3	206891_at	MAPK14	211087_x_at
ACTN4	200601_at	MAPK14	211561_x_at
ACTR2	1554390_s_at	MAPK3	212046_x_at

Gene	Probe ID	Gene	Probe ID
ACTR2	1558015_s_at	MAX	208403_x_at
ACTR2	200727_s_at	MAX	209331_s_at
ACTR2	200728_at	MAX	209332_s_at
ACTR2	200729_s_at	MAX	210734_x_at
ACTR2	234210_x_at	MAX	214108_at
ACTR2	234212_at	MIF	217871_s_at
ACTR3	200996_at	MPO	203948_s_at
ACTR3	213101_s_at	MPO	203949_at
ACTR3	213102_at	MSN	200600_at
ACTR3	228603_at	MSN	233749_at
ACTR3	239170_at	MXD1	206877_at
ACTR3B	1555487_a_at	MXD1	226275_at
ACTR3B	218868_at	MXD1	228846_at
ADAM17	205745_x_at	MYB	204798_at
ADAM17	205746_s_at	MYB	215152_at
ADAM17	213532_at	MYC	202431_s_at
ADAM17	237897_at	MYH1	205951_at
AKT1	207163_s_at	MYH10	212372_at
AKT2	1560689_s_at	MYH10	213067_at
AKT2	203808_at	MYH11	1568760_at
AKT2	203809_s_at	MYH11	201495_x_at
AKT2	211453_s_at	MYH11	201496_x_at
AKT2	225471_s_at	MYH11	201497_x_at
AKT2	226156_at	MYH11	207961_x_at
AKT2	236664_at	MYH11	228133_s_at
AKT3	212607_at	MYH11	228134_at
AKT3	212609_s_at	MYH11	239307_at
AKT3	219393_s_at	MYH13	208208_at
AKT3	222880_at	MYH14	217545_at
AKT3	224229_s_at	MYH14	217660_at
AKT3	242876_at	MYH14	219946_x_at
AKT3	242879_x_at	MYH14	226988_s_at
ANPEP	202888_s_at	MYH14	232977_x_at
ANPEP	234458_at	MYH14	234290_x_at
ANPEP	234576_at	MYH15	215331_at
ARPC1A	200950_at	MYH16	1564072_at
ARPC1B	201954_at	MYH2	204631_at
ARPC2	207988_s_at	MYH3	205940_at
ARPC2	208679_s_at	MYH4	208148_at
ARPC2	213513_x_at	MYH6	214468_at
ARPC3	208736_at	MYH7	204737_s_at
ARPC4	211672_s_at	MYH7	216265_x_at
ARPC4	217817_at	MYH8	206717_at
ARPC4	217818_s_at	MYH8	34471_at
ARPC5	1555797_a_at	MYH9	211926_s_at
ARPC5	1569325_at	MYL1	209888_s_at
ARPC5	211963_s_at	MYL12A	1555976_s_at
ARPC5	237387_at	MYL12A	1555977_at
BDKRB1	207510_at	MYL12A	1555978_s_at
C5	205500_at	MYL12A	201318_s_at
C5AR1	220088_at	MYL12A	201319_at
CCL15	210390_s_at	MYL12B	221474_at
CCL2	216598_s_at	MYL2	209742_s_at
CCL20	205476_at	MYL3	205589_at

Gene	Probe ID	Gene	Probe ID
CCL3	205114_s_at	MYL4	210088_x_at
CCL5	1405_i_at	MYL4	210395_x_at
CCL5	1555759_a_at	MYL4	216054_x_at
CCL5	204655_at	MYL4	217274_x_at
CCL7	208075_s_at	MYL5	205145_s_at
CCR1	205098_at	MYL6	212082_s_at
CCR1	205099_s_at	MYL6	214002_at
CCR2	206978_at	MYL6B	204173_at
CCR2	207794_at	MYL7	219942_at
CCR3	208304_at	MYL9	201058_s_at
CCR5	206991_s_at	MYL9	244149_at
CD177	219669_at	MYLK	1563466_at
CD34	209543_s_at	MYLK	1568770_at
CEACAM1	206576_s_at	MYLK	1569956_at
CEACAM1	209498_at	MYLK	202555_s_at
CEACAM1	210610_at	MYLK	224823_at
CEACAM1	211883_x_at	MYLK2	231792_at
CEACAM1	211889_x_at	MYLK3	1562411_at
CEACAM3	208052_x_at	MYLK3	1568925_at
CEACAM3	210789_x_at	MYLK3	1568926_x_at
CEACAM3	217209_at	MYLK3	217623_at
CEBPA	204039_at	MYLK3	238834_at
CEBPE	214523_at	MYLPF	205163_at
CFL1	1555730_a_at	NCF1	204961_s_at
CFL1	200021_at	NCF1	214084_x_at
CFL1	230870_at	NCF2	209949_at
CFL1	236792_at	NCOA3	1562439_at
CFL2	224352_s_at	NCOA3	207700_s_at
CFL2	224663_s_at	NCOA3	209060_x_at
CFL2	233496_s_at	NCOA3	209061_at
CLEC4C	1552552_s_at	NCOA3	209062_x_at
CLEC4C	1555687_a_at	NCOA3	211352_s_at
CR1	206244_at	NFKB1	209239_at
CR1	208488_s_at	NFKB2	207535_s_at
CR1	217484_at	NFKB2	209636_at
CR1	217552_x_at	NFKB2	211524_at
CR1	244313_at	OSM	214637_at
CSF3	207442_at	OSM	230170_at
CSF3R	1553297_a_at	PAK1	1565772_at
CSF3R	203591_s_at	PAK1	209615_s_at
CXCL1	204470_at	PAK1	226507_at
CXCL2	1569203_at	PAK1	230100_x_at
CXCL2	209774_x_at	PDPK1	204524_at
CXCL2	230101_at	PDPK1	221244_s_at
CXCL3	207850_at	PDPK1	224986_s_at
CXCL5	207852_at	PDPK1	244629_s_at
CXCL5	214974_x_at	PDPK1	244630_at
CXCL5	215101_s_at	PDPK1	32029_at
CXCL8	202859_x_at	PECAM1	1558397_at
CXCL8	211506_s_at	PECAM1	1559921_at
CXCR1	207094_at	PECAM1	208981_at
CXCR2	207008_at	PECAM1	208982_at
CYBB	203922_s_at	PECAM1	208983_s_at
CYBB	203923_s_at	PGF	209652_s_at

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Gene	Probe ID	Gene	Probe ID
CYBB	217431_x_at	PGF	215179_x_at
CYBB	233538_s_at	PIK3CG	206369_s_at
DEFB124	1568375_at	PIK3CG	206370_at
DEFB124	1568377_x_at	PIK3CG	239294_at
E2F1	2028_s_at	PIK3R5	220566_at
E2F1	204947_at	PIK3R5	227553_at
EGR1	201693_s_at	PIK3R5	227645_at
EGR1	201694_s_at	PIP5K1A	207391_s_at
EGR1	227404_s_at	PIP5K1A	210256_s_at
EGR3	206115_at	PIP5K1A	211205_x_at
ELANE	206871_at	PIP5K1B	205632_s_at
EZR	208621_s_at	PIP5K1B	217477_at
EZR	208622_s_at	PIP5K1C	212518_at
EZR	208623_s_at	PLCB2	204046_at
EZR	217230_at	PLCB2	210388_at
EZR	217234_s_at	PLD1	1557126_a_at
FES	205418_at	PLD1	177_at
FLT1	204406_at	PLD1	205203_at
FLT1	210287_s_at	PLD1	215723_s_at
FLT1	222033_s_at	PLD1	215724_at
FLT1	226497_s_at	PLD1	226636_at
FLT1	226498_at	PLD1	232530_at
FLT1	232809_s_at	PLPP6	227385_at
FOS	209189_at	PMAIP1	204285_s_at
FPR1	205118_at	PMAIP1	204286_s_at
FPR1	205119_s_at	PPP1CB	201407_s_at
FPR2	210772_at	PPP1CB	201408_at
FPR2	210773_s_at	PPP1CB	201409_s_at
GATA1	1555590_a_at	PPP1CB	228222_at
GATA1	210446_at	PPP1R12A	201602_s_at
GNAI1	209576_at	PPP1R12A	201603_at
GNAI1	227692_at	PPP1R12A	201604_s_at
GNAI2	201040_at	PREX1	224909_s_at
GNAI2	215996_at	PREX1	224925_at
GNAI2	217271_at	PRKCA	1560074_at
GNAI3	201179_s_at	PRKCA	206923_at
GNAI3	201180_s_at	PRKCA	213093_at
GNAI3	201181_at	PRKCA	215194_at
GNAO1	204762_s_at	PRKCA	215195_at
GNAO1	204763_s_at	PRKCB	207957_s_at
GNAO1	215912_at	PRKCB	209685_s_at
GNAO1	231951_at	PRKCB	227817_at
GNAZ	204993_at	PRKCB	227824_at
GNB1	200744_s_at	PRKCB	228795_at
GNB1	200745_s_at	PRKCB	230437_s_at
GNB1	200746_s_at	PRKCD	202545_at
GNB2	200852_x_at	PRKCE	206248_at
GNB3	206047_at	PRKCE	226101_at
GNB4	223487_x_at	PRKCE	234089_at
GNB4	223488_s_at	PRKCE	236459_at
GNB4	225710_at	PRKCE	239011_at
GNB5	1554346_at	PRKCG	206270_at
GNB5	204000_at	PRKCG	236195_x_at
GNB5	207124_s_at	PRKCH	206099_at

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Gene	Probe ID	Gene	Probe ID
GNB5	211871_x_at	PRKCH	218764_at
GNB5	242404_at	PRKCH	230124_at
GNG10	201921_at	PRKCI	209677_at
GNG11	204115_at	PRKCI	209678_s_at
GNG11	239942_at	PRKCI	213518_at
GNG12	1555240_s_at	PRKCQ	210038_at
GNG12	212294_at	PRKCQ	210039_s_at
GNG12	222834_s_at	PRKCZ	1569748_at
GNG13	220806_x_at	PRKCZ	202178_at
GNG2	1555766_a_at	PRKD1	205880_at
GNG2	223943_s_at	PRKD1	217705_at
GNG2	224964_s_at	PRKD2	209282_at
GNG2	224965_at	PRKD2	241669_x_at
GNG3	222005_s_at	PRKD2	38269_at
GNG4	1555765_a_at	PRKD3	1554910_at
GNG4	1555867_at	PRKD3	211084_x_at
GNG4	1566513_a_at	PRKD3	218236_s_at
GNG4	205184_at	PRKD3	222565_s_at
GNG5	207157_s_at	PRKD3	242549_at
GNG7	206896_s_at	PRTN3	207341_at
GNG7	214227_at	PTAFR	206278_at
GNG7	228831_s_at	PTAFR	211661_x_at
GNG7	232043_at	PTAFR	227184_at
GNG8	233416_at	PTGS2	1554997_a_at
GNG8	234284_at	PTGS2	204748_at
GNGT1	207166_at	PTPRC	1552480_s_at
GNGT2	235139_at	PTPRC	1569830_at
H1F0	208886_at	PTPRC	207238_s_at
HSPA14	219212_at	PTPRC	212587_s_at
HSPA14	226887_at	PTPRC	212588_at
HSPA14	227650_at	PXN	201087_at
HSPA1L	210189_at	PXN	211823_s_at
HSPA1L	233694_at	RAC1	1567457_at
HSPA2	211538_s_at	RAC1	1567458_s_at
HSPA4	208814_at	RAC1	208640_at
HSPA4	208815_x_at	RAC1	208641_s_at
HSPA4	211015_s_at	RAC2	207419_s_at
HSPA4	211016_x_at	RAC2	213603_s_at
HSPA5	211936_at	RARA	1565358_at
HSPA5	230031_at	RARA	203749_s_at
HSPA6	117_at	RARA	203750_s_at
HSPA6	213418_at	RARA	211605_s_at
HSPA8	208687_x_at	RARA	216300_x_at
HSPA8	210338_s_at	REL	206035_at
HSPA8	221891_x_at	REL	206036_s_at
HSPA8	224187_x_at	REL	228812_at
HSPA9	200690_at	REL	235242_at
HSPA9	200691_s_at	REL	239486_at
HSPA9	200692_s_at	RELA	201783_s_at
HSPA9	232200_at	RELA	209878_s_at
ICAM1	202637_s_at	RELA	230202_at
ICAM1	202638_s_at	RELB	205205_at
ICAM1	215485_s_at	RXRA	202426_s_at
ICAM2	204683_at	RXRA	202449_s_at

Gene	Probe ID	Gene	Probe ID
ICAM2	213620_s_at	S100P	204351_at
IFITM1	201601_x_at	SELL	204563_at
IFITM1	214022_s_at	SOCS3	206359_at
IL1B	205067_at	SOCS3	206360_s_at
IL1B	39402_at	SOCS3	214105_at
IL1R1	202948_at	SOCS3	227697_at
IL1R1	215561_s_at	SPI1	205312_at
ITGAL	1554240_a_at	SPTBN1	200671_s_at
ITGAL	213475_s_at	SPTBN1	200672_x_at
ITGAM	205785_at	SPTBN1	212071_s_at
ITGAM	205786_s_at	SPTBN1	213914_s_at
ITGB2	1555349_a_at	SPTBN1	214856_at
ITGB2	202803_s_at	SPTBN1	215918_s_at
ITGB2	236988_x_at	SPTBN1	226342_at
ITPR1	1562373_at	SPTBN1	226765_at
ITPR1	203710_at	SPTBN1	228246_s_at
ITPR1	211323_s_at	SPTBN1	230540_at
ITPR1	216944_s_at	SPTBN1	242220_at
ITPR1	240052_at	SSH2	1554114_s_at
ITPR2	202660_at	SSH2	1555423_at
ITPR2	202661_at	SSH2	1555425_x_at
ITPR2	202662_s_at	SSH2	1560306_at
ITPR2	211360_s_at	SSH2	226080_at
ITPR3	201187_s_at	STAT3	208991_at
ITPR3	201188_s_at	STAT3	208992_s_at
ITPR3	201189_s_at	STAT3	225289_at
ITPR3	239542_at	STAT3	243213_at
JAK1	1552610_a_at	STAT5A	203010_at
JAK1	1552611_a_at	STAT5B	1555086_at
JAK1	201648_at	STAT5B	1555088_x_at
JAK1	239695_at	STAT5B	205026_at
JAK1	240613_at	STAT5B	212549_at
JAK2	1562031_at	STAT5B	212550_at
JAK2	205841_at	SYAP1	225154_at
JAK2	205842_s_at	TAC1	206552_s_at
JUN	201464_x_at	TACR1	208048_at
JUN	201465_s_at	TACR1	208049_s_at
JUN	201466_s_at	TACR1	210637_at
JUN	213281_at	TACR1	230908_at
KLK1	216699_s_at	TARP	211144_x_at
KLK10	209792_s_at	TARP	216920_s_at
KLK10	215808_at	TARP	217381_s_at
KLK11	205470_s_at	TBC1D22A	209650_s_at
KLK12	220782_x_at	TBC1D22A	210144_at
KLK12	233586_s_at	TBC1D22A	33778_at
KLK12	234316_x_at	TLN1	203254_s_at
KLK13	205783_at	TLN1	232763_at
KLK13	216670_at	TLN1	236132_at
KLK13	217315_s_at	TLN2	212701_at
KLK14	220573_at	TLN2	212703_at
KLK15	221462_x_at	TLN2	232625_at
KLK15	233477_at	TLR10	223750_s_at
KLK15	234495_at	TLR10	223751_x_at
KLK15	234966_at	TLR2	204924_at

Gene	Probe ID	Gene	Probe ID
KLK2	1555545_at	TLR4	1552798_a_at
KLK2	209854_s_at	TLR4	221060_s_at
KLK2	209855_s_at	TLR4	224341_x_at
KLK2	210339_s_at	TLR4	232068_s_at
KLK3	204582_s_at	TNF	1563357_at
KLK3	204583_x_at	TNF	207113_s_at
KLK3	231629_x_at	TNFRSF1A	207643_s_at
KLK4	1555697_at	TNFRSF1B	203508_at
KLK4	1555737_a_at	TREML2	219748_at
KLK4	224062_x_at	TTPAL	219633_at
KLK4	231782_s_at	TTPAL	228031_at
KLK4	233854_x_at	VAV1	206219_s_at
KLK5	222242_s_at	VCL	200930_s_at
KLK6	204733_at	VCL	200931_s_at
KLK7	205778_at	VPS37B	221704_s_at

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as Subject whom have completed their final visit (day 84). • Withdrawn subjects will not be replaced in the study. • 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.

13.7.2. 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 by the use of 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.
PD	• Any values below the Lower Limit of Quantification (LLQ) will be assigned a value of ½ LLQ for display purposes in Figures and for computation of summary statistics. Any values above the Upper Limit of Quantification (ULQ) will be assigned to the ULQ for display purposes in Figures and for computation of summary statistics. If multiple LLQ and /or ULQ values are available per assay (for example if multiple runs with different standard curves are utilised) then the LLQ and/or ULQ value used for the above imputation shall be the minimum of the available LLQs and/or the maximum of the ULQs. Where biomarker concentrations are from an assay of an increased dilution factor the LLQ and ULQ will be multiplied by this factor. • If the number of LLQ (and/or ULQ) values is large for an individual biomarker then an alternative analysis method, such as TOBIT analysis, may be required. "Large" is hard to define prospectively and may depend upon the dataset in question. Any such methodology will be documented in the statistical contributions to the study report. • Imputed values will be used in tables and figures, unless the proportion of imputed values at a given time point is large, in which case the summary statistics may not be presented for that time point and/or alternative actions will be taken and documented in the study report. • Where values are imputed, the number of such imputations will be included as a summary statistic in the relevant summary tables.
HRCT	• No missing data imputation methods will be used. • Note that for the HRCT data, there may be instances such that measurements from a particular Lobe cannot be distinguished between another Lobe, for example the iVlobe may be measured from both the LLL and LUL lobes. In such a case, the Lobe will be denoted as LLL + LUL. Therefore, for the statistical analysis purpose, since analysis is performed on a lobar level, the LLL and LUL Lobes will be set to missing and will

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>therefore not be included in the analysis. Below is a table of all possible scenarios, where the data is set to missing and not used in the statistical analysis:
<table>
<tr><th colspan="5">Lobes</th><th rowspan="2">Label</th></tr>
<tr><th>RUL</th><th>RML</th><th>RLL</th><th>LUL</th><th>LLL</th></tr>
<tr><td>x</td><td>x</td><td></td><td></td><td></td><td>RUL + RML</td></tr>
<tr><td></td><td>x</td><td>x</td><td></td><td></td><td>RML + RLL</td></tr>
<tr><td>x</td><td></td><td>x</td><td></td><td></td><td>RUL + RLL</td></tr>
<tr><td>x</td><td>x</td><td>x</td><td></td><td></td><td>RUL + RML + RLL</td></tr>
<tr><td></td><td></td><td></td><td>x</td><td>x</td><td>LUL + LLL</td></tr>
</table></td></tr>
</table>

13.7.2.1. 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: ○ Missing Start Day: First of the month will be used unless this 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.

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
Haemoglobin	g/L	Male		180
		Female		180
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
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 U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

13.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 500 [1]
Absolute PR Interval	msec	< 110 [1]	> 220 [2]
Absolute QRS Interval	msec	< 75 [1]	> 110 [2]

NOTES:
[1] An upper limit of 450 would represent standard ECG values of PCI for HV studies, this has been extended to 500 as often with exacerbations the treatment can result in a short term prolongation of QTc up to 500.
[2] Represent standard ECG values of PCI for HV studies

13.8.3. 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

13.9. Appendix 9: Abbreviations & Trade Marks

13.9.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
AT	Air Trapping Score (% of iVlobe)
BVD	Blood Vessel Density (% of iVlobe)
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CENTRAL	Central lung region
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CT	Computed tomography
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
Diameter	Diameter
DISTAL	Distal lung region
DLco	Diffusion capacity
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
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
FRI	Functional respiratory imaging
FRC	Functional residual capacity
GSK	GlaxoSmithKline
GUI	Guidance
HRCT	High Resolution Computed Tomography
IA	Interim Analysis
IALD	Internal Airflow Lobar Distribution
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IL-8	Interleukin 8
IL-6	Interleukin 6

Abbreviation	Description
IMMS	International Modules Management System
IP	Investigational Product
iRaw	Imaging Airway Resistance
ITT	Intent-To-Treat
iVlobe	Lobar Volume
iVlobepred	Percent Predicted Lobar Volume
iVaw	Imaging Airway Volume
iVaww	Airway Wall Volume
LAS	Low Attenuation Score (% of iVlobe)
Length	Length
LL	Lung, lower lobes
LLL	Lung, left lower lobe
LOC	Last Observation Carries Forward
LUL	Lung, left upper lobe
LUL+LLL	Lung, left upper and lower lobe
MMP9	Matrix metallopeptidase 9
MMRC	Modified Medical Research Council
MMRM	Mixed Model Repeated Measures
NQ	Non-quantifiable
OTU	Operational Taxonomic Unit
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PEF	peak expiratory flow
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
qPCR	Quantitative polymerase chain reaction
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RLL	Lung, right lower lobe
RML	Lung, right middle lobe
RML+RLL	Lung, right middle and lower lobe
RUL	Lung, right upper lobe
RUL+RLL	Lung, right upper and lower lobe
RUL+RML	Lung, right upper and middle lobe
RUL+RML+RLL	Lung, right upper, middle and lower lobe
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
sGaw	Specific conductance
siRaw	Specific Imaging Airway Resistance

Abbreviation	Description
siVaw	Specific Imaging Airway Volume
siVaww	Specific Airway Wall Volume
SoC	Standard of Care
SOP	Standard Operation Procedure
sRaw	Specific Resistance
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TLC	Total lung capacity
TNFα	Tumor necrosis factor alpha
TOTAL	Total lung region
TRACHEA	Trachea
UL	Lung, upper lobes

13.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
ELLIPTA	FluidDA
HARP	Quest
RAMOS NG	SAS
RANDALL NG	WinNonlin

13.10. Appendix 10: List of Data Displays

13.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.17	N/A
Efficacy	2.1 to 2.68	2.1
Safety	3.1 to 3.20	N/A
Pharmacokinetic	4.1 to 4.4	4.1
Pharmacodynamic and / or Biomarker	6.1 to 6.21	6.1
Section	**Listings**	
ICH Listings	1 to 34	
Other Listings	35 to 49	

13.10.2. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

13.10.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Subject	ES1	Summary of Subject Disposition	ICH E3, FDAAA, EudraCT	SAC
1.2.	All Subject	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.3.	APE	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.4.	All Subject	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.5.	All Subject	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.6.	APE	SP1	Summary of Study Populations	IDSL	SAC
1.7.	All Subject	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
Demographic and Baseline Characteristics					
1.8.	All Subject	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.9.	APE	DM11	Summary of Age Ranges	EudraCT	SAC
1.10.	All Subject	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.11.	All Subject	DM6	Summary of Race and Racial Combinations Details		SAC
1.12.	All Subject	PII116678/final/ Table 2.109	Summary of Index Exacerbation Severity		

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
1.13.	All Subject	MH1	Summary of Current Medical Conditions	ICH E3	SAC
1.14.	All Subject	MH1	Summary of Past Medical Conditions	ICH E3	SAC
1.15.	All Subject	CM1	Summary of Prior Medications	ICH E3	SAC
1.16.	All Subject	CM1	Summary of Concomitant Medications	ICH E3	SAC
Exposure and Treatment Compliance					
1.17.	All Subject	EX1	Summary of Exposure to Study Treatment	ICH E3 Include Daily Dose, Cumulative does and Days on study drug per template.	SAC

13.10.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HRCT Imaging Endpoints					
2.1.	All subjects	PII116678/ final/ Table 2.1	Summary of iVaw (mL) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.2.	All subjects	PII116678/ final/ Table 2.2	Summary of iVaw (mL) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC
2.3.	All subjects	PII116678/ final/ Table 2.3	Summary of iVaw (mL) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC
2.4.	All subjects	PII116678/ final/ Table 2.4	Summary of iVaw (mL) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.5.	All subjects	PII116678/ final/ Table 2.9	Summary of siVaw (mL/L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.6.	All subjects	PII116678/ final/ Table 2.10	Summary of siVaw (mL/L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC
2.7.	All subjects	PII116678/final/ Table 2.11	Summary of siVaw (mL/L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC
2.8.	All subjects	PII116678/final/ Table 2.12	Summary of siVaw (mL/L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC
2.9.	All subjects	PII116678/final/ Table 2.17	Summary of iRaw (kPa*s/L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.10.	All subjects	PII116678/final/ Table 2.18	Summary of iRaw (kPa*s/L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.11.	All subjects	PII116678/final/ Table 2.19	Summary of iRaw (kPa*s/L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used	SAC
2.12.	All subjects	PII116678/final/ Table 2.20	Summary of iRaw (kPa*s/L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.13.	All subjects	PII116678/final/ Table 2.25	Summary of siRaw (kPa*s) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.14.	All subjects	PII116678/final/ Table 2.26	Summary of siRaw (kPa*s) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.15.	All subjects	PII116678/final/ Table 2.27	Summary of siRaw (kPa*s) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used	SAC
2.16.	All subjects	PII116678/final/ Table 2.28	Summary of siRaw (kPa*s) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page No longitudinal endpoints Footnote any transformations used Footnote baseline	SAC
2.17.	All subjects	PII116678/final/ Table 2.33	Summary of iVlobe (L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.18.	All subjects	PII116678/final/ Table 2.34	Summary of iVlobe (L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.19.	All subjects	PII116678/final/ Table 2.35	Summary of iVlobe (L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.20.	All subjects	PII116678/final/ Table 2.36	Summary of iVlobe (L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.21.	All subjects	PII116678/final/ Table 2.41	Summary of Percent Predicted iVlobe (%) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Note in HARP to output (%) it may be necessary to input (%%)	SAC
2.22.	All subjects	PII116678/final/ Table 2.42	Summary of Percent Predicted iVlobe (%) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline Note in HARP to output (%) it may be necessary to input (%%)	SAC
2.23.	All subjects	PII116678/final/ Table 2.43	Summary of Percent Predicted iVlobe (%) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Note in HARP to output (%) it may be necessary to input (%%)	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.24.	All subjects	PII116678/final/ Table 2.44	Summary of Percent Predicted iVlobe (%) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline Note in HARP to output (%) it may be necessary to input (%%)	SAC
2.25.	All subjects	PII116678/final/ Table 2.49	Summary of LAS (% of iVlobe) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.26.	All subjects	PII116678/final/ Table 2.50	Summary of LAS (% of iVlobe) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.27.	All subjects	PII116678/final/ Table 2.51	Summary of LAS (% of iVlobe) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.28.	All subjects	PII116678/final/ Table 2.52	Summary of LAS (% of iVlobe) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.29.	All subjects	PII116678/final/ Table 2.55	Summary of IALD (%) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.30.	All subjects	PII116678/final/ Table 2.56	Summary of IALD (%) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.31.	All subjects	PII116678/final/ Table 2.57	Summary of IALD (%) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central, Distal and Total do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.32.	All subjects	PII116678/final/ Table 2.58	Summary of IALD (%) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central, Distal and Total do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.33.	All subjects	PII116678/final/ Table 2.61	Summary of AT (% of iVlobe) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.34.	All subjects	PII116678/final/ Table 2.62	Summary of AT (% of iVlobe) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.35.	All subjects	PII116678/final/ Table 2.63	Summary of AT (% of iVlobe) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.36.	All subjects	PII116678/final/ Table 2.64	Summary of AT (% of iVlobe) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.37.	All subjects	PII116678/final/ Table 2.67	Summary of BVD (% of iVlobe) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used	SAC
2.38.	All subjects	PII116678/final/ Table 2.68	Summary of BVD (% of iVlobe) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.39.	All subjects	PII116678/final/ Table 2.69	Summary of BVD (% of iVlobe) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used	SAC
2.40.	All subjects	PII116678/final/ Table 2.70	Summary of BVD (% of iVlobe) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Regions Central and Distal do not exist No Scan Trimming endpoints Footnote any transformations used Footnote baseline	SAC
2.41.	All subjects	PII116678/final/ Table 2.73	Summary of iVaww (mL) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.42.	All subjects	PII116678/final/ Table 2.74	Summary of iVaww (mL) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.43.	All subjects	PII116678/final/ Table 2.75	Summary of iVaww (mL) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC
2.44.	All subjects	PII116678/final/ Table 2.76	Summary of iVaww (mL) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC
2.45.	All subjects	PII116678/final/ Table 2.79	Summary of siVaww (mL/L) (Absolute), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used	SAC
2.46.	All subjects	PII116678/final/ Table 2.80	Summary of siVaww (mL/L) (Change from Baseline), for Individual Lobes	Ensure no overlapping information across pages for each Lobe, hence if required start each Lobe on a separate page Footnote any transformations used Footnote baseline	SAC
2.47.	All subjects	PII116678/final/ Table 2.81	Summary of siVaww (mL/L) (Absolute), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.48.	All subjects	PII116678/final/ Table 2.82	Summary of siVaww (mL/L) (Change from Baseline), for Individual Regions	Ensure no overlapping information across pages for each Region, hence if required start each Region on a separate page Footnote any transformations used Footnote baseline	SAC
2.49.	All subjects	PII116678/final/ Table 2.85	Summary of Trachea Length (mm), Diameter (mm) and Length /Diameter (mm/mm) (Absolute)	Footnote any transformations used	SAC
2.50.	All subjects	PII116678/final/ Table 2.86	Summary of Trachea Length (mm), Diameter (mm) and Length /Diameter (mm/mm) (Change from Baseline)	Footnote any transformations used Footnote baseline	SAC
2.51.	All subjects	PII116678/final/ Table 2.14	Summary of Statistical Analysis for siVaw (mL/L), for Individual Lobes at FRC using Untrimmed Data	Ensure no overlapping information across pages for each Lobe Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.52.	All subjects	PII116678/final/ Table 2.16	Summary of Statistical Analysis for siVaw (mL/L), for Individual Regions at FRC using Untrimmed Data	Ensure no overlapping information across pages for each Lobe Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.53.	All subjects	Refer to: PII116678/final/ Table 2.16 Note: there will be less regions	Summary of Statistical Analysis for siVaw (mL/L), for Distal Region at FRC using Scan Trimmed Data	Ensure no overlapping information across pages for each Lobe Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.54.	All subjects	Refer to: PII116678/final/ Table 2.29 Note: there will be less regions	Summary of Statistical Analysis for siRaw (kPa*s), for Distal Region at FRC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.55.	All subjects	Refer to: PII116678/final/ Table 2.54 Note: there will be less regions	Summary of Statistical Analysis for LAS (% of iVlobe), for Total Region at TLC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.56.	All subjects	Refer to: PII116678/final/ Table 2.60 Note: there will be less regions	Summary of Statistical Analysis for IALD (%), for Upper and Lower Regions	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.57.	All subjects	Refer to: PII116678/final/ Table 2.66 Note: there will be less regions	Summary of Statistical Analysis for AT (% of iVlobe), for Total Region at FRC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.58.	All subjects	Refer to: PII116678/final/ Table 2.72 Note: there will be less regions	Summary of Statistical Analysis for BVD (% of iVlobe), for Total Region at TLC	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.59.	All subjects	Refer to: PII116678/final/ Table 2.84 Note: there will be less regions	Summary of Statistical Analysis for siVaww (mL/L), for Distal Region at TLC using Untrimmed Data	Ensure no overlapping information across pages for each Region No longitudinal endpoints Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
Lung Function					
2.60.	All subjects	PII115119/ Part_A /Table 3.18	Summary of FEV1 (ml) and FVC (ml) (Absolute Values)	Summaries by Visit Footnote any transformations used	SAC
2.61.	All subjects	PII115119/ Part_A /Table 3.19	Summary of FEV1 (ml) and FVC (ml) (Change from Baseline)	Summaries by Visit Footnote any transformations used Footnote Baseline	SAC
2.62.	All subjects	PII116678/ final /Table 2.88	Summary of Statistical Analysis for FEV1 (ml) (Change from Baseline)	Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
2.63.	All subjects	PII116678/ postcsr_2017_01 /Table 2.1	Sub Group Analysis: by Index Exacerbation Severity Summary of Statistical Analysis for FEV1 (ml) (Change from Baseline)	Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.64.	All subjects	PII116678/ final /Table 2.88	Summary of Statistical Analysis for FVC (ml) (Change from Baseline)	Footnote to include the statistical analysis conducted, including covariates, co-variance matrix and prior assumptions. Footnote any transformations used Footnote baseline	SAC
Relief Medication					
2.65.	All subjects	Refer to programming notes	Summary of Rescue Medication Free Days	Use the standard tu_sumstatsinrows to summarise Rescue Medication Free days by time period and treatment. Include columns for time period, treatment, N, n, mean, 95% CI, SD, median, min and max	SAC
2.66.	All subjects	Refer to programming notes	Summary of Mean Number of Occasions of Rescue Use per Day	Use the standard tu_sumstatsinrows to summarise Mean Number of Occasions of Rescue Use per Day by time period and treatment. Include columns for timeperiod, treatment, N, n, mean, 95% CI, SD, median, min and max	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exacerbations					
2.67.	All subjects	Refer to PII116678/ final /Table 2.97 And programming notes	Summary of Investigator Defined Exacerbations	Update rows to be consistent with data i.e. include 6, 7, etc exacerbations as appropriate	SAC
2.68.	All subjects	Refer to PII116678/ final /Table 2.116 And programming notes	Summary of Concomitant Medication Defined Exacerbations	Update rows to be consistent with data i.e. include 6, 7, etc exacerbations as appropriate	SAC

13.10.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Lung Function					
2.1.	All subjects	Refer to PII116678/final/ Table 2.2 but update the number of plots based on the data as appropriate	Summary of PEF (morning)	X-axis to contain each Day, with Means and confidence intervals, grouped by Treatment. Include baseline as a subheading per example shell	SAC

13.10.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	All Subject	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
3.2.	All Subject	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency	ICH E3	SAC
3.3.	All Subject	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3 Include flag for serious	SAC
3.4.	All Subject	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT	SAC
Serious and Other Significant Adverse Events					
3.5.	All Subject	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.6.	All Subject	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL	SAC
Laboratory: Chemistry					
3.7.	All Subject	LB1	Summary of Chemistry	ICH E3	SAC
3.8.	All Subject	LB15	Summary of Worst Case Emergent Laboratory Chemistry Results Relative to Normal Range		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Hematology					
3.9.	All Subject	LB1	Summary of Hematology	ICH E3	SAC
3.10.	All Subject	LB15	Summary of Worst Case Emergent Laboratory Hematology Results Relative to Normal Range		SAC
Laboratory: Urinalysis					
3.11.	All Subject	LB1	Summary of Urine Concentration	ICH E3	SAC
3.12.	All Subject	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline		SAC
Laboratory: Hepatobiliary (Liver)					
3.13.	All Subject	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC
3.14.	All Subject	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.15.	All Subject	EG1	Summary of ECG Findings	IDSL	SAC
3.16.	All Subject	EG2	Summary of ECG Values by Visit		SAC
3.17.	All Subject	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
Vital Signs					
3.18.	All Subject	VS1	Summary of Vital Signs		SAC
3.19.	All Subject	VS1	Summary of Change from Baseline in Vital Signs	ICH E3 Includes Baseline Values	SAC
3.20.	All Subject	VS7	Summary of Emergent Vital Sign Results by Potential Clinical Importance (PCI) Criteria		SAC

13.10.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma Concentration					
4.1.	PK	PK01 PII116678/final/Table 4.1	Summary of Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL)	All visits/timepoints, include a column for visit. Summarise PK data on original scale. Produce 95% CIs Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Excluding the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.2.	PK	PK01 PII116678/final/Table 4.2	Summary of Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL) Including All PK Concentrations Analysed	All visits/timepoints, include a column for visit. Summarise PK data on original scale. Produce 95% CIs Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Including the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC
4.3.	PK	PII116678/final/Table 4.3	Summary of Log-Transformed Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL)	All visits/timepoints, include a column for visit and planned time. Summarise PK data on original scale. Produce n, No. imputed, geometric mean and corresponding 95% Cis SD Logs and %CVb Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Excluding the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.4.	PK	PII116678/final/Table 4.4	Summary of Log-Transformed Plasma Nemiralisib Pharmacokinetic Concentration – Time Data (ng/mL) Including All PK Concentrations Analysed	All visits/timepoints, include a column for visit and planned time. Summarise PK data on original scale. Produce n, No. imputed, geometric mean and corresponding 95% Cis SD Logs and %CVb Note: Use the separate NEMI Diskus and NEMI ELLIPTA treatment groups Including the two subjects who were noted to not comply with inhalation instructions – include footnote	SAC

13.10.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma Concentration					
4.1.	PK	Refer to PII116678/ final/ Figure 4.1 But include additional timepoints per programming notes	Box and Whisker Plot of Plasma Concentration	Two figures to be created: 1st: Plasma Concentration at Day 1 (5 min and 24 hours post-dose) and Day 12 2nd: Plasma Concentration at Day 12, Day 28, Day 56 and Day 84 Note: Use the separate NEMI Diskus and NEMI ELLIPTA	SAC

13.10.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
MRNa					
6.1.	All subjects	PII115119/ Part A/ Listing 40	Summary of Statistical Analysis of mRNA Transcriptome in Induced Sputum (Selected Probe Sets Related to Neutrophil Function)	Summarise fold changes, 95% CI and p-values. Rank by p-value and fold change within timepoint.	SAC
6.2.	All subjects	PII115119/ Part A/ Listing 40	Summary of Statistical Analysis of mRNA Transcriptome in Blood (All Probe Sets)	Summarise fold changes, 95% CI and p-values. Rank by p-value and fold change within timepoint.	SAC
6.3.	All subjects	PII115119/ Part A/ Listing 40	Summary of Additional Statistical Analysis of mRNA Transcriptome in Induced Sputum (All Probe Sets)	Summarise fold changes, 95% CI and p-values. Rank by p-value and fold change within timepoint.	SAC
Cell Count Data and PMN Differentials					
6.4.	All subjects	PII115119/ Part A/Table 5.7	Summary Statistics (Absolute): Total Cell Count Data in Sputum by Treatment and Time.	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.5.	All subjects	PII115119/ Part A/Table 5.8	Summary Statistics (Change from Baseline): Total Cell Count Data in Sputum by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.6.	All subjects	PII115119/ Part A/Table 5.9	Summary Statistics (Absolute): PMNs Differentials in Sputum by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.7.	All subjects	PII115119/ Part A/Table 5.10	Summary Statistics (Change from Baseline): PMNs Differentials in Sputum by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.8.	All subjects	PII115119/ Part A/Table 5.11	Summary Statistics (Absolute): Total Cell Count Data in Blood by Treatment and Time.	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.9.	All subjects	PII115119/ Part A/Table 5.12	Summary Statistics (Change from Baseline): Total Cell Count Data in Blood by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.10.	All subjects	PII115119/ Part A/Table 5.13	Summary Statistics (Absolute): PMNs Differentials in Blood by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.11.	All subjects	PII115119/ Part A/Table 5.14	Summary Statistics (Change from Baseline): PMNs Differentials in Blood by Treatment and Time	Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
Inflammatory Biomarkers					
6.12.	All subjects	PII115119/ Part A/Table 5.17	Summary Statistics (Absolute): Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for this Table (6.12) and a log transformation will be required for Table 6.14. However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.13.	All subjects	PII115119/ Part A/Table 5.18	Summary Statistics (Change from Baseline): Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for this Table (6.13) and a log transformation will be required for Table 6.15. However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.14.	All subjects	PII115119/ Part A/Table 5.19	Summary Statistics (Log-Transformed Absolute) Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for Table 6.12 and a log transformation will be required for this Table (6.14). However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.15.	All subjects	PII115119/ Part A/Table 5.20	Summary Statistics (Log-Transformed Change from Baseline) Inflammatory Biomarkers by Treatment and Time	It is expected that no transformation will be required for Table 6.13 and a log transformation will be required for this Table (6.15). However appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
Microbiome (16S rRNA) and qPCR					
6.16.	All subjects	PD4 and Refer to programming notes	Summary Statistics (Absolute): Microbiome (16S rRNA) Relative Abundance by Treatment and Time	If Data available Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.17.	All subjects	PD4 and Refer to programming notes	Summary Statistics (Percentage Change from Baseline): Microbiome (16S rRNA) Relative Abundance by Treatment and Time	If Data available. Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.18.	All subjects	PII115119/ Part A/Table 5.24	Summary Statistics (Absolute): qPCR delta Ct by Treatment and Time	If Data available. Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
6.19.	All subjects	PII115119/ Part A/Table 5.25	Summary Statistics (Log-Transformed Absolute): qPCR fold change by Treatment and Time	If Data available. Appropriate transformation should be used prior to summarising data. Ensure transformation is clearly documented and update column labels as appropriate	SAC
Bacterial Culture					
6.20.	All subjects	PII115119/ Part A/Table 5.26	Frequency Table of Bacterial Culture (Presence) by Treatment and Time		SAC

13.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	APE	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	All Subjects	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	All Subjects	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4.	All Subjects	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC
5.	All Subjects	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
6.	All Subjects	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
7.	All Subjects	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
8.	APE	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
9.	All Subjects	DM2	Listing of Demographic Characteristics	ICH E3	SAC
10.	All Subjects	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
11.	All Subjects	CM3	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
12.	All Subjects	EX3	Listing of Exposure Data	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
13.	All Subjects	AE8	Listing of All Adverse Events	ICH E3	SAC
14.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
15.	All Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
16.	All Subjects	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC
17.	All Subjects	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
18.	All Subjects	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
19.	All Subjects	AE8	Listing of Adverse Events Leading to Withdrawal from Study or Permanent Discontinuation of Study Treatment	ICH E3	SAC
Hepatobiliary (Liver)					
20.	All Subjects	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
21.	All Subjects	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC
22.	All Subjects	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC
23.	All Subjects	LIVER7	Listing of Liver Biopsy Details		SAC
24.	All Subjects	LIVER8	Listing of Liver Imaging Details		SAC
All Laboratory					
25.	All Subjects	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
26.	All Subjects	LB5	Listing of Laboratory Values of Potential Clinical Importance		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
27.	All Subjects	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
28.	All Subjects	UR2A	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
ECG					
29.	All Subjects	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
30.	All Subjects	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
31.	All Subjects	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
32.	All Subjects	EG5	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
33.	All Subjects	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
34.	All Subjects	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC

13.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demography and Baseline Characteristics					
35.	All Subjects	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC
36.	All Subjects	Refer to Programming notes	COPD Disease duration and Exacerbation Duration	Include investigator ID, subject ID, country, treatment group, COPD Disease Duration (in years and months) and Exacerbation History (number requiring oral/systemic corticosteroids and/or antibiotics and number requiring hospitalisation) as columns	SAC
37.	All Subjects	PREG1a	Listing of Subjects Who Became Pregnant During the Study	Also indicate if the female partners of subjects became pregnant during the study	
Labs					
38.	All Subjects	LB13	Listing of Laboratory Reference Ranges		SAC
39.	All Subjects	CP_LB5	Listing of Laboratory Values Outside Normal Reference Range		SAC
ECG					
40.	All Subjects	CP_EG5	Listing of All ECG findings for Subjects with an Abnormal Finding		SAC
PK					
41.	PK	PK07	Listing of Individual Subjects Plasma Concentrations at all time points		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PD/Biomarkers					
42.	All subjects	PII115119/ Part A/Listing 25	Listing of Sputum Collection	Include sample ID if available	SAC
43.	All subjects	PII115119/ Part A/Listing 26	Listing of Blood Collection for RNA		SAC
44.	All subjects	PII115119/ Part A/Listing 31	Listing of Cell Count Data		SAC
45.	All subjects	PII115119/ Part A/Listing 32	Listing of PMNs Differentials		SAC
46.	All subjects	PII115119/ Part A/Listing 34	Listing of Individual Subject Inflammatory Cytokine Biomarker Data		SAC
47.	All subjects	PII115119/ Part A/Listing 35	Listing of Microbiome (16S rRNA) Biomarker Data		SAC
48.	All subjects	PII115119/ Part A/Listing 36	Listing of qPCR Data		SAC
49.	All subjects	PII115119/ Part A/Listing 37	Listing of Bacterial Culture Data		SAC

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP) - Critical Components

Title	:	Critical Components of Reporting and Analysis Plan for Study 201928: A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GSK2269557
Effective Date	:	25-SEP-2015

Description :

The purpose of this CC-RAP (Critical Components of the Reporting and Analysis Plan) is to capture the following Critical Components, by First Subject First Visit:

- Analysis Population
- Protocol Deviations (Reflect the agreements from the plan for managing protocol deviations and define the reporting & analysis of all important deviations, as defined in the ICH guidelines)
- Statistical Evaluation (Primary/critical endpoints) and Statistical Analysis Considerations

Author's Name and Functional Area:

PPD	25-SEP-2015
Principal Statistician (Clinical Statistics)	

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201928

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1. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All subjects who were screened.	• Demography • Screening failure details • Eligibility criteria • Protocol Deviations • Serious adverse events
All subject	• All randomised subjects who receive at least one dose of the study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Pharmacodynamics • Safety • Efficacy
Pharmacokinetic	• Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.	• PK

1.1. 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.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations 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.

2. PRIMARY STATISTICAL ANALYSES

2.1. Pharmacodynamic / Biomarker Analyses

2.1.1. Overview of Planned Pharmacodynamic / Biomarker Analyses

The pharmacodynamic analyses will be based on the "All Subjects" population, unless otherwise specified.

2.1.2. Planned Pharmacodynamic / Biomarker Statistical Analyses

Planned Statistical Analyses
Endpoint(s)
• Alterations in the previously identified immune cell mechanisms specifically related to Neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Model Specification
• The analyses proposed in this section may be adapted before database freeze, in the light of emerging findings from other studies. • The analysis will be conducted by Target Sciences statistics, GSK. • The mRNA data gives results from 54000 genes captured through >54000 probe sets. The subset of these 54000 genes which comprise the primary endpoint data will be specified in advance of DBF. • For each probe set, repeated measures modelling (using measurements taken at Screening, Day 12, Day 28 and Day 84) will be used to estimate differences in mRNA intensities between treatment groups. • Back transformed screening-adjusted means along with 95% CIs will be calculated for each treatment group and timepoint. Additionally, screening-adjusted fold changes between GSK2269557 1000 mcg and placebo will be calculated for Day 12, Day 28, and Day 84 along with 95% CI and p-values. • A spreadsheet containing the output from each model for all probe sets in scope for the primary analysis will be generated and ranked by p-value for the comparison GSK2269557 1000 mcg vs. Placebo at Day 84. A separate tab in the spreadsheet will only include probe sets where the p-value for the comparison GSK2269557 1000mcg vs. placebo, is <0.05 (this cut-off criteria may be relaxed slightly if few probe sets are selected). Such probe sets will be ranked by fold change, with the expectation that, in general, a greater than a 1.5 fold change is scientifically meaningful. • Following review by the study team of the results, a subset of probe sets will be identified and included in an Excel file for further reporting.
Model Checking
• Details of Model Checking and Diagnostics for Statistical Analyses will be provided in the full RAP.

3. SECONDARY STATISTICAL ANALYSES

3.1. Pharmacodynamic / Biomarker Analyses

3.1.1. Overview of Planned Pharmacodynamic / Biomarker Analyses

The pharmacodynamic analyses will be based on the "All Subjects" population, unless otherwise specified.

3.1.2. Planned Pharmacodynamic / Biomarker Statistical Analyses

Planned Statistical Analyses

Endpoint(s)

- Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.

The analyses proposed in this section may be adapted before database freeze, in the light of emerging findings from other studies.

Imaging:
The HRCT scans will be conducted at Screening, Day 12 and Day 28 (longitudinal in nature). However due to positioning of subjects whilst taking a scan, it can be that some airways are visible in some scans and not in other scans. For these reasons some HRCT imaging endpoints will be calculated to include only airways that are visible in both scans. For example the schematic below shows visible airways on Screening alone and Day 12 alone. It then shows the airways that are visible on both Screening & Day 12 scans, through removing/trimming airways that are not present in both scans.

Screening:

Day 12:

Scan Trimming Screening & Day 12:

For such reasons, the table below shows the HRCT endpoints and the results that will be captured

	Longitudinal			Scan Trimming, based on:		
Endpoints	**Screening**	**Day 12**	**Day 28**	**Screening and Day 12 scans**	**Screening and Day 28 scans**	**Day 12 and Day 28 scans**
iVaw	x	x	x	x (Screening) x (day 12)	x (Screening) x (day 28)	x (day12) x (day 28)
siVaw	x	x	x	x (Screening) x (day 12)	x (Screening) x (day 28)	x (day12) x (day 28)
iRaw				x (Screening) x (day 12)	x (Screening) x (day 28)	x (day12) x (day 28)
siRaw				x (Screening) x (day 12)	x (Screening) x (day 28)	x (day12) x (day 28)
iVlobe	X	x	x			
iVlobe Pred	X	x	x			

Planned Statistical Analyses

Trachea length	X	x	x			
Trachea Diameter	X	x	x			

Model Specification

Imaging Endpoints with longitudinal data (iVaw, siVaw, iVlobe, ivlobe Pred)

- The data will be inspected during statistical analysis to determine whether a data transformation is required. It is likely that the data will approximately follow a lognormal distribution (for the iVaw and siVaw) and a log transformation with an offset (for the iRaw and siRaw); however the most appropriate distribution should be used.
- It is thought that the use of bronchodilators could affect the HRCT results. The database will contain information on whether or not relief medication was used in the 4h prior to each scan, and this information may be used in sensitivity analyses of the HRCT results.
- The FRC and TLC will be analysed in separate statistical models.
- The change from baseline (where baseline is screening) will be analysed in a multivariate model to account for the correlation between the multiple Regions (Total, Lower, Upper, Central and Distal), under a Bayesian framework. The model will have a separate intercept for each Region (by fitting a class parameter, and having no overall intercept) and will also include a baseline*Visit*Region and a Treatment*Visit*Region parameter. The Visit will consist of two levels: Day 12 and Day 28, and the Treatment will consist of two levels: GSK2269557 1000 mcg and Placebo. The Region will consist of 5 levels: Total, Lower, Upper, Central and Distal, however note that if one of the Regions is a linear combination of other Regions then only non linear combination Regions should be fitted, however all results (e.g Treatment medians and differences) for that particular Region should be retrospectively calculated though the known linear combination. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior.
- The change from baseline across the different Visits and Regions (accounting for the average baseline associated to the Region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% equi-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios if applicable.
- The difference between the treatment arms, for the change from baseline across the different Visits and Regions will be represented via adjusted posterior medians, as well as their associated 95% equi-tailed credible intervals. These results will be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios if applicable. For parameters that require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arms, and then (ii) using these back transformed values, the ratio of the treatment arms (Active/Placebo) will be calculated for each posterior sample, and finally summarised accordingly.
- The probabilities that the true treatment ratio is greater than 1, in addition to any other values

Planned Statistical Analyses

appropriately selected based on the data, will also be computed for each Visit and Region. These results will be presented in tabular format.

Imaging Endpoints with Scan Trimming (iVaw, siVaw, iRaw, siRaw)

- It is likely that the data will approximately follow a lognormal distribution (for the iVaw and siVaw) and a log transformation with an offset (for the iRaw and siRaw); however the most appropriate distribution should be used.
- The FRC and TLC will be analysed in separate statistical models.
- The responses of interest are the change from baseline based on (i) Airways present on scans taken at Screening and Day 12, (ii) Airways present on scans taken at Screening and Day 28, and (iii) Airways present on scans taken at Screening and Day 28. The baselines for each of these endpoints are provided in the table below.

	(i) Screening & Day12 Scan trimming	(ii) Screening & Day28 Scan trimming	(iii) Day 12 & Day 28 Scan trimming
Screening Result	✓ (baseline)	✓ (baseline)	
Day 12 Result	✓ (postdose)		✓ (baseline)
Day 28 Result		✓ (postdose)	✓ (postdose)

- The modeling below assumes that the Scan trimming endpoints (Screening&Day12, Screening&Day28 and Day12&Day28) will be analysed in a single multivariate model. This is subject to sensitivity analysis.
- The change from baseline (where baseline is defined in the table above) will be analysed in a multivariate model to account for the correlation between the multiple Scan Trimmings (Screening&Day12, Screening&Day28 and Day12&Day28) and Regions (Total, Lower, Upper, Central and Distal), under a Bayesian framework. The model will have a separate intercept for each Region and Scan Trimming combination (by fitting a class parameter Region*ScanTrimming, and having no overall intercept), and will also include a baseline*ScanTrimming*Region and a Treatment*ScanTrimming*Region parameter. The Visit will consist of two levels: Day 12 and Day 28, the scan trimming will consist of three levels Screening&Day12, Screening&Day28 and Day12&Day28, and the Treatment will consist of two levels: GSK2269557 1000 mcg and Placebo. The Region will consist of 5 levels: Total, Lower, Upper, Central and Distal, however note that if one of the Regions is a linear combination of other Regions then only non linear combination Regions should be fitted, however all results (e.g. Treatment medians and differences) for that particular Region should be retrospectively calculated though the known linear combination. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e. covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior.
- The change from baseline across the different Scan Trimmings and Regions (accounting for the average baseline associated to the Region of interest) will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% equi-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios if applicable.

Planned Statistical Analyses

- The difference between the treatment arms, for the change from baseline across the different Scan Trimming and Regions will be represented via adjusted posterior medians, as well as their associated 95% equi-tailed credible intervals. These results will also be presented in tabular form, and will be presented after the data have been appropriately back transformed to give median ratios if applicable. For parameters that require a log transformation with an offset, for each posterior sample (i) appropriately back transformed values will be calculated for each treatment arm, and then (ii) using these back transformed values, the ratio of the treatment arms (Active/Placebo) will be calculated for each posterior sample, and finally summarised accordingly.
- The probabilities that the true treatment ratio is greater than 1, in addition to other values appropriately selected based on the data, will also be computed for each Visit and Region. These results will be presented in tabular format.

Trachea Length and Diameter

- The data will be inspected during statistical analysis to determine whether a data transformation is required.
- The FRC and TLC will be analysed in separate statistical models.
- The data will be analysed in a multivariate model to account for the correlation between the multiple endpoints ((i)Trachea length and (ii) Trachea Diameter), under a Bayesian framework. The model will have separate intercepts for each endpoint (by fitting a class variable "Endpoint", and having no overall intercept), and will also include a baseline*Visit*Endpoint and a Treatment*Visit*Endpoint parameter. The Visit will consist of two levels: Day 12 and Day 28, the Treatment will consist of two levels: GSK2269557 1000 mcg and Placebo, whilst the Endpoint will consist of two levels: Trachea Length and Diameter. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior.
- The predicted values across the different Endpoints and Visits will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% equi-tailed credible intervals. These results will also be presented in a tabular format.
- The difference between the treatment arms across the different Endpoints and Visits will be represented via adjusted posterior medians, as well as their associated 95% equi-tailed credible intervals. These results will also be presented in a tabular format.
- Through the use of a Bayesian framework, for each posterior sample the following will be calculated:
    - The predicted Trachea Length (for each Visit and Treatment for an average baseline)
    - The predicted Trachea Diameter (for each Visit and Treatment for an average baseline)
- The predicted Trachea length (1.) for each Visit and Treatment will be divided by the predicted Diameter (2.). This will be summarised and represented through calculating a posterior median, with 95% equi-tailed credible intervals. These results will also be presented in a tabular format.
- The difference between Treatment Arms (at each Visit) for the predicted Trachea / Diameter Ratio will be calculated using the posterior samples (generated in the bullet point above). This

Planned Statistical Analyses
will be summarised and represented through calculating a posterior median, with 95% equi-tailed credible intervals. These results will also be presented in a tabular format.
Model Checking
• Details of Model Checking and Diagnostics for Statistical Analyses will be provided in the full RAP.

3.2. Safety Analyses

3.2.1. Overview of Planned Analyses

The safety analyses will be based on the "All Subjects" population, unless otherwise specified. Details of the analyses of safety data will be included in the full RAP.

3.3. Pharmacokinetic Analyses

3.3.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the "Pharmacokinetic" population, unless otherwise specified. Details of the analyses of PK data will be included in the full RAP.

3.4. Efficacy Analyses

3.4.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the "All Subjects" population, unless otherwise specified.

3.4.2. Planned Efficacy Statistical Analyses

Planned Statistical Analyses
Endpoint(s)
• $FEV_{1\ and}$ FVC at clinic prior to sputum induction • Daily PEF • Daily reliever usage
Model Specification
FEV_1 (L) and FVC (L) at clinic prior to sputum induction • The data will be inspected prior to analysis to determine whether a data transformation is required. • The analysis will include all available values. If there are values which were recorded within 4h after the subject had taken relief medication, a sensitivity analysis may be done which excludes these values. • The endpoints (FEV_1,and FVC) will be analysed in separate statistical models. The change from baseline in the endpoint will be analysed in a Bayesian repeated measures model, with a baseline by Visit covariate and Treatment by Visit class parameter. The Treatment will have

Planned Statistical Analyses
two levels: GSK2269557 1000 mcg and Placebo, and the Visit will have two levels: Day 12 and Day 28. No fixed assumption around the structure of the covariance matrix will be enforced. The priors for the mean vector for each of the parameters (i.e covariates) will each follow a normal distribution and the prior for the variance-covariance will follow an inverse Wishart distribution. Sensitivity analysis will be conducted to select appropriate parameters for both distributions such that the priors are non-informative with respect to the posterior. • The change from baseline at each of the Visits will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% equi-tailed credible intervals. These results will also be presented in a tabular format. • The difference between the treatment arms, for the change from baseline will be represented via adjusted posterior medians for each of the Treatment Arms, as well as their associated 95% equi-tailed credible intervals. These results will also be presented in a tabular format. • The probabilities that the treatment difference is greater than 0 (or 1, if a lognormal distribution is used) will also be computed at each Visit, in addition to any other values appropriately selected based on the data. These results will be presented in tabular format. **Daily PEF** • Mean and 95% CIs of AM PEF readings will be plotted by study treatment vs. Study Day **Reliever usage** • A reliever medication-free day is defined for statistical analysis as a 24-hour period in which the number of relief medication inhalations is zero. • The number of occasions per day on which reliever medication was used will be averaged per day and plotted in the same way as the PEF daily endpoint above. If the data are non-normally distributed then the median and upper and lower quartiles will be plotted instead of the mean and 95% CIs. The percentage of reliever medication free days will be calculated over the treatment period and summarised by study treatment.
Model Checking & Diagnostics
• Details of Model Checking and Diagnostics for Statistical Analyses will be provided in the full RAP.

4. OTHER STATISTICAL ANALYSES

4.1. Exploratory Pharmacodynamic / Biomarker Analyses

4.1.1. Overview of Planned Exploratory Pharmacodynamic / Biomarker Analyses

The exploratory pharmacodynamic/biomarker analyses will be based on the "All Subjects" population, unless otherwise specified.

4.1.2. Planned Exploratory Pharmacodynamic / Biomarker Statistical Analyses

Planned Statistical Analyses

Endpoint(s)

- Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment.
- Induced sputum endpoints may include, but are not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.
- Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.
- Correlations of sputum biomarker data with CT parameters.

The table below shows the exploratory HRCT endpoints and the results that will be captured:

	Longitudinal			Scan Trimming, based on:		
Endpoints	**Screening**	**Day 12**	**Day 28**	**Screening and Day 12 scans**	**Screening and Day 28 scans**	**Day 12 and Day 28 scans**
IALD	X	x	x			
LAS	X	x	x			
AT	X	x	x			
BVD	X	x	x			
iVaww				x (Screening) x (day 12)	x (Screening) x (day 28)	x (day12) x (day 28)
siVaww				x (Screening) x (day 12)	x (Screening) x (day 28)	x (day12) x (day 28)

Model Specification

- Analyses for mRNA (from induced sputum and blood) and further CT endpoints will follow the methods outlined for the corresponding primary and secondary endpoints respectively, or as appropriate to the type of endpoint. Details will be covered in the full RAP. As noted in the above sections, the analyses proposed for these endpoints may be adapted before database freeze, in the light of emerging findings from other studies.The analysis of induced sputum parameters will be described in the full RAP.
- An outline plan for correlations of sputum biomarker data with CT parameters will be included in the full RAP.
- As these analyses are exploratory in nature, additional non-RAP-specified analyses may be performed.