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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for 204745: An open-label, single arm study to investigate the safety, pharmacokinetics and pharmacodynamics of repeat doses of inhaled GSK2269557 in patients with APDS/PASLI
Compound Number	:	GSK2269557
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204745.
- This RAP is intended to describe the final analyses required for the study.
- This version of the RAP includes amendments to the originally approved Critical Components of the RAP.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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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:		
2015N238311_00	23-OCT-2015	Original
2015N238311_01	25-FEB-2016	Amendment No. 1 [Update to include modification requested by MHRA to extend the duration of contraception after end of study}
2015N238311_02	02-NOV_2016	Amendment No. 2 [To change IMP device from Diskus to Ellipta]
2015N238311_03	15-JUN-2017	Amendment No. 3 [New formulation GSK2269557 will be administered via the ELLIPTA™ dry powder inhaler (DPI) formulated in a blend containing 0.4% MgSt (magnesium stearate). The previous formulation contained 0.6% MgSt.]

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were 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**
The exploratory endpoints specified in Protocol amendment 3 were: Endpoints may include, but are not limited to: In blood and sputum, analysis of: • Cellular PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Immune cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Exploratory messenger ribonucleic acid (mRNA) biomarkers In BAL cell pellet/lavage supernatant when available, analysis of: • Lymphocyte cell subsets	The exploratory endpoints specified in this RAP are: Endpoints may include, but are not limited to: In blood and sputum, analysis of: • Cellular PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Immune cell subsets (In Sputum only) • Lymphocyte cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Antibody levels In BAL cell pellet/lavage supernatant when available, analysis of: • Lymphocyte cell subsets	Exploratory mRNA biomarkers (in blood, sputum, BAL cell pellet/lavage supernatant); proteomic markers (in lavage supernatant) and bacterial DNA fragments (in blood) analysis were not conducted. As a result, they have been removed from the RAP.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Exploratory phospho-protein biomarkers (e.g. pAKT) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Exploratory mRNA biomarkers • Proteomic markers (lavage supernatant only) • Antibody levels In blood, analysis of: • Bacterial DNA fragments	• Exploratory phospho-protein biomarkers (e.g. pAKT) • Immune cell subsets • Soluble proinflammatory mediators (IL-8, IL-6, TNFα & MMP9)	

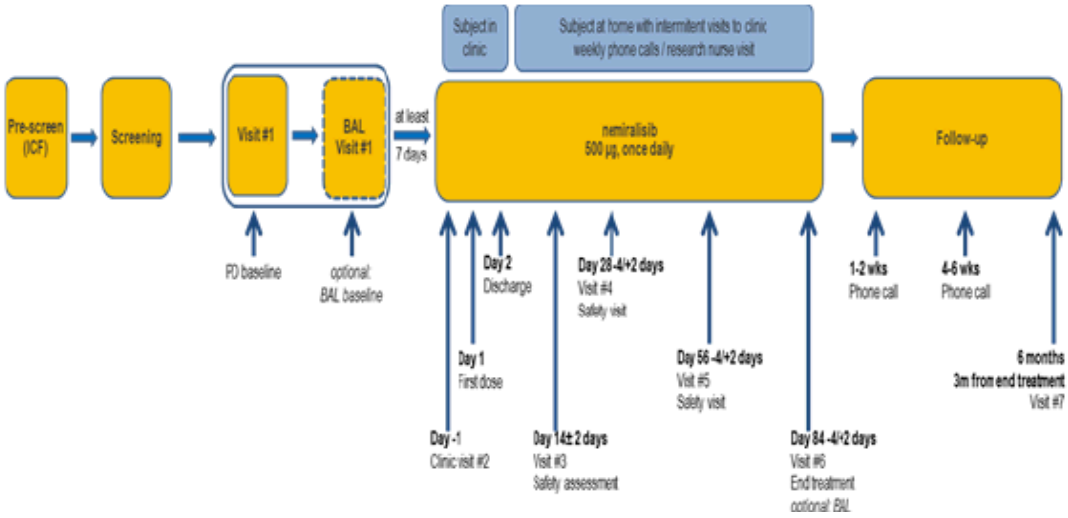
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
Safety • To assess the safety and tolerability of 84 days repeat dosing of inhaled nemiralisib in patients with APDS	• Adverse Events (AE) • Vital signs • 12-lead electrocardiogram (ECG) • Clinical laboratory parameters • Spirometry (forced expiratory volume in 1 second (FEV1)1 hr post-dose)
Secondary Objectives	**Secondary Endpoints**
Pharmacokinetics • To define the plasma pharmacokinetics (PK) of inhaled nemiralisib following repeat dosing in patients with APDS.	• Nemiralisib trough plasma concentration following single and repeated treatment.
Exploratory Objectives	**Exploratory Endpoints**
Pharmacodynamics: • To understand lung disease biology in patients with APDS and to explore the pharmacodynamic effects of inhaled nemiralisib.	Endpoints may include, but are not limited to: **In blood and sputum, analysis of:** • Cellular PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) • Soluble proinflammatory mediators (IL-8, IL-6, TNFα & MMP9) • Immune cell subsets (In Sputum Only) • Lymphocyte cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Antibody Levels **In BAL cell pellet/lavage supernatant when available, analysis of:** • Lymphocyte cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Immune cell subsets

Objectives	Endpoints
	• Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9)
Pharmacokinetics: • To define the lung trough concentration of nemiralisib after repeat dosing	• Trough nemiralisib concentration in lung epithelial lining fluid (ELF) and Bronchoalveolar lavage (BAL) cell pellet at Day 84 visit.
Efficacy: • To assess the efficacy of inhaled • nemiralisib administered once daily for 84 days in patients with APDS.	• The number and rate of pulmonary and/or ear and sinus infections requiring anti-microbial treatment compared to subject's historical baseline. • Change from baseline (Day 1) in trough FEV1 at Day 14 and Day 83 (prebronchodilator)

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is a single-center, open-label, uncontrolled, single group, study designed to provide initial information on the mechanism of disease including airway biology in rare APDS patient population, and to identify any initial safety and tolerability issues following 12-weeks dosing with 500 µg nemiralisib. • Eligible subjects will be enrolled in the study and receive nemiralisib 500 µg once daily for 83 days (-4/+2 days). • Nemiralisib will be administered via the ELLIPTA™ Dry Powder Inhaler (DPI). In an optional sub-study, subjects will undergo bronchoalveolar lavage (BAL) to investigate lymphocyte biology in the lungs after dosing with nemiralisib for 84 days (-4/+2 days).
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• This is an open-label single group study; all subjects will receive Nemiralisib once daily for up to 83 days (-4/+2 days). • Note: due to the protocol amendments subjects may have been assigned to Nemiralisib 1000 µg via the Diskus device, Nemiralisib 700 µg via the Ellipta device or Nemiralisib 500 µg via the Ellipta device depending on the protocol amendment they were enrolled on. These treatments are intended to be comparable.
Interim Analysis	• No interim analysis will be performed in this study. However, safety and pharmacodynamic data will be reviewed on an ongoing basis for internal decision-making purposes, to ensure subject safety and in order to maximize the ability to measure multiple PD markers, based on sample availability

2.4. Statistical Hypotheses / Statistical Analyses

No formal statistical hypotheses will be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

Formal interim analyses will not be performed. However, safety, pharmacokinetic and pharmacodynamic data will be reviewed on an ongoing basis for internal decision-making purposes, to ensure subject safety and to maximise the ability to measure multiple PD markers based on sample availability.

3.2. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility • This population will be based on the treatment the subject received. ○ If participants receive no treatment, then they will be summarised according to "No Treatment"	• Study Population
All Subjects	• All subjects who receive at least one dose of the study treatment. • This population will be based on the treatment the subject received.	• Study Population • Safety • Efficacy • PD/Biomarker
Pharmacokinetic (PK)	• All participants in the 'All Subjects' population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • This population will be based on the treatment the subject received. Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded.	• PK

Refer to Appendix 10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan Version2.0 [19/Feb/2019].

- Data will be reviewed prior to 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 listing of all inclusion/exclusion criteria deviations will be provided. This 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
A	GSK2269557 1000 mcg	NEMI 1000mcg Diskus	1
B	GSK2269557 700 mcg	NEMI 700mcg Ellipta	2
C	Nemiralisib 500 mcg	NEMI 500mcg Ellipta	3
This will be derived as subjects in RandALL codes A/B/C		All NEMI	4
This will be derived as subjects who did not receive any treatment		No Treatment	5

Note:

- Due to the protocol amendments subjects may have been assigned to Nemiralisib 1000 µg via the Diskus device, Nemiralisib 700 µg via the Ellipta device or Nemiralisib 500 µg via the Ellipta device depending on the protocol amendment they were enrolled on. These treatments were intended to be comparable hence the "All NEMI" Treatment group will be created.
- Pharmacodynamic and Biomarker, Efficacy and study population (except exposure summary) domain summaries will be presented for "All NEMI" Treatment group only.
- "NEMI 1000mcg Diskus" / "NEMI 700mcg Ellipta"/ "NEMI 500mcg Ellipta" treatment groups will be presented in PK domain and all listings.
- "NEMI 1000mcg Diskus" / "NEMI 700mcg Ellipta"/ "NEMI 500mcg Ellipta" and "All NEMI" treatment groups will be presented in Safety Domain summaries and Exposure Summary Tables.

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	Clinic Visit 1	Day -1	Day 1 (Pre-Dose)	
Efficacy					
FEV1[1]	X			X	Day 1 (Pre dose)
Ear, sinus and pulmonary infection history	X				Screening
Safety					
Vital signs	X	X	X	X	Day 1 (Pre dose)
12-lead ECG	X	X	X	X	Day 1 (Pre dose)
Spirometry	X			X	Day 1(Pre dose)
Laboratory assessments	X	X	X		Day -1
Pharmacodynamic and Biomarkers					
PD blood sample[2]		X	X		Day -1
BAL sub-study only: Bronchoscopy/BAL		X			Clinic Visit 1 (At least 7 days prior to dosing)
BAL sub-study only: Additional haematology Assessments[3]		X			Clinic Visit 1 (At least 7 days prior to dosing)

1 – prebronchodilator

2 - PD blood sample to include, but not limited to Lymphocyte assessments, PIP2/PIP3 assessments, soluble proinflammatory mediators

3 - For clotting status (Activated partial thromboplastin time (aPTT), Prothrombin time (PT))

5.3. 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
12.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
12.4	Appendix 4: Data Display Standards & Handling Conventions
12.5	Appendix 5: Derived and Transformed Data
12.6	Appendix 6: Reporting Standards for Missing Data
12.7	Appendix 7: 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. SAFETY ANALYSES

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

7.1. 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.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology 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.

7.3. 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.

8. PHARMACOKINETIC ANALYSES

8.1. Secondary Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

- Nemiralisib plasma concentration

8.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 12.4.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters

No pharmacokinetic parameters will be calculated. concentration measured 24 hours post-dose/pre-dose are assumed to be trough concentrations.

8.1.2. Summary Measure

The geometric mean of Nemiralisib plasma concentration following single (Day 1: Pre-dose, 5 min, 3 h and 24 h post-dose) and repeated treatment (Day 14 Pre-dose, Day 83 Pre-dose and Early withdrawal) will be summarised for the treatment groups: “NEMI 1000mcg Diskus”, “NEMI 700mcg Ellipta” and “NEMI 500mcg Ellipta”. Flag will be derived to see whether values range fall within the 2-fold range to check data decision framework as detailed in Section 12.8

8.1.3. Population of Interest

The plasma pharmacokinetic summaries will be based on the “Pharmacokinetic” population.

8.1.4. Strategy for Intercurrent Events

Intercurrent events have been considered e.g. discontinuation of treatment and treatment switching. Due to the exploratory nature of this study and small sample size we accept these intercurrent events may have an impact on the endpoints which we are unable to quantify. Therefore, a treatment policy approach will be adopted hence the actual values of the endpoint, regardless of whether the intercurrent event has occurred, will be analysed.

8.1.5. 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 and listed.

8.2. Exploratory Pharmacokinetic Analyses

8.2.1. Endpoint / Variables

Nemiralisib concentration in lung epithelial lining fluid (ELF) and Bronchoalveolar lavage (BAL) cell pellet at Day 84 visit.

8.2.1.1. Drug Concentration Measures

Lung epithelial lining fluid (ELF) and BAL cell pellet analysis for nemiralisib will be performed under the management of PTS-DMPK, GlaxoSmithKline. Concentrations of nemiralisib will be determined using the currently approved bioanalytical methodology.

8.2.1.2. Derived Pharmacokinetic Parameters

No lung pharmacokinetic parameters will be calculated; concentration measured 24 hours post-dose/pre-dose are assumed to be trough concentrations.

8.2.2. Summary Measure

The geometric mean of Nemiralisib concentration in the lung epithelial lining fluid (ELF) and Bronchoalveolar lavage (BAL) cell pellet at Day 84 visit will be summarised for the treatment groups: “NEMI 1000mcg Diskus”, “NEMI 700mcg Ellipta” and “NEMI 500mcg Ellipta”.

- BAL fluid and plasma urea data, along with the derived Dilution Factor (see Section 12.5.4 for derivation) for each wash, will be listed. See Section 12.6.2 for the handling of BLQ values when calculating the Dilution Factor
- BAL fluid concentrations of GSK2269557 and derived ELF concentrations of GSK2269557 (corrected for by Dilution Factor) for each wash will be listed. In addition, volumes of ELF and the amount of GSK2269557 in the BAL fluid sample will be included in the listing, in order to derive the pooled ELF concentration of GSK2269557 (across all the washes). All applicable derivations are detailed in Section 12.5.4

8.2.3. Population of Interest

The lung pharmacokinetic summaries will be based on the “Pharmacokinetic” population.

8.2.4. Strategy for Intercurrent Events

Intercurrent events have been considered e.g. discontinuation of treatment, treatment switching and death. Due to the exploratory nature of this study and small sample size we accept these intercurrent events may have an impact on the endpoints which we are unable to quantify. Therefore, a treatment policy approach will be adopted hence the actual values of the endpoint regardless of whether the intercurrent event has occurred will be analysed.

8.2.5. 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 and listed.

9. PHARMACODYNAMIC AND BIOMARKER ANALYSES

9.1. Exploratory Pharmacodynamic and Biomarker Analyses

9.1.1. Endpoint / Variables

Endpoints may include, but are not limited to:

In blood and sputum, analysis of:
- Cellular PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area)
- Soluble proinflammatory mediators (IL-8, IL-6, TNFα & MMP9)
- Immune cell subsets (In Sputum Only)
- Lymphocyte cell subsets
- Exploratory phospho-protein biomarkers (e.g. pAKT)
- Antibody Levels

In BAL cell pellet/lavage supernatant when available, analysis of:
- Lymphocyte cell subsets
- Exploratory phospho-protein biomarkers (e.g. pAKT)
- Immune cell subsets
- Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9)

9.1.2. Summary Measure

Absolute and Change from Baseline/Ratio to Baseline will summarised using descriptive statistics for each timepoint as defined in Section 9.1.1

9.1.3. Population of Interest

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

9.1.4. Strategy for Intercurrent Events

Several intercurrent events have been considered e.g. infections, use of rescue medication, discontinuation of treatment, treatment switching and death. Due to the exploratory nature of this study and small sample size we accept these intercurrent events may have an impact on the endpoints which we are unable to quantify. Therefore, a treatment policy approach will be adopted hence the actual values of the endpoint regardless of whether the intercurrent event has occurred will be analysed.

9.1.5. 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 10.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9.1.5.1. Statistical Methodology Specification

Endpoint / Variables
Loge-transformed PIP3 Area Proportion
Model Specification

• will be analyzed using mixed models repeated measures (MMRM) models for Blood Sample Type.
• Terms fitted in the model will include:
  o Fixed Effect: Processing Type, Visit
  o Random Effect: Subject
  o Repeated: Visit
Note: Per the analysis population all subjects will be within the "All NEMI" treatment group and as such treatment arm need not be included as a fixed effect in the model
• 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, the estimates will not be reported.
• Point estimates for the adjusted means on the loge scale, the mean ratio between processing Type and associated 95% confidence interval will be constructed using the residual variance for the following combination of interest:
  o Unstimulated+DMSO / Stimulated+DMSO
  o Unstimulated+DMSO / Unstimulated+NEMI
  o Stimulated+DMSO / Stimulated+NEMI

Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation

• The point estimate and confidence interval obtained from MMRM analysis will be exponentially back-transformed to obtain Adjusted (least square) geometric means for each processing type
• The adjusted mean ratio and associated 95% confidence interval for the following processing type combinations:
  o Unstimulated+DMSO / Stimulated+DMSO
  o Unstimulated+DMSO / Unstimulated+NEMI
  o Stimulated+DMSO / Stimulated+NEMI

10. EFFICACY ANALYSES

10.1. Exploratory Efficacy Analyses

10.1.1. Endpoint / Variables

- Pulmonary and/or ear and sinus infections requiring anti-microbial treatment, refer to Section 12.5.6. for how these will be programmatically identified.
- FEV1

10.1.2. Summary Measure

The number and rate (per 84 days) of pulmonary and/or ear and sinus infections requiring anti- microbial treatment will be calculated for each subject.

Mean change from baseline FEV1 at Day 14:pre-dose, Day 83:pre-dose, early withdrawal and 3 month follow up will be summarised for the "All NEMI" treatment group.

10.1.3. Strategy for Intercurrent Events

Several intercurrent events have been considered e.g. infections, use of rescue medication, discontinuation of treatment, treatment switching and death. Due to the exploratory nature of this study and small sample size we accept these intercurrent events may have an impact on the endpoints which we are unable to quantify. Therefore, a treatment policy approach will be adopted hence the actual values of the endpoint regardless of whether the intercurrent event has occurred will be analysed.

10.1.4. 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 10.1.1 will be listed.

11. REFERENCES

GlaxoSmithKline Document Number 2012N141231_10. Nemiralisib (GSK2269557) Investigator's Brochure: 03-AUG-2018

GlaxoSmithKline Document Number 2015N238311_03. An open-label, single arm study to investigate the safety, pharmacokinetics and pharmacodynamics of repeat doses of inhaled nemiralisib in patients with APDS/PASLI 30-MAY-2017

12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management

Instream and final analysis population reviews as per SOP 130050 will be conducted. Please Refer to Section 4.1 for handling and Reporting of Protocol Deviations.

12.2. Appendix 2: Schedule of Activities

Time and Events Table for Screening and Run-in Period

Procedure	Pre-Screening	Screening (up to 42 days prior to dosing)	Clinic visit #1 At least 7 days prior to dosing	Notes
Informed consent	X			Pre-screening and screening may occur on the same visit, if appropriate
Concomitant medication review	X			
Review of exacerbation history	X			
Demography	X	X		
SAE review	X	X	X	
Inclusion and exclusion criteria		X		
Full physical exam, including height and weight		X		
Brief physical examination			X	
Medical history (includes substance usage and Family history of premature CV disease)		X		Substances: Drugs, Alcohol, tobacco
Past and current medical conditions (including ear, sinus and pulmonary infection history, cardiovascular medical history and therapy history)		X		
Vital signs (Blood pressure (BP), heart rate (HR), temperature and respiratory rate)		X	X	Triplicate measurements of BP and HR
12-lead ECG		X	X	Triplicate

Procedure	Pre-Screening	Screening (up to 42 days prior to dosing)	Clinic visit #1 At least 7 days prior to dosing	Notes
Spirometry (incl. reversibility)		X		
Laboratory assessments (include hematology, biochemistry, Urinalysis)		X	X	
HIV, Hep B and Hep C screen		X		
Blood pregnancy test (only WCBP)		X		
PD blood sample: Lymphocyte assessments (subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, immunoglobulins.)			X	
PD blood sample: PIP_2/PIP_3 assessments			X	
PD blood sample: mRNA biomarkers			X	
PD blood sample: bacterial DNA fragment analysis			X	
Sputum induction			X	Should sputum induction fail or be insufficient, the subject will be allowed to return within 48 hours for a further attempt to obtain an adequate sample
BAL sub-study only: Bronchoscopy/BAL			*X*	*Performed on a different day to the sputum induction. For measurement of PD*
BAL sub-study only: Additional haematology assessments			*X*	*For clotting status (Activated partial thromboplastin time (aPTT), Prothrombin time (PT))*

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Time and Events Table for Treatment Period and Follow-up

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early with-drawal (within 2 wks)	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days	-4 / +2 days			±2 weeks	
In-Patient	X	X	X										
Out-Patient				X		X	X	X	X	X		X	
Telephone Contact/ Research nurse visit					X weekly						X		Except weeks where subjects have a clinic visit
SAFETY ASSESSMENTS													
Brief physical exam	X			X		X	X	X		X		X	Pre-dose
AE/SAE review	←==========→										X	X	
Concomitant medication review	←==========→										X	X	
Vital signs	X	X		X		X	X	X	X	X		X	Pre-dose. Single assessment
12-lead ECG	X	X		X		X	X	X		X		X	Pre-dose. Single assessment
Urine pregnancy test	X			X			X	X		X			only WCBP
Laboratory assessments (include haematology, biochemistry, Urinalysis)	X			X		X	X	X		X		X	Pre-dose
STUDY TREATMENT													
ELLIPTA inhaler training	X												Review of the Patient Information Leaflet with the subject (no device will be used). Additional training may be conducted at the discretion of the investigator
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

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Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early with-drawal (within 2 wks)	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days	-4 / +2 days			±2 weeks	
In-Patient	X	X	X										
Out-Patient				X		X	X	X	X	X		X	
Telephone Contact/ Research nurse visit					X weekly						X		Except weeks where subjects have a clinic visit
													be dosed at the clinic).
Assessment of study treatment compliance				X		X	X	X		X			
EFFICACY ASSESSMENTS													
Exit interview								X		X			Exit interview may be held at the study clinic or the subject's home, within 7 days of last dose.
OTHER ASSESSMENTS													
Review of APDS exacerbation and respiratory tract infection history				X		X	X	X		X	X	X	Including ear, sinus and pulmonary infections.
FEV1 Pre-Dose		X		X				X		X		X	For efficacy
FEV1 1hr Post-Dose		X	X	X									For safety
Blood sample for PK		X		X				X		X			Day 1: Pre-dose, 5 min, 3 h and 24 h post-dose. Pre-dose at all other visits.
PD blood sample: Lymphocyte assessments	X			X				X		X		X	Pre-dose. Subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, immunoglobulins.
PD blood sample: PIP_2/PIP_3 assessments	X			X				X		X		X	Pre-dose.

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Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal (within 2 wks)	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days	-4 / +2 days			±2 weeks	
In-Patient	X	X	X										
Out-Patient				X		X	X	X	X	X		X	
Telephone Contact/ Research nurse visit					X weekly						X		Except weeks where subjects have a clinic visit
PD blood sample: mRNA biomarkers	X			X				X		X		X	Pre-dose.
PD blood sample: bacterial DNA fragment analysis	X			X				X		X		X	Pre-dose.
Sputum induction	X			X				X				X	Pre-dose. Should sputum induction fail or be insufficient, the subject will be allowed to return within 48 hours for a further attempt to obtain an adequate sample
BAL sub-study only: Additional haematology assessments								X					*For clotting status (Activated partial thromboplastin time (aPTT), Prothrombin time (PT))*
BAL sub-study only: Bronchoscopy/BAL									X				For measurement of PK and PD
BAL sub-study only: Blood sample for urea PK									X				
BAL sub-study only: Blood sample for plasma PK									X				
Genetic Sample	X												Optional assessment – the subject must provide additional consent for the genetic sample. Genetic sample can be taken at any time after randomisation.

‡ Day 84 visit will only occur if a subject has agreed to take part in the BAL sub-study, dosing will continue until the D84 visit.

12.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

12.3.1. Study Phases

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

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

NOTES:

- Time of study treatment dosing and start/stop time of assessments and events should be considered, if collected.

12.3.1.1. 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 6: 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.

12.3.2. 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

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.

12.3.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date

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.

12.4. Appendix 4: Data Display Standards & Handling Conventions

12.4.1. 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/mid204745
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	

12.4.2. 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 and/or figures • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

12.4.3. 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

12.5. Appendix 5: Derived and Transformed Data

12.5.1. General

Multiple Measurements at One Analysis Time Point
Where multiple measurements are recorded for a particular time point, all available data will be listed. The mean of the measurements will be calculated and used in the derivation of summary statistics; except in the following cases: • FEV1 data: in the calculation of summary statistics, the maximum of triplicate readings will be used. • Biomarker data: in the calculation of summary statistics/for statistical analyses, assuming the data appears log normally distributed, the geometric mean of the two replicates will be used. If there are two values within a protocol scheduled visit 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

12.5.2. Study Population

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]
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 assigned a treatment 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 Container Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

12.5.3. Safety

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, 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 Place = '> x' becomes x + 0.1
  - Example 3: 0 Decimal Places = '< x' becomes x – 1

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:

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

12.5.4. Pharmacokinetic

ELF Drug Concentrations

Urea concentration data in plasma and BAL will be used to calculate the dilution effect of the lavage which is used to extract the epithelial lining fluid (ELF) from the lung compartment. A correction for dilution will be applied to all BAL analytes to derive corrected concentrations i.e. each BAL analyte will be adjusted to account for the magnitude of dilution during the BAL procedure using urea plasma concentration as a reference point. A correction for dilution will be applied to all BAL fluid drug concentrations for each wash as follows:

$$ELF\ Concentration\ (pg/ml) = BAL\ Drug\ Concentration\ (pg/ml) * Dilution\ Factor$$

Where

$$Dilution\ Factor = \frac{Urea\ Plasma_{\ pre-bronch}}{Urea\ BAL}$$

Additionally, for each wash, the Volume of ELF in BAL fluid and the Total Drug in BAL fluid will be calculated as follows:

$$Volume\ of\ ELF\ in\ BAL\ Fluid\ (mL) = \frac{BAL\ Fluid\ Volume\ (mL)}{Dilution\ Factor}$$

$$Drug\ in\ BAL\ Fluid\ (pg) = BAL\ Fluid\ Drug\ Concentration\ \left(\frac{pg}{mL}\right) *\ BAL\ Fluid\ Volume\ (mL)$$

Data will then be pooled across all three washes as follows:

$$Total\ Volume\ of\ ELF\ in\ BAL\ Fluid\ (mL) = Volume\ of\ ELF\ in\ BAL_{wash1} + Volume\ of\ ELF\ in\ BAL_{wash2} + Volume\ of\ ELF\ in\ BAL_{wash3}$$

$$Total\ Drug\ in\ BAL\ Fluid\ (pg) = Drug\ in\ BAL_{wash1} + Drug\ in\ BAL_{wash2} + Drug\ in\ BAL_{wash3}$$

$$Pooled\ ELF\ Drug\ Concentration\ \left(\frac{pg}{mL}\right) = \frac{Total\ Drug\ in\ BAL\ Fluid\ (pg)}{TotalVolume\ of\ ELF\ in\ BAL\ Fluid(mL)}$$

BAL Cell Pellet Drug Concentration

Cell pellet samples are diluted in a 1:5 ratio. Concentrations will be corrected for the dilution before the ratio is calculated on an individual subject level between the raw lavage result for wash 2 and the cell pellet concentration:

$$Derived\ cell\ pellet\ concentration = \frac{cell\ pellet\ concentration * 5}{wash\ 2\ lavage\ concentration} * derived\ pooled\ lavage\ ELF\ concentration$$

Only the derived concentrations will be included in the listing.

12.5.5. Pharmacodynamic and Biomarker

Pharmacodynamic

PIP3 Peak Area Proportion for Sputum Sample

- PIP3 is the analyte of primary interest for the phospholipid data in sputum/Whole Blood, and Peak Area data from the mass spectrometer is the endpoint of interest. However, it is acknowledged that there will be some degree of variability between sputum/Whole blood samples due to differences in cell counts, and therefore it is favoured to first normalise PIP3 Peak Area values for each sample (by PIP2 Peak Area and PIP3 Peak Area); prior to analysis.

- More specifically the parameter of interest is: PIP3 Peak Area proportion.
  PIP3 Peak Area proportion is calculated from PIP2 Peak Area and PIP3 Peak Area, as follows:

$$PIP3\ \ Peak\ \ Area\ \ proportion = \frac{PIP3\ Peak\ Area}{PIP2\ Peak\ Area\ + PIP3\ Peak\ Area}$$

- Evaluability was also assessed by the vendor based on sample outputs being above QC instrumentation criteria. Any non-evaluable data (as indicated in the database BIDEVCD=F) will be flagged and excluded from any summaries and analyses.
- PIP3 Peak Area, PIP2 Peak Area and, PIP3 Peak Area proportion, will be summarised by treatment group and study day

PIP3 For Peak Area Proportion for Whole Blood Sample

PBMCs isolated from whole blood and split 4 ways: -

- Unstimulated+DMSO (this is an unstimulated sample with the vehicle DMSO added)
- Unstimulated+NEMI (this is an unstimulated sample incubated with NEMI)
- Stimulated+DMSO (this is a sample stimulated with CD3+CD28 with the vehicle DMSO added)
- Stimulated+NEMI (this is a sample stimulated with CD3+CD28 and incubated with NEMI)

Individual Subject level Ratio for each of the below list group will be calculated for PIP3 Area proportion parameter for each of the timepoint separately

- Unstimulated+DMSO / Stimulated+DMSO
- Unstimulated+DMSO / Unstimulated+NEMI
- Stimulated+DMSO / Stimulated+NEMI

Note: PIP 3 Peak Area Proportion will be calculated separately for each of the above processing types.

Exploratory phospho-protein biomarkers(pAKT, AKT)

Individual Subject level Ratio for each of the below list group will be calculated for each parameter for each of the timepoint separately

- Unstimulated+DMSO / Stimulated+DMSO
- Unstimulated+DMSO / Unstimulated+NEMI
- Stimulated+DMSO / Stimulated+NEMI

12.5.6. Efficacy

Efficacy
Episodes of pulmonary and/or ear and sinus infections requiring anti- microbial treatment
Episodes of pulmonary and/or ear and sinus infections requiring anti- microbial treatment will be programmatically identified as follows: 1. Adverse Event dataset will be reviewed to identify any pulmonary and/or ear and sinus infections • If no AEs of pulmonary and/or ear and sinus infections were recorded, then no pulmonary and/or ear and sinus infections requiring anti- microbial treatment will be reported. • If AEs of pulmonary and/or ear and sinus infections were recorded, then proceed to step 2 2. A list of all concomitant medication (i.e. CONMEDS dataset with duplicated removed) will be sent to the Medical Monitor to identify and flag any anti-microbial treatments • If no anti-microbial treatments were identified, then no pulmonary and/or ear and sinus infections requiring anti- microbial treatment will be reported. • If anti-microbial treatments were identified, then proceed to step 3 3. Compare each pulmonary and/or ear and sinus infections AE with anti-microbial treatments concomitant medication • if antimicrobial treatment was taken within 7 days of the pulmonary and/or ear and sinus infections AE, then record as a pulmonary and/or ear and sinus infections requiring anti-microbial treatment else no pulmonary and/or ear and sinus infections requiring anti- microbial treatment will be reported

12.6. Appendix 6: Reporting Standards for Missing Data

12.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as subject who has completed all phases of the study including the follow-up visit. • Withdrawn subjects were not 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.

12.6.2. 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.
Soluble proinflammatory mediators	• 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 team are already adjusted for this dilution factor 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.
Plasma and BAL Urea Data	BLQ values will be imputed with the relevant (plasma or BAL fluid) LLQ divided by 2 • for the purpose of deriving the Dilution Factor.
Phospholipid Data(PIP2,PIP3)	There is no quantifiable value for the LLQ for the phospholipid data. However, data with a particularly high noise/signal ratio will be deemed non evaluable by the external vendor. A flag for evaluability will be included in the listings and non-evaluable subjects will be excluded from summaries and analyses.

12.6.2.1. Handling of Missing and Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.</td></tr>
<tr><td>Adverse Events</td><td>• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.
• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
○ If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
○ Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
○ Else set start date = January 1.</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
• Completely missing start or end dates will remain missing, with no imputation applied.</td></tr>
<tr><td>Concomitant Medications</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
○ If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
○ Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
• Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
The recorded partial date will be displayed in listings.
</td></tr>
</table>

12.7. Appendix 7: Values of Potential Clinical Importance

12.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male	0.33	0.65
		Female	0.33	0.65
Haemoglobin	g/L		115	175
Platelet Count	$x10^9$/ L		100	600
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	55
Calcium	mmol/L		2	2.75
Creatinine	umol/L		40	120
Glucose (Non-fasting)	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	155

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	≥ 1.5X ULN
T. Bilirubin + ALT	µmol/L U/L	High	≥ 1.5X ULN T. Bilirubin + ≥ 2X ULN ALT

12.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec		≥ 500
Absolute PR Interval	msec	< 100	>240
Absolute QRS Interval	msec	< 80	> 120
HR (Ventricular rate)	bpm	< 35	>100
Change from Baseline			
Increase from Baseline QTc	msec		≥ 60

12.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<80	>160
Diastolic Blood Pressure	mmHg	≤ 40	≥ 100
Heart Rate	bpm	≤ 40	≥ 100
Temperature	ºC	≤35.5	≥ 37.5
Respiration rate	breaths/min	≤ 8	≥ 20

12.8. Appendix 8: Data Output Framework

To ensure transparent reporting of this study we have considered a decision framework in line with the study objectives outlined in Section 2.2.

- Original aim (primary endpoint) was to understand safety of PI3Kd inhibition in these patients. It was unknown at the time what would happen when turning the kinase off in an activated mutation state. Safety has been reviewed in stream, with no limiting effects observed.
- Secondary endpoint was PK. It is key to show similar (<2-fold) difference in PK vs COPD to be convinced of lung exposure.
- Exploratory endpoints are target engagement (PIP3), and downstream pharmacology (inflammatory cytokines)
- Team would want to see >30% reduction in PIP3 and >30% reduction in cytokines to be convinced of drug action in these patients.
- Team have significant experience in measuring PIP3 to show target engagement and have confidence in this readout.
- Team also have significant experience in lung cytokine measurement and feel this is higher risk due to variability. However, the inflammation should be entirely PI3Kd-dependent.

Thus the APDS Study Minimum Thresholds are as follows:

Endpoint	APDS Study Minimum Thresholds
Safety (Primary)	Safety reviewed in stream, with no limiting AEs reported (n=4). No cough to date, but post-inhalation wheeze reported in one subject
PK (Secondary)	Comparable Existing NEMI exposure(C_{tau}) data is listed in below table Day 1: 24h Post-dose — Existing NEMI exposure C_{tao} (pg/mL) value: 166 — <2 Fold difference Interval for Geo. Mean: (83, 332) Day 14: Pre-dose — 687 — (344,1374) Day 83: Pre-dose — 528 — (264,1056) • Flag will be derived to indicate whether Geometric Mean of Plasma Ctrough concentration is at particular timepoint mentioned above is within comparable <2 fold difference range.
Sputum PIP3 (Exploratory: Target Engagement)	>30% reduction PIP3 proportion from baseline
Sputum Cytokines (Exploratory: Downstream Pharmacology)	>30% reduction from baseline IL-8, IL-6, TNFα, MMP9
PIP3 in PBMCs (Exploratory: Confirmation of patient sensitivity to PI3Kδ Inhibition)	PIP3 in PBMCs • >30% inhibition (of unstimulated) • >50% inhibition (stimulated)

12.9. Appendix 9: Abbreviations & Trade Marks

12.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
ELF	Epithelial lining fluid
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

12.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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12.10. Appendix 10: List of Data Displays

12.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.10	
Efficacy	2.1 to 2.2	
Safety	3.1 to 3.12	
Pharmacokinetic	4.1 to 4.4	
Pharmacodynamic and Biomarker	6.1 to 6.11	6.1 to 6.6
Section	**Listings**	
ICH Listings	1 to 29	
Other Listings	30 to 41	

12.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock shells for Data Displays

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic and Biomarker	PD_Fn	PD_Tn	PD_Ln

NOTES:

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

12.10.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

12.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Subjects	ES1	Summary of Participant Disposition for the Participant Conclusion Record	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.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
Protocol Deviation					
1.4.	All Subjects	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Demographic and Baseline Characteristics					
1.5.	All Subjects	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.6.	All Subjects	DM11	Summary of Age Ranges	EudraCT	SAC
1.7.	All Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
Population Analysed					
1.8.	Screened	SP1	Summary of Study Populations	Summarize by each treatment group (i.e. NEMI 1000mcg Diskus, NEMI 700mcg Ellipta, NEMI 500mcg Ellipta) and ALL NEMI, No Treatment group Refer to Table 1.6 in gsk2269557/mid201928/final_01	SAC
Prior and Concomitant Medications					
1.9.	All Subjects	CM1	Summary of Concomitant Medications	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure and Treatment Compliance					
1.10.	All Subjects	EX1	Summary of Exposure to Study Treatment		SAC

12.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
FEV1					
2.1.	All Subjects	PFT1	Summary of Absolute FEV1 (L) Data	Refer PII115119/ Part_A /Table 3.18 Add footnote "Note: Maximum value of the three readings has been used."	SAC
2.2.	All Subjects	PFT3	Summary of Change from Baseline FEV1 (L) Data	Refer PII115119/ Part_A /Table 3.19	SAC

12.10.6. 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	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
3.3.	All Subjects	AE15	Summary of Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Required by Register Disclosure for FDAAA and EudraCT.	SAC
Serious and Other Significant Adverse Events					
3.4.	All Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.5.	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					
3.6.	All Subjects	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC
Laboratory: Hematology					
3.7.	All Subjects	LB1	Summary of Hematology Changes from Baseline	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
3.8.	All Subjects	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.9.	All Subjects	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.10.	All Subjects	EG1	Summary of ECG Findings	IDSL	SAC
3.11.	All Subjects	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
Vital Signs					
3.12.	All Subjects	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC

12.10.7. Pharmacokinetics Table

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma PK					
4.1.	PK	PK01	Summary of Plasma Nemiralisib Pharmacokinetic Concentration-Time Data		SAC
4.2.	PK	PK_T1	Summary of Log-Transformed Plasma Nemiralisib Pharmacokinetic Concentration - Time Data (pg/mL)	Include flag derived for minimum threshold criteria as mentioned in Section 12.8.	SAC
Lung epithelial lining fluid (ELF) and Bronchoalveolar lavage (BAL)					
4.3.	PK	PK_T2	Summary of Urea Dilution Factor Data		SAC
4.4.	PK	PK_T3	Summary of Derived Lung ELF and Cell Pellet Nemiralisib Pharmacokinetic Concentrations and Volume Data		SAC

12.10.8. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PIP2/PIP3					
6.1.	All Subjects	PD_T1	Summary of Phospholipid Data (Absolute) in Sputum		SAC
6.2.	All Subjects	PD_T3	Summary of Phospholipid Data (Change from Baseline) in Sputum	Includes only PIP3 Proportion parameter	SAC
6.3.	All Subjects	PD_T2	Summary of Phospholipid Data (Absolute) in Blood		SAC
6.4.	All Subjects	PD_T4	Summary of Phospholipid Data (Change from Baseline) in Blood	Includes only PIP3 Proportion parameter	SAC
6.5.	All Subjects	PD_T5	Summary of statistical analysis of Loge transformed PIP3 Area Proportion	Refer Table 2.62 in 201928/final_02 RE	SAC
Soluble Proinflammatory Mediators					
6.6.	All Subjects	PD_T6	Summary Statistics (Absolute): Soluble proinflammatory mediators	Includes IL-8, IL-6, TNFa & MMP9	SAC
6.7.	All Subjects	PD_T6	Summary Statistics (Change from Baseline): Soluble proinflammatory mediators	Includes IL-8, IL-6, TNFa & MMP9	SAC
6.8.	All Subjects	PD_T7	Summary Statistics (Log-Transformed Absolute): Soluble proinflammatory mediators	Includes IL-8, IL-6, TNFa & MMP9	SAC
6.9.	All Subjects	PD_T7	Summary Statistics (Log-Transformed Change from Baseline): Soluble proinflammatory mediators	Includes IL-8, IL-6, TNFa & MMP9	SAC
Immune cell and Lymphocyte cell subsets					
6.10.	All Subjects	LB1	Summary of Blood Lymphocyte Cell Subsets (Change from Baseline)	Include Blood Sample type data only	SAC
Phospho-protein biomarkers(pAKT,AKT)					
6.11.	All Subjects	PD_T2	Summary of Phospho-protein Biomarkers (Absolute)	Include Sample type (i.e. Sputum, BAL etc) as Page by Variable Include pAKT ,AKT parameter	SAC

12.10.9. Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PIP2, PIP3					
6.1.	All Subjects	PD_F1	Individual subjects profile plot of Phospholipid Data in Sputum	Different colour legend for each subject . Ignore processing type panel in mock shell for Sputum data. Page by Parameter (PIP2,PIP3,PIP3 proportion)	SAC
6.2.	All Subjects	PD_F2	Geometric Mean and 95% Confidence Interval for Phospholipid Data in Sputum	Different colour legend for each parameter	SAC
6.3.	All Subjects	PD_F1	Individual subjects profile plot of Phospholipid Data in Blood	Page by Parameter (PIP2, PIP3, PIP3 proportion) Different colour legend for each subject Different plot of processing type and (1st page include 4 different processing type and 2nd page is for 3different processing type comparison values)	SAC
6.4.	All Subjects	PD_F2	Geometric Mean and 95% Confidence Interval for Phospholipid Data in Blood by Processing Type	Different colour legend for each processing type 1st page include figure having 4 different line for each processing type estimates and 2nd plot is for 3different processing type comparison values)	SAC
Phospho-protein biomarkers(pAKT,AKT)					
6.5.	All Subjects	PD_F1	Individual subjects profile plot for phospho-protein biomarkers Data in Blood	Different plot of processing type and (1st page include 4 different processing type and 2nd page is for 3 different processing type comparison values)	SAC
6.6.	All Subjects	PD_F2	Geometric Mean and 95% Confidence Interval for phospho-protein Biomarkers in Blood by Processing Type	Different colour legend for each processing type 1st page include figure having 4 different line for each processing type estimates and 2nd plot is for 3different processing type comparison values)	SAC

12.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES6	Listing of Reasons for Screen Failure		SAC
2.	Screened	ES9	Listing of Subjects Who Were Rescreened		SAC
3.	All Subjects	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
4.	All Subjects	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
5.	All Subjects	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
6.	Screened	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.	Screened	SP3	Listing of Participants Excluded from Any Population		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
12.	All Subjects	POP_L1	Listing of Ear, Sinus and Pulmonary Infection History over Previous Two Years		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure and Treatment Compliance					
13.	All Subjects	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
14.	All Subjects	AE8	Listing of All Adverse Events	ICH E3	SAC
15.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
16.	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					
17.	All Subjects	AE8	Listing of Serious Adverse Events	ICH E3 Include a column to flag fatal and non-fatal SAEs	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 / 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
All Laboratory					
23.	All Subjects	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
24.	All Subjects	LB5	Listing of Laboratory Values of Potential Clinical Importance		SAC
25.	All Subjects	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
26.	All Subjects	UR2	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
ECG					
27.	All Subjects	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
28.	All Subjects	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
Vital Signs					
29.	All Subjects	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC

12.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic					
30.	PK	PK07	Listing of Plasma Nemiralisib Concentration-time Data		SAC
31.	PK	PK_L1	Listing of Plasma Urea and BAL Fluid Urea Data		SAC
32.	PK	PK_L2	Listing of BAL Fluid and Derived Lung ELF Nemiralisib Pharmacokinetic Concentration Data		SAC
Pharmacodynamic (PIP2/PIP3)					
33.	All Subjects	PD_L1	Listing of Phospholipid Data in Sputum		SAC
34.	All Subjects	PD_L2	Listing of Phospholipid Data in Blood		SAC
Pharmacodynamic (Soluble proinflammatory mediators)					
35.	All Subjects	PD_L3	Listing of Individual Subject Soluble proinflammatory mediators Data	Refer PII115119/Part A/Listing 34	SAC
Pharmacodynamic (Immune cell and Lymphocyte cell subsets)					
36.	All Subjects	PD_L4	Listing of Immune Cell Count Data		SAC
37.	All Subjects	PD_L4	Listing of Lymphocyte cell subsets		SAC
Pharmacodynamic (pAKT/AKT)					
38.	All Subjects	PD_L6	Listing of Phospho-protein biomarkers		SAC
Pharmacodynamic (Antibody Level)					
39.	All Subjects	PD_L5	Listing of Antibody Level		SAC
Efficacy					
40.	All Subjects	PFT8	Listing of FEV1 (L) Data		SAC
41.	All Subjects	EFF_L1	Listing of Episodes of Pulmonary and/or Ear and Sinus Infections Requiring Anti-Microbial Treatment		SAC

12.11. Appendix 11: Example Mock shells for Data Displays

Data Display Specification will be made available on request