Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	A double-blind (sponsor unblind), randomized, placebo controlled, single and repeat escalating dose study to investigate the safety, tolerability, and pharmacokinetics of CCI15106 inhalation powder in healthy participants and participants with moderate chronic obstructive pulmonary disease (COPD) including evaluation of environmental and healthy by-stander exposure levels during dosing.
Compound Number	:	CCI15106
Effective Date	:	30-Oct-2018

Description:

- The purpose of this RAP is to describe the planned safety, tolerability and pharmacokinetic analyses and outputs to be presented in the Clinical Study Report for the study 205822. This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.
- Bystander and Environmental Exposure Analyses is tabulated and reported in a separate report.

RAP Author(s):

Approver	Date	Approval Method
PPD Clinical Statistics, ID	30-Oct-2018	PharmaTMF

RAP Team Approvals:

Approver	Date	Approval Method
PPD Executive Medical Director, R&D Infectious Diseases	29-Oct-2018	Email Approval
PPD Director, Clinical Pharmacology	30-Oct-2018	Email Approval
PPD Regional Study Manager, NLD CRT PCPS	29-Oct-2018	PharmaTMF
PPD Principal Clinical Data Manager, RD, PCPS	29-Oct-2018	PharmaTMF
PPD Associate Manager (ID, Clinical Programming)	30-Oct-2018	PharmaTMF
PPD Principal Programmer/Analyst, RD PCPS	29-Oct-2018	PharmaTMF

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Statistics Director, RD PCPS	30-Oct-2018	PharmaTMF
PPD Associate Manager (ID, Clinical Programming)	29-Oct-2018	PharmaTMF

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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:		
2016N290366_02	11-OCT-2017	Amendment 2

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Bystander and Environmental Exposure Analyses will be reported in a separate report.

The Lung ELF Concentration population for analysis is renamed to BAL PK in order to keep it consistent with the other Phase I study (202031).

The All Participants Screened, Safety, Systemic Pharmacokinetic Concentration (PK), the BAL PK analysis populations are not defined separately for Part 1 and Part 2 as mentioned in the protocol.

For the data disclosure outputs regarding "Summary of Age Ranges", the Enrolled population is defined in this RAP.

The term "Subjects" is used to refer to the "Participants" in certain sections of this document including the TFLs.

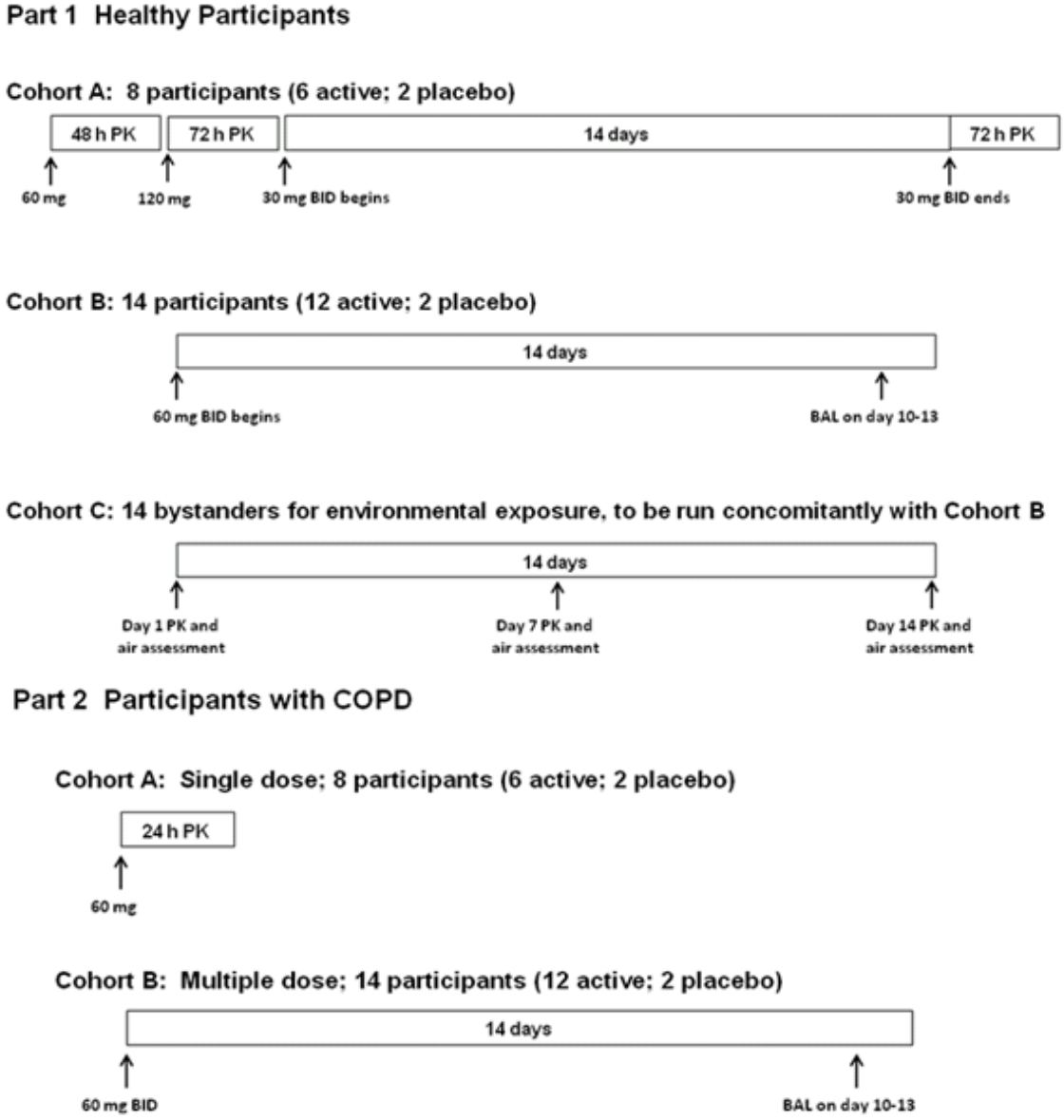
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To investigate the safety and tolerability of CCI15106-IP following single and repeat escalating doses in healthy participants and participants with moderate COPD.	• Adverse events (AEs), clinical laboratory, electrocardiogram (ECG), telemetry, spirometry, and vital signs assessments.
• To determine systemic PK of CCI15106 following single and repeat escalating doses of CCI15106-IP in healthy participants and participants with moderate COPD.	• Derived systemic PK parameters of CCI15106: Single dose: area under the curve (AUC) from time zero to the time of last quantifiable concentration (AUC[0-last]), concentration at maximum (Cmax), time of maximum concentration (tmax), AUC from time zero to infinity (AUC[0-∞]) elimination half-life (t1/2), clearance (CL/F), as data permit. Repeat dose: AUC from time zero to end of dosing interval (AUC[0-τ]) (τ=12 hours [h] for twice daily dose regimen), Cmax, tmax, elimination half-life (t1/2) as data permit.
• To evaluate potential inhalation exposure of bystanders to airborne	• Concentration of CCI15106 in plasma of bystanders 15-20 minutes (min) after dosing (at predicted tmax) and

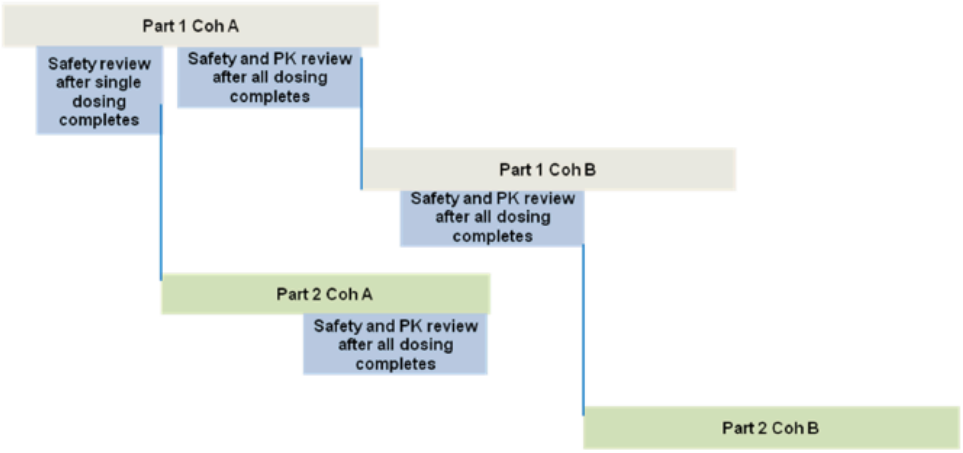
Objectives	Endpoints
CCI15106 during self-administered dosing of participants.	amount of CCI15106 accumulated on filters fitted on bystander over 15 min after dosing.
• To evaluate the distribution and persistence of airborne CCI15106 in room air post-dosing.	• Amount of CC15106 in room air assessed by measuring amount of CCI15106 accumulated over 20 and 60 min intervals during and immediately post-dosing on filters fitted on stationary pumps placed in the room.
Secondary Objectives	**Secondary Endpoints**
• To determine the concentration of CCI15106 in the lung of healthy participants and participants with moderate COPD following repeat dosing of CCI15106-IP.	• Concentrations of CCI15106 in lung epithelial lining fluid (ELF) assessed by bronchoalveolar lavage (BAL).
• To investigate the performance of the Monodose RS01 device for the administration of CCI15106-IP in healthy participants and participants with moderate COPD.	• Device safety and performance parameters, including medical device incidents reporting, as well as systemic PK and lung CCI15106 concentrations.
Exploratory Objectives	**Exploratory Endpoints**
• To assess dose proportionality of CCI15106-IP versus systemic PK parameters.	• Comparisons of doses administered and systemic PK parameters of CCI15106: AUC(0-24) or AUC(0-τ) and Cmax.
• To explore the relationship of drug exposure to safety and tolerability parameters after single and repeat escalating doses of CCI15106-IP in healthy participants and participants with moderate COPD.	• The dose or plasma exposure parameters for CCI15106 and the relationship of these to safety and tolerability parameters, as data permit.
• To extrapolate study outcomes to a realistic worst case real-life scenario of dosing multiple patients in a single room in a nursing home.	• Comparison of the study room with a potential nursing home room, including room dimensions, patient density, ventilation (air change rates per hour).

2.3. Study Design

Overview of Study Design and Key Features



Design Features	This is a two-part, double-blind (sponsor unblind), randomized, placebo-controlled, single and repeat escalating dose study. Investigator and participants will be blinded to treatment type (active or placebo), but will know what dose of the medication is being administered. Part 1 will investigate single and repeat ascending doses in healthy participants and investigate environmental and bystander exposure. Part 2 will evaluate single and repeat dose in participants with moderate COPD. Participants may only be enrolled in one study part and randomized to one cohort per the randomization schedule.

Overview of Study Design and Key Features	
	The following reviews will be conducted during the study progression: 
Dosing	• For Cohort A Part 1, 60 mg single dose will be administered on Day 1; 120 mg single dose will be administered on Day 3; and then 30 mg dose will be administered BID on Days 6-19. • For Cohort B Part 1, Repeat Dose Schedule of Activities (SoA) will be followed for the duration of the study. Dosing will begin on the morning of Day 1 and continue for 14 days BID. Dosing frequency and duration may be adjusted based on emerging safety and tolerability data. • For Cohort C Part 1, 14 healthy participants will be enrolled to evaluate bystander exposure and will follow Cohort C Part 1 SoA. Bystanders and air exposure will be evaluated concomitantly with Cohort B Part 1. • For Cohort A Part 2, Single Dose SoA will be followed for the duration of the study. • For Cohort B Part 2, Repeat Dose SoA will be followed for the duration of the study. Dosing will begin on the morning of Day 1 and continue for 14 days BID. Dosing frequency and duration may be adjusted based on emerging safety and tolerability data.
Time & Events	Details of the Schedule of Activities can be found in Appendix 2, Section 11.2
Treatment Assignment	In Cohort A Part 1 and in Cohort A Part 2, participants will be randomized to CCI15106- IP or Placebo with 3:1 ratio. In Cohort B Part 1 and Cohort B Part 2, participants will be randomized with 6:1 ratio. Cohort C Part 1 will not be randomized or dosed, but each bystander participant will be assigned to a dosing participant. Screening visit will occur within 30 days of dosing for cohorts in Part 1 and within 45 days of dosing for cohorts in Part 2.
Interim Analysis	No formal interim analyses are planned for this study. Safety and tolerability will be evaluated as described in the design features above. Systemic and, where available, lung PK may also be evaluated.

2.4. Statistical Hypotheses

The primary objective of the study is to investigate the safety and tolerability of CCI15106-IP following single and repeat escalating doses in healthy participants and participants with moderate COPD. No statistical hypotheses will be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses are planned for this study. Safety and tolerability will be evaluated as described in Section 2.3. Systemic and, where available, lung PK may also be evaluated.

3.2. Final Analyses

Safety and PK analyses are the primary statistical analyses for this study.

Data will be listed and summarized according to GSK reporting standards, where applicable. All the displays will be split by part. Study population tables would be presented by cohort and a combined placebo (of all cohorts with the exception of Part 1, Cohort C (bystanders)). For Safety displays, listings will be sorted by dose, participant and time; summaries will be presented by dose and time for different parts of the study. Participants receiving placebo may be combined into one treatment group in the summaries within each part.

Descriptive summaries will include n, mean, standard deviation (SD), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-participant coefficient of variation (%CVb) for continuous variables related to PK parameters, n and percent will be used as summary statistics for categorical variables.

Version 9.4 or higher of the SAS system will be used to analyse the data as well as to generate tables, figures, and listings.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Participants Screened	• Comprises of all participants who consent to participate in the clinical study.	• Screen Failures
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Safety	• Comprises of all participants who receive at least one dose of study treatment during the study. • This population will be based on the treatment the participant actually received.	• Safety • Study Population
Systemic Pharmacokinetic Concentration (PK)	• Participants who receive at least one dose of study treatment and who undergo plasma PK sampling and have at least one post-dose concentration result. • PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether	• PK

Population	Definition / Criteria	Analyses Evaluated
	or not the sample will be excluded.	
BAL PK	• Healthy participants who receive at least one dose of study treatment and who undergo BAL sampling and have post-dose lung ELF CCI15106 and urea concentration result. • Lung ELF 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.	• BAL
Bystander Safety Population (Part 1, Cohort C)	• Participants who are present at least once in the room with the participant receiving the dose.	• Safety • Study Population
Bystander PK Population (Part 1, Cohort C)	• Participants who are present at least once in the room with the participant receiving the dose, undergo plasma PK sampling and have post-dose concentration result. • 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 11: 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 Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.

- This dataset will be the basis for the summaries and listings of protocol deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

- There are no planned examinations of covariates and subgroups.
- There are no planned adjustments made for multiple centres in this study as this is a single centre study.
- There are no planned adjustments for multiple comparisons or multiplicity.

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
RandAll NG		Data Displays for Reporting		
Code	Description	Display Header	Footnote Treatment Description	Order [1]
S1	CCI15106-IP 60 mg – Single Dose	CCI15106 SD 60mg(HV)	CCI15106-IP 60 mg Single Dose for Part 1, Cohort A	1
S2	CCI15106-IP 120 mg – Single Dose	CCI15106 SD 120mg(HV)	CCI15106-IP 120 mg Single Dose for Part 1, Cohort A	2
R1	CCI15106-IP 30 mg – BID	CCI15106 BID 30mg(HV)	CCI15106-IP 30 mg BID for Part 1, Cohort A	3
R2	CCI15106-IP 60 mg – BID	CCI15106 BID 60mg(HV)	CCI15106-IP 60 mg BID For Part 1, Cohort B	4
P	Placebo	Placebo(HV)	Placebo for Part 1 Cohorts A and B	5
S1	CCI15106-IP 60 mg – Single Dose	CCI15106 SD 60mg(COPD)	CCI15106-IP 60 mg Single Dose for Part 2, Cohort A COPD	6
R2	CCI15106-IP 60 mg – BID	CCI15106 BID 60mg(COPD)	CCI15106-IP 60 mg BID for Part 2, Cohort B COPD	7
P	Placebo	Placebo(COPD)	Placebo for Single Dose and BID for COPD	8
BYS	Bystander Cohort	Bystander	Bystander	9

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

5.2. Baseline Definitions

5.2.1. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment.

For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
12 Lead ECG & Vital Signs	X	-	X	Day 1 (Pre-Dose)
Spirometry	X	-	X	Day 1 (Pre-Dose)
Haematology/Chemistry/Urinalysis	X	X	-	Day - 1
Telemetry	-	-	X	Day 1 (Pre-Dose)

NOTES:

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 5.2.1 will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data are missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on change from baseline displays wherever applicable.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
11.2	Appendix 2: Assessment Windows
11.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data

Section	Component
11.6	Appendix 6: Reporting Standards for Missing Data
11.7	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 "Safety" population, unless otherwise specified.

All the displays will be split by part. Study population tables would be presented by cohort and a combined placebo (of all cohorts).

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Randomization			
Randomization			Y
Subject Disposition			
Subject Disposition	Y		Y
Reason for Screening Failures	Y		Y
Reason for Withdrawals			Y
Protocol Deviations	Y		Y
Inclusion and Exclusion Criteria Deviations			Y
Study Populations	Y		
Demography			
Demographics Characteristics	Y		Y
Race & Racial Combinations	Y		Y
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)	Y		Y
Concomitant Medications	Y		Y

NOTES:

- Y = Yes display generated.

6.1.1. Disposition and Withdrawals

All participants who provide informed consent will be accounted for in this study. In each study part, subject disposition will be tabulated for each study treatment and for all participants combined with the number of participants who are randomly assigned to treatment, complete the study and prematurely discontinue as well as the reason for early discontinuation. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each participant.

Listings of study eligibility, treatment randomization and study treatment administration will be provided for each study part based on the layout mentioned above.

6.1.2. Demographic and other Baseline Characteristics

Individual subject demographics and baseline characteristics (medical history and results from drug and alcohol screens, smoking/nicotine history) will be presented in listings for each study part.

Demographic characteristics such as age, sex, race, ethnicity, height, weight, and body mass index (BMI) will be summarized and tabulated by treatment and for all participants overall for each study part. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percent will be presented for sex, race and ethnicity.

6.1.3. Medications

All prior and concomitant medications will be listed for each study part based on the layout mentioned earlier. Summaries of all medications taken during the course of the study will be presented in tabular form for each study part using GSK Drug Dictionary 1.3. The number and percentage of participants taking concomitant medications will be summarized by cohort and overall for each study part separately. For each participant, the medication will be counted only once within a given preferred drug name level. A participant may appear more than once if he/she has more than one concomitant medication coded under different categories, however, the participant will be counted only once in the overall category.

Please refer to Appendix 3: Study Phases and Treatment Emergent Adverse Events for definition of prior, concomitant and post-treatment medications. Handling of partial dates for medications is outlined in Appendix 6: Reporting Standards for Missing Data.

7. SAFETY ANALYSES

The primary safety analyses for this study will be based on the Safety population for each dose taken, analysed separately for study parts, unless otherwise specified.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by dose, participant and time; summaries will be presented by dose and time for different parts of the study. Participants receiving placebo may be combined into one treatment group in the summaries within each part.

For categorical variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of variable will be presented. Continuous variables will be summarized using descriptive statistics, including N, mean, standard deviation (SD), median, minimum and maximum values.

Table 3 provides an overview of the planned safety analyses for each study part, unless otherwise specified, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Safety Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Extent of Exposure	Y			Y				
Adverse Events[1]								
All AE's	Y			Y				
Serious AE's	Y			Y				
Treatment related AE's	Y			Y				
AE's leading to Withdrawal	Y			Y				
Laboratory Values								
Clinical Chemistry[2]	Y			Y	Y			
Hematology	Y			Y	Y			
Coagulation	Y			Y				
Urinalysis				Y				Y
ECG's[3]								
ECG Findings	Y			Y				
ECG Values	Y			Y	Y			
Vital Signs[3]								
Vitals Values	Y			Y	Y			
Spirometry								
Spiromtery	Y			Y				
Telemetry								
Telemetry Findings	Y			Y				

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual participant observed raw data.

1. Listings will include participant's numbers for individual AE's & AE system organ classes, preferred terms and verbatim text.
2. Chemistry summaries will include both changes from baseline & emergent results by PCI criteria.
3. Listings and summaries for ECGs and vital signs include treatment emergent PCI results

7.1. Study Medication Exposure

Exposure to study medication as the number of doses administered will be presented for each treatment for each Part.

7.2. Adverse Events Analyses

Adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 21.0.

See Appendix 3: Study Phases and Treatment Emergent Adverse Events to determine treatment states for AE data. Handling of partial dates for AEs is outlined in Appendix 6: Reporting Standards for Missing Data. In the rare case when it is not possible to assess treatment emergence, the AE will be classified as treatment emergent (i.e. the worst case).

AE Severity is classified as mild (grade = 1), moderate (grade = 2), or severe (grade = 3). AEs with a missing severity will be classified as severe. If a participant reports an AE more than once within that SOC (System Organ Class)/ PT (Preferred Term), the AE with the worst case severity will be used in the corresponding severity summaries.

Relationship to study treatment, as indicated by the Investigator, is classified as "not related" or "related". AEs with a missing relationship to study medication will be regarded as "related" to study medication.

All AE tabulations will be performed separately for Part 1 and Part 2, by dose, and will include the number and percentage of participants. For each study part and cohort, incidence of AEs will be tabulated by the following:

- All AEs by SOC and PT
- All related AEs by SOC and PT
- All AEs by SOC, PT and Severity
- All related AEs by SOC, PT and Severity

All AEs leading to permanent discontinuation of study treatment will be identified by using the variable pertaining to outcome on the Adverse Events page of the CRF, and listed separately for each study part and cohort.

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the CRF, and will be listed separately for each study part.

The details of the planned displays are provided in Appendix 11: List of Data Displays.

7.3. Clinical Laboratory Analyses

Laboratory results will be included in the reporting of this study for hematology, coagulation, clinical chemistry, and urinalysis.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. The statistics will be presented for each scheduled assessment during the study and change from baseline to each scheduled assessment. Presentations will use SI Units, as provided by the labs or converted from values in other units. Clinical laboratory data collected during unscheduled visits of study conduct that were not required per protocol, such as for special testing to evaluate an AE, will be listed and not summarized.

Based upon laboratory normal ranges, the laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within the normal range) and high (above the upper limit). Summary statistics for change from baseline based on PCI will also be tabulated. The details of the planned displays are in Appendix 11: List of Data Displays.

7.4. ECG Evaluations

The following ECG parameters will be reported for each study part: PR, QRS, QT, QTc, QTcF and HR (bpm). Replicate quantitative values taken per time point will be averaged for all analysis and reporting. Summary statistics for change from baseline will also be tabulated.

Overall assessment of ECG (Investigator's judgment) will be recorded as follows:

- Normal
- Abnormal, Not Clinically Significant
- Abnormal, Clinically Significant

7.5. Telemetry Evaluations

Overall assessment of Telemetry (Investigator's judgment) will be recorded as follows:

- Normal

- Abnormal, Not Clinically Significant
- Abnormal, Clinically Significant

All measurements will be listed.

7.6. Spirometry Evaluations

The following parameters will be reported for each timepoint: FEV1 and FVC. The maximum of the measurements will be calculated. All measurements will be listed.

% Predicted Normal FEV1 = (Max FEV1/Predicted Normal FEV1)x100

% Predicted FVC = (Max FVC/Predicted Normal FVC)x100

7.7. Vital Signs

The following Vital Signs measurements will be reported for each study part: supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature.

For participants undergoing BAL, vital signs will also include oxygen saturation.

Triplicate quantitative values taken per time point will be averaged for all analysis and reporting.

Summary statistics for collected vital signs, change from baseline, and summary of PCI will also be tabulated.

7.8. Bystander and Environmental Exposure Analyses

The bystander and environmental analysis will be analyzed and presented in a separate report.

8. PHARMACOKINETIC ANALYSES

8.1. Overview of Planned Pharmacokinetic Analyses

The PK analyses will be based on the "Systemic Pharmacokinetic Concentration" population for the plasma drug concentration data, and "BAL PK Population" for the lung ELF concentration data, unless otherwise specified.

Table 4 provides an overview of the planned analyses, with full details being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Plasma Drug Concentrations				Y	Y [1] [2] [3] [4]	Y [1]	Y					Y [1] [2]	Y [1]	
Derived PK Parameters	Y			Y			Y	Y	Y [7]	Y [8]				
Lung ELF CCI15106 Concentration				Y	Y [5]	Y [6]	Y						Y [1]	

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual participant observed raw data.

1. Linear and Semi-Log plots will be created on the same display.
2. Separate Mean (± SD) and Median plots will be generated, for the BD cohorts, overlay the day 1 and day 14 on same plot where possible.
3. Mean (± SD) and Median plots by cohorts a) to compare over the first 12hours for 60mg in HV (part 1) and COPD (part 2); b) to compare the 60mg SD (over 24h) HV vs COPD; c) to compare the 60mg BD HV vs COPD one for each of the intense sampling day (day 1, day 14).
4. Boxplot of plasma drug concentration at the follow up visit by cohort.
5. Boxplot of Lung CCI15106 concentration by cohort (HV vs COPD).
6. Lung CCI15106 concentration by Subject ID.
7. Dose proportionality of single and repeat dose and accumulation ratios from Cohorts A and B will be evaluated in Part 1 and Part 2.
8. Supportive SAS Output from Statistical Analysis of Loge-transformed Plasma PK Parameters.

8.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions.

8.1.1.1. Derivation of Lung ELF Drug (CCI15106) Concentration Data

Urea concentration data will be used to calculate the dilution effect of the BAL A correction for dilution will be applied to all BAL drug concentrations as follows:

$$Lung\ Drug\ Concentration\ (ng/mL) = \frac{BAL}{Drug\ Concentration}\ (ng/mL) \times Dilution\ Factor$$

where

$$Dilution\ Factor = \frac{Plasma\ Urea_{pre-BAL}}{BAL\ Urea}$$

8.1.2. Pharmacokinetic Parameters

8.1.2.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions for the treatment of concentrations below the assay's lower limit of quantification (LLQ).
- The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin™ 6.4 or higher (Pharsight Corporation, a Certara Company, Princeton, NJ), and/or SAS™ Version 9.4 or higher. Graphics may be prepared using the same versions of SAS™, or Phoenix WinNonlin™, or with SigmaPlot™ 12.5, or higher (Systat Software, Inc., San Jose, California).
- All calculations of non-compartmental parameters will be based on actual sampling times, except for the purpose of interim reviews where nominal sampling times will be used.
- Pharmacokinetic parameters described in Table 5 (Cohorts A, Part 1 and Part 2) and Table 6 (Cohort A, Part 1, Cohorts B, Part 1 and Part 2) will be determined from the plasma concentration-time data, as data permits, for CCI15106 (ribavirin).

Table 5 Derived Pharmacokinetic Parameters (Cohorts A, Part 1 and Part 2 – Single dose)

Parameter	Parameter Description
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (ng·h/mL) after each single dose will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_{(0-\infty)}$	Area under the concentration-time curve extrapolated to infinity (ng·h/mL) will be calculated by linear up/log down trapezoidal summation as: $AUC = AUC_{(0-t)} + C(t) / \lambda_z$
$AUC_{(0-12)}$	Area under the concentration-time curve from time zero to 12 hours post dose, e.g. for

Parameter	Parameter Description
	cohort A part 1, $AUC_{(0-12)}$ will be calculated after the 60mg SD (day 1), 120mg SD (day 3), and first dose of 30mg BD (day 6)
$AUC_{(0-24)}$	Area under the concentration-time curve from time zero to 24 hours post dose, e.g. for cohort A part 1, $AUC_{(0-24)}$ will be calculated after the 60mg SD (day 1), 120mg SD (day 3)
$AUC_{(0-48)}$	Area under the concentration-time curve from time zero to 48 hours post dose, e.g. for cohort A part 1, $AUC_{(0-24)}$ will be calculated after the 60mg SD (day 1), 120mg SD (day 3)
C_{max}	Maximum observed concentration in plasma (ng/mL), determined directly from the concentration-time data.
t_{max}	Time to reach C_{max} (h), determined directly from the concentration-time data.
$t_{½}$	Apparent terminal half-life (h) will be calculated as: $t_{½} = ln2 / \lambda_z$
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.
CL/F	Apparent inhaled plasma clearance after dosing (L/h), calculated as administered dose divided by AUC(0-∞).

NOTES:

- Additional parameters may be included as required.

Table 6 Derived Pharmacokinetic Parameters (Cohort A, Part 1, Cohorts B, Part 1 and Part 2 – Repeat Dose)

Parameter	Parameter Description
AUC(0-τ)	Area under the concentration-time curve in the plasma during a dosing interval (ng·h/mL) on day 1 and day 14, calculated by linear up/log down trapezoidal summation. Actual elapsed time at the end of the dosing interval will be used for the calculation. τ=12 for BID dosing regimen
C_{max}	Maximum observed concentration in plasma (ng/mL), determined directly from the concentration-time data.
t_{max}	Time to reach C_{max} (h), determined directly from the concentration-time data.
$t_{½}$	Apparent terminal half-life (h) will be calculated as: $t_{½} = ln2 / \lambda_z$
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.

NOTES:

- Additional parameters may be included as required.

Individual lung ELF concentration data will be summarised, listed and displayed graphically on both linear and semi-logarithmic scales for the Cohorts with available ELF data. Where data permit, the individual lung ELF concentration data may be plotted against the plasma concentration measured prior to BAL sampling.

8.1.2.2. Statistical Analysis of Pharmacokinetic Parameters

Geometric mean will be included for PK parameters, wherever applicable.

The following PK statistical analyses will only be performed, if sufficient data is available (i.e. if participants have well defined plasma profiles).

Pharmacokinetic Statistical Analyses
Endpoint(s)
• All endpoints, except tmax and %AUCex, will be natural-log transformed prior to the analysis • Dose Proportionality: $AUC_{(0-24)}$ or $AUC_{(0-48)}$, or $AUC_{(0-\tau)}$ and Cmax, for single dose and repeat dose of Part 1 • Steady State Assessment in BID dosing: Ctrough (using pre-dose concentration from day 6 in Cohort A Part 1, and day 2 onwards in Cohorts B, Part 1 and Part 2) • Accumulation in BID dosing: accumulation ratio will be calculated for $AUC_{(0-\tau)}$ as [$AUC_{(0-\tau)}$, on Day 19/$AUC_{(0--\tau)}$, on Day 6 for Cohort A in Part 1, or $AUC_{(0-\tau)}$ on Day 14/$AUC_{(0--\tau)}$ on Day 1 for Cohorts B of both Part 1 and Part 2, from the ANOVA model
Model Specification
• Dose Proportionality will be assessed separately by means of power model: $y = \alpha * dose^{\beta}$ where y denotes the PK parameter being analyzed. PK parameters will be normalized to 60mg dose and then log transformed prior to analysis If the power model does not show dose proportionality then pairwise analysis of variance (ANOVA) may be used as an exploratory analysis to understand the dose where dose proportionality fails • Analysis of variance (ANOVA), considering study Day as fixed effect and subject as a random effect in the model, will be performed using SAS Mixed Linear Models procedure to evaluate in the assessment of steady state in models included at least 3 days of pre-dose concentrations (like Days 4,6,8; Days 6,8,10, Days 10,12,14 relative to first dose of repeat dosing). This will be done for each of the repeat dose treatments. • Analysis of variance (ANOVA), considering study Day as fixed effect and subject as a random effect in the model, will be performed using SAS Mixed Linear Models procedure to evaluate in the assessment accumulation, where geometric least squares mean ratio of $AUC_{(0-\tau)}$ on Day 19/$AUC_{(0-\tau)}$ on Day 6 for Cohort A in Part 1, $AUC_{(0-\tau)}$ on Day 14/$AUC_{(0--\tau)}$ on Day 1 for Cohorts B and 90% CI will be calculated. Note: Subjects will be fit as a fixed effect for the assessment of accumulation if the model fails to converge. • Estimates of within-subject variability for Cmax, t1/2, $AUC_{(0-\tau)}$ and CL/F will be provided, where CVw(%) = SQRT(exp(MSE) – 1)×100 and MSE is the residual mean squared error from the model. CVw represents a pooled measure of within-subject variability in repeat dose group.
Model Results Presentation
• Dose Proportionality: The intercept α and the slope β with corresponding 90% CIs will be estimated and presented for each PK parameter • Steady State Assessment: Estimated slope parameter with 90% CI will be presented. • Accumulation and Time Invariance: Geometric means with 90% CIs by parameter and day will be presented. Ratio of geometric means with corresponding 90% CIs for Day 14/ Day 1 for Cohort B or Day 19/Day 6 for Cohort A of Part 1 will also be presented. • Comparative Plot of Individual Plasma PK Parameter Versus Treatment will be generated. • Individual and box plots of Pre-dose concentrations will be generated. • The SAS output from the statistical models will be included in a listing of supportive SAS output.

9. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

Population pharmacokinetics modelling may be conducted and reported separately.

The detailed PopPK methodology will be described in a separate RAP where appropriate. The required data for the analyses are provided in Appendix 8: Population Pharmacokinetic (PopPK) Analyses and are subject to delivery soon after DBF.

10. REFERENCES

GlaxoSmithKline Document Numbers 2015N238595_00 (Original – 24-SEP-2015): A Double-Blind, Placebo-Controlled, Dose Escalation, First Time in Human Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Doses of GSK3389404 in Healthy Subjects.

Whitehead J. Easy-to-implement Bayesian methods for dose-escalation studies in healthy subjects. *Biostatistics*. 2001; 2:47-61.

11. APPENDICES

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

11.1.1. Exclusions from Per Protocol Population

N/A

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

Screening and follow-up procedures for all cohorts

Procedure	Screening, ≤ 30 days before D1 for Part 1 or ≤ 45 days before D1 for Part 2[1]	Follow up 30±2 days after the last dosing day	Notes
Informed consent	X		1. Screening assessments can be performed over multiple screening visits 2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required 3. To be drawn fasting (for at least 8 h) 4. To be administered to participants with COPD only, 15-30 minutes prior to spirometry 5. To be done at screening for participants with COPD only, following salbutamol dosing 6. To be performed in the bronchoalveolar lavage (BAL) cohorts only to confirm participant eligibility 7. To be performed in the BAL cohorts only to confirm participant eligibility. Can be done pre-dose on Day -1 instead, if required
Inclusion and exclusion criteria	X		
Demography	X		
Full physical examination including height and weight, oral examination	X		
Brief physical examination, oral examination		X	
Medical history (includes substance usage and Family history of premature CV disease)	X		
Substance testing (drugs, alcohol)	X		
Assessment of child-bearing potential for females	X		
Serum pregnancy test in women	X	X	
Human immunodeficiency virus (HIV), Hepatitis B (Hep B) and Hepatitis C (Hep C) screen[2]	X		
Haematology, clinical chemistry and urinalysis (include liver chemistries)[3]	X	X	
Salbutamol administration[4]	X		
Spirometry[5]	X		
12-lead ECG and vital signs	X	X	
Coagulation parameters[6]	X		
Capillary pCO_2[7]	X		
PK blood sample		X	
AE review		X	
SAE review	X	X	
Concomitant medication review	X	X	

Schedule for Cohort A Part 1

Procedure	Treatment Period, Days																						
	-1	1[1]	2	3[1]	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Inclusion and exclusion criteria	X																						
Brief physical examination, oral examination	X																						X
Substance testing (drugs, alcohol, tobacco)	X																						
Inhaler device training[2]	X																						
Serum pregnancy test in women	X																						
Admittance to clinic	X																						
Randomization	X[3]																						
Discharge																							X[4]
Haematology, clinical chem and urinalysis (include liver chem)[5]	X		X			X							X										X
Spirometry		X[1]		X[1]			X[6]		X[7]			X[7]					X[7]			X[6]			
Telemetry (starting 30 min pre-morning dose and continuous at least 4h post-morning dose)		X[1]		X[1]			X						X						X				
12-lead ECG and vital signs	XX X	X[1]		X[1]			X[8]		X[8]	X[8]		X[8]	X[8]	X[8]		X[8]		X[8]					
CCI15106-IP or placebo treatment, device incident assessment		X[1]		X[1]			X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]			
PK blood sample[10]		X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X
AE review		←==========																					→
SAE review		←==========																					→
Concomitant medication review		←==========																					→

1. Single dose days. Follow schedule for Day 1 of Part 2 Cohort A
2. Day -1 inhaler training may be done on Day 1 instead, before the first dose administration. Other time-points may be added per investigators discretion.
3. Can be performed on Day 1 prior to dosing
4. After all procedures and assessments are complete
5. To be drawn fasting (for at least 8 h)
6. To be performed at the following timepoints in the mornings only: pre-dose, and 0.25, 0.5, 1, 4 h post-dose
7. To be performed at the following timepoints in the mornings only: pre-dose and 4 h post-dose
8. ECG and vital signs to be obtained 2 h after the morning dose

9. BID
10. PK samples on days 1, 3, 6, and 19 will be collected at the following timepoints: pre-dose, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12 h. On day 2, one sample in the morning (24h post day 1 dose). On days 4 and 5, one sample on each morning (24h and 48h post day 3 dose). On days 6 and 19, the evening dose will be given after 12 h post-dose sample is collected. On all other days, PK sample will be collected once, before the morning dose (if on dosing days).

Schedule for Cohort A Part 2 (and all other single dose administrations)

Procedure	Treatment Period, Days (D) and hours (h)													
	D-1	D1												D2
		Pre-dose	0h	0.25h	0.5h	0.75h	1h	2h	4h	6h	8h	10h	12h	24h
Inclusion and exclusion criteria	X													
Brief physical examination, oral examination	X													X
Substance testing (drugs, alcohol)	X													
Serum pregnancy test in women	X													
Admittance to clinic	X													
Inhaler device training[1]	X													
Randomization	X[2]													
Discharge														X[3]
Haematology, clinical chem and urinalysis (include liver chem)[4]	X													X
Spirometry		X[5]		X[6]	X		X[6]		X[6]					
Telemetry			30 min pre-dose and continuous until at least 4 h post-dose											
12-lead ECG and vital signs		XXX		X			X	X	X		X		X	
CCI15106-IP or placebo treatment			X											
PK blood sample[7]		X		X	X	X	X	X	X	X	X	X	X	X
AE review		←==========												→
SAE review	←==========													→
Concomitant medication review	←==========													→

1. Day -1 inhaler training may be done on Day 1 instead, before the first dose administration. Other time-points may be added per investigators discretion
2. Can be performed on Day 1 prior to dosing
3. After all assessments are completed
4. To be drawn fasting (for at least 8 h)
5. To be performed within 15 to 60 minutes pre-dose
6. To be performed **after** ECG, VS and PK blood draw are obtained
7. Additional PK collection time points may be added to better characterize the PK profile

Repeat dose schedule to be followed for repeat dose cohorts in Parts 1 and 2 (other than Cohort A Part 1)

Procedure	Treatment Period, Days															
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Inclusion and exclusion criteria	X															
Brief physical examination, oral examination	X															X
Substance testing (drugs, alcohol, tobacco[1])	X															
Inhaler device training[2]	X															
Serum pregnancy test in women	X															
Admittance to clinic	X															
Randomization	X[3]															
Discharge																X[4]
Dosing procedure training with bystanders		X[5]														
Haematology, clinical chem and urinalysis (include liver chem)[6]	X							X								X
Spirometry		X[7]		X[8]			X[8]					X[8]			X[7]	
Telemetry (starting 30 min pre-morning dose and continuous at least 4h post-morning dose)		X						X						X[9]		
12-lead ECG and vital signs[10]	XXX	X		X	X		X	X	X		X[11]		X[11]			
CCI15106-IP or placebo treatment BID, device incident assessment BID[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood sample[13]		X	X		X		X		X		X		X		X	X
BAL											X[14]					
Urea blood sample											X[15]					
AE review		←==========														→
SAE review	←==========															→
Concomitant medication review	←==========															→

1. Tobacco test to be performed only in healthy participants
2. Day -1 inhaler training may be done on Day 1 instead, before the first dose administration. Other time-points may be added per investigators discretion.
3. Can be performed on Day 1 prior to dosing
4. After all procedures and assessments are complete
5. To be done only in Cohort(s) where bystanders are present. Can be performed on Day -1 instead, if desired. Other time-points may be added per investigators discretion.
6. To be drawn fasting (for at least 8 h)
7. To be performed at the following timepoints in the mornings only: pre-dose, and 0.25 (in participants with COPD only), 0.5, 1, 4 h post-dose
8. To be performed at the following timepoints in the mornings only: pre-dose and 4 h post-dose

9. Telemetry may be performed on Days 11 or 12 instead, not to coincide with the BAL procedure.
10. ECG and vital signs to be obtained 2 h after the morning dose
11. When BAL is performed, vital signs and ECG will be performed before and after the procedure and oxygen saturation will be measured continuously.
12. For cohort with bystanders, BID doses may have ±1.5 h window.
13. PK samples on days 1 and 14 will be collected at the following timepoints: pre-dose, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12 h. The evening dose will be given after 12 h post-dose sample is collected. On all other days, PK sample will be collected once, before the morning dose. When BAL is performed, one additional PK sample will be collected after dosing immediately prior to bronchoscopy
14. Done once during these four days, as soon as possible (within 1 h) after the first dose of the day
15. To be collected immediately before bronchoscopy

Schedule for Cohort C Part 1 (bystanders and air monitoring), to be executed concomitantly with Cohort B Part 1

Procedure	Treatment Period, Days															
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Inclusion and exclusion criteria	X															
Brief physical examination, oral examination	X															X
Substance testing (drugs, alcohol, tobacco)	X															
Serum pregnancy test in women	X															
Admittance to clinic	X															
Discharge																X[1]
Training[2]	X															
Haematology, clinical chem and urinalysis (include liver chem)[3]	X							X								X
Exposure to dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood sample		X[4]						X[4]							X[4]	X
Stationary pump air monitoring[5]		X						X							X	
Personal exposure pump monitoring[6]		X						X							X	
12-lead ECG and vital signs	XXX	X[7]		X[7]	X[7]		X[7]	X[7]	X[7]		X[7]		X[7]			
AE review		←==========														→
SAE review	←==========															→
Concomitant medication review	←==========															→

1. After all procedures and assessments are complete
2. Day -1 training may be done on Day 1 instead, before the first dose administration. Other time-points may be added per investigators discretion
3. To be drawn fasting (for at least 8 h)
4. PK samples will be collected pre-dose and 15 min after the dosing participant takes their first daily dose. In addition, on days 7 and 14, one sample on each day will be collected before the dosing participant takes the first daily dose. On day 15, one sample will be collected before discharge.
5. Samples of air to be collected for 20 and 60 min during and after the first morning dose
6. Samples of air to be collected for 15 min during and after the first morning dose
7. ECG and vital signs to be obtained 2 h after the exposure to morning dose

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

11.3.1. Study Phases

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

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

11.3.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days 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.

11.3.2. Treatment States for Adverse Events Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date if AE start time not available; else AE Start Date time < Study Treatment Start Date time
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 = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = 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 CRF OR value is missing.

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used to perform all data analyses, generate tables, figures and listings.	
Reporting Area	
HARP Server	: us1salx00259
HARP Compound	: \arprod\cci15106\mid205822\final_03
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (AdaM IG Version 1.0). • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files may be generated for SAC tables..	

11.4.2. 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

Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • 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. • Numeric data will be reported at the precision collected on the CRF. • The reported precision from non CRF 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 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. and Standards for the Transfer and Reporting of PK Data using HARP	

11.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to [Insert document name]. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Data	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of log-transformed data and between geometric coefficient of variation (CVb (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log Transformed	N, n, geometric mean, 95% CI (Lower, Upper), standard deviation (SD), median, minimum and maximum
Listings	Interval, number of observations included in calculation of lambda_z, regression coefficient and percent AUC extrapolated (%AUCex)

11.5. Appendix 5: Derived and Transformed Data

11.5.1. 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. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits 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 randomisation date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Date ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

11.5.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing day will have this imputed as day '15'.
  o 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]**
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** • Subjects 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.

11.5.3. 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 Significant Digits = '< x ' becomes x – 0.01 • Example 2: 1 Significant Digit = '> x' becomes x + 0.1 Example 3: 0 Significant Digits = '< x' becomes x – 1

11.6. Appendix 6: Reporting Standards for Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completion of all visits of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study. • All available data from subjects 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.

11.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument: ○ 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 are excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.6.2.1. 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 3: 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.

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. 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
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20
[Insert as Required]	[Units]			

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

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

11.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450	<480
		≥ 480	< 500
		≥ 500	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75 [	> 110
Change from Baseline			
Increase from Baseline QTc	msec	> 30	< 60
	msec	≥ 60	

11.7.3. Vital Signs

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

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

11.8. Appendix 8: Pop PK Dataset Specification

For the purpose of population PK analysis, the raw plasma concentration data in the systemic PK population (including all the available plasma concentration data) will be merged for each individual with the following demographic and baseline/screening variables where available. In addition, the 12-ECG data as listed below will be merged with plasma concentration data by the planned time.

The dataset will be a comma delimited ASCII text file, named as: NM.205822.PK.v1.csv.

Variable	Description	Format	*Unit*	Missing	Note
AGE	Subject Age	Num	*Specify*	-99	From source data.
SEX	Subject gender	Integer	None	Never	0=Male, 1=Female
SEXTEXT	Subject gender text	Char	None	Never	Text corresponding to code for SEX
BMI	Baseline Body Mass Index	Num	*Specify*	-99	From source data. Formula: Weight(kg)/(height(m)**2)
WT	Baseline Subject weight	Num	*Specify*	-99	From source data.
HT	Baseline Subject height	Num	*Specify*	-99	From source data.
RACE	Subject race code1	Integer	None	-99	From source data e.g. 1=African American / African Heritage 2=American Indian or Alaska Native 3=Asian – Central / South Asian Heritage 4=Asian – East Asian Heritage 5=Asian – Japanese Heritage 6=Asian – South East Asian Heritage 7=Asian – Mixed Race 8=Native Hawaiian or other Pacific Islander 9=White – Arabic / North African Heritage 10=White – White / Caucasian / European Heritage 11=White – Mixed Race 12=Mixed Race
RACETXT	Subject race text	Char	None	Never	Text corresponding to code for RACE
ETHN	Subject ethnicity	Num	None	-99	From source data definition. E.g 1=Hispanic or Latino, 2=Non-Hispanic
ETHNTEXT	Subject ethnicity text	Char	None	Never	Text corresponding to code for ETHN.
SCR	Serum Creatinine	Num	micromol/L	-99	Baseline/screening defined in the source dataset
CRCL	Baseline Creatinine Clearance	Num	mL/min	-99	From source data. *formula e.g.* Creatinine Clearance will be calculated based on the Cockcroft-Gault equation. • CrCL (ml/min) = [140 – AGE (in years)]*Weight(kg)*0.85 (for female patients) / [72* Serum Creatinine (micromol/L) * 0.0113
ALT	Alanine aminotransferase	Num		-99	Baseline/screening defined in the source dataset
AST	Aspartate aminotransferase	Num		-99	Baseline/screening defined in the source dataset
ALB	Albumin	Num		-99	Baseline/screening defined in the source

Variable	Description	Format	*Unit*	Missing	Note
					dataset
TBIL	Total bilirubin	Num		-99	Baseline/screening defined in the source dataset
ECGTM	Clock time of ECG recording in hours	Num			ECGTM should be calculated as: hr + min/60 e.g. if clock time of ECG recording is 09:30, then ECGTM= 9 + 30/60= 9.5
HR	Heart rate in bpm	Num	*bpm*		As in source dataset
HRBL	Baseline heart rate in bpm	Num	*bpm*		As in source dataset
PR	PR interval in ms	Num	*ms*		As in source dataset
PRBL	Baseline corresponding PR interval in ms	Num	*ms*		As in source dataset
QRS	QRS complex duration in ms	Num	ms		As in source dataset
QRSBL	Baseline corresponding QRS interval in ms	Num	ms		As in source dataset
QT	Uncorrected QT interval in ms	Num	ms		As in source dataset
QTBL	Baseline uncorrected QT interval in ms	Num	ms		As in source dataset
QTcF	QT with Fridericia's correction in ms	Num	ms		As in source dataset
QTcFBL	Baseline QT with Fridericia's correction in ms	Num	ms		As in source dataset
RR	RR interval in ms	Num	ms		As in source dataset
RRBL	Baseline corresponding RR interval in ms	Num	ms		As in source dataset

11.9. Appendix 9: Abbreviations & Trade Marks

11.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
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
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
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
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
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan

Abbreviation	Description
SDTM	Study Data Tabulation Model
SoA	Schedule of Activities
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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SAS
SigmaPlot
WinNonlin

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NONMEM

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.30	N/A
Efficacy	N/A	N/A
Safety	3.1 to 3.60	N/A
Pharmacokinetic	4.1 to 4.7	4.1 to 4.12
Population Pharmacokinetic (PopPK)	N/A	N/A
Pharmacodynamic and / or Biomarker	N/A	N/A
Pharmacokinetic / Pharmacodynamic	N/A	N/A
Section	**Listings**	
ICH Listings	1 to 66	
Other Listings	66 to 82	

11.10.2. 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
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

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

11.10.3. Deliverables

Delivery [Priority] [1]	Description
DS [X]	During Study
DE [X]	Dose Escalation
IA SAC [X]	Interim Analysis Statistical Analysis Complete
SAC [X]	Final Statistical Analysis Complete

NOTES:

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

11.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Summary of Participant Disposition – Part 1	The general layout of all the study population tables would follow mock shell SAFE_T1 for the column headers and order for both Part 1 and Part 2 tables. This will not include Cohort C, Part 1.	SAC
1.2.	Safety	ES1	Summary of Participant Disposition – Part 2		SAC
1.3.	Bystander Safety (Part 1, Cohort C)	ES1	Summary of Participant Disposition – Bystander	Only for Cohort C, Part 1.	SAC
1.4.	All Participants Screened)	ES6	Summary of Screening Status and Reasons for Screen Failure – Part 1	This will not include Cohort C, Part 1.	SAC
1.5.	All Participants Screened	ES6	Summary of Screening Status and Reasons for Screen Failure – Part 2		SAC
1.6.	All Participants Screened	ES6	Summary of Screening Status and Reasons for Screen Failure – Bystander	Only for Cohort C, Part 1.	SAC
Protocol Deviation					
1.7.	Safety	DV1	Summary of Important Protocol Deviations – Part 1	This will not include Cohort C, Part 1.	SAC
1.8.	Safety	DV1	Summary of Important Protocol Deviations – Part 2		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.9.	Bystander Safety (Part 1, Cohort C)	DV1	Summary of Important Protocol Deviations - Bystander	Only for Cohort C, Part 1.	SAC
Population Analysed					
1.10.	All Screened	SP1A	Summary of Study Populations – Part 1		SAC
1.11.	All Screened	SP1A	Summary of Study Populations – Part 2		SAC
1.12.	Bystander Safety (Part 1, Cohort C)	SP1A	Summary of Study Populations – Bystander	Only for Cohort C, Part 1.	SAC
Demographic and Baseline Characteristics					
1.13.	Safety	DM1	Summary of Demographic Characteristics – Part 1	This will not include Cohort C, Part 1.	SAC
1.14.	Safety	DM1	Summary of Demographic Characteristics – Part 2		SAC
1.15.	Bystander Safety (Part 1, Cohort C)	DM1	Summary of Demographic Characteristics – Bystander	Only for Cohort C, Part 1.	SAC
1.16.	Safety	DM5	Summary of Race and Racial Combinations – Part 1	This will not include Cohort C, Part 1.	SAC
1.17.	Safety (Part 2)	DM5	Summary of Race and Racial Combinations – Part 2		SAC
1.18.	Bystander Safety (Part 1, Cohort C)	DM5	Summary of Race and Racial Combinations – Bystander	Only for Cohort C, Part 1.	SAC
1.19.	Safety	DM6	Summary of Race and Racial Combination Details – Part 1	This will not include Cohort C, Part 1.	SAC
1.20.	Safety (Part 2)	DM6	Summary of Race and Racial Combination Details – Part 2		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.21.	Bystander Safety (Part 1, Cohort C)	DM6	Summary of Race and Racial Combination Details – Bystander	Only for Cohort C, Part 1.	SAC
1.22.	Enrolled	DM11	Summary of Age Ranges – Part 1	This will not include Cohort C, Part 1. Please include the footnote: "[1] Age is calculated based on screening date, using date of birth, truncated to integer value. Note that only the year of birth has been collected where the day and month would be 30th June for all subjects."	SAC
1.23.	Enrolled	DM11	Summary of Age Ranges – Part 2	Please include the footnote: "[1] Age is calculated based on screening date, using date of birth, truncated to integer value. Note that only the year of birth has been collected where the day and month would be 30th June for all subjects."	SAC
1.24.	Enrolled	DM11	Summary of Age Ranges – Bystander	Only for Cohort C, Part 1. Please include the footnote: "[1] Age is calculated based on screening date, using date of birth, truncated to integer value. Note that only the year of birth has been collected where the day and month would be 30th June for all subjects."	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
1.25.	Safety	MH1	Summary of [Current/Past] Medical Conditions – Part 1	This will not include Cohort C, Part 1.	SAC
1.26.	Safety	MH1	Summary of [Current/Past] Medical Conditions – Part 2		SAC
1.27.	Bystander Safety (Part 1, Cohort C)	MH1	Summary of [Current/Past] Medical Conditions - Bystander	Only for Cohort C, Part 1.	SAC
1.28.	Safety	CM1	Summary of Concomitant Medications – Part 1	This will not include Cohort C, Part 1.	SAC
1.29.	Safety	CM1	Summary of Concomitant Medications – Part 2		SAC
1.30.	Bystander Safety (Part 1, Cohort C)	CM1	Summary of Concomitant Medications – Bystander	Only for Cohort C, Part 1.	SAC
1.31.	Safety	NS1	Summary of Number of Subjects by Country and Site ID - Part 1	This will not include Cohort C, Part 1.	SAC
1.32.	Safety	NS1	Summary of Number of Subjects by Country and Site ID - Part 2		SAC
1.33.	Bystander Safety (Part 1, Cohort C)	NS1	Summary of Number of Subjects by Country and Site ID - Bystander	Only for Cohort C, Part 1.	SAC

11.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Part 1	The general layout of all the safety tables would follow mock shell SAFE_T4 for the column headers and order for both Part 1 and Part 2 tables. This will not include Cohort C, Part 1.	SAC
3.2.	Safety	AE1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Part 2		SAC
3.3.	Bystander Safety (Part 1, Cohort C)	AE1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Bystander		SAC
3.4.	Safety	AE1	Summary of Treatment Related Adverse Events by System Organ Class and Preferred Term – Part 1	This will not include Cohort C, Part 1.	SAC
3.5.	Safety	AE1	Summary of Treatment Related Adverse Events by System Organ Class and Preferred Term – Part 2		SAC
3.6.	Bystander Safety (Part 1, Cohort C)	AE1	Summary of Treatment Related Adverse Events by System Organ Class and Preferred Term – Bystander		SAC
3.7.	Safety	AE5A	Summary of Treatment Emergent Adverse Events by System Organ Class and Maximum Severity – Part 1	This will not include Cohort C, Part 1.	SAC
3.8.	Safety	AE5A	Summary of Treatment Emergent Adverse Events by System Organ Class and Maximum Severity – Part 2		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.	Bystander Safety (Part 1, Cohort C)	AE5A	Summary of Treatment Emergent Adverse Events by System Organ Class and Maximum Severity – Bystander		SAC
3.10.	Safety	AE5A	Summary of Treatment Related Adverse Events by System Organ Class and Maximum Severity – Part 1	This will not include Cohort C, Part 1.	SAC
3.11.	Safety	AE5A	Summary of Treatment Related Adverse Events by System Organ Class and Maximum Severity – Part 2		SAC
3.12.	Bystander Safety (Part 1, Cohort C)	AE5A	Summary of Treatment Related Adverse Events by System Organ Class and Maximum Severity – Bystander		SAC
3.13.	Safety	AE1	Summary of All Serious Adverse Events – Part 1	This will not include Cohort C, Part 1.	SAC
3.14.	Safety	AE1	Summary of All Serious Adverse Events – Part 2		SAC
3.15.	Bystander Safety (Part 1, Cohort C)	AE1	Summary of All Serious Adverse Events – Bystander	Only for Cohort C, Part 1.	SAC
3.16.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study – Part 1	This will not include Cohort C, Part 1.	SAC
3.17.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study – Part 2		SAC
3.18.	Bystander Safety (Part 1, Cohort C)	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study – Bystander		SAC
Laboratory: Chemistry					
3.19.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit – Part 1	This will not include Cohort C, Part 1.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.20.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit – Part 2		SAC
3.21.	Bystander Safety (Part 1, Cohort C)	LB1	Summary of Chemistry Changes from Baseline by Visit – Bystander	Only for Cohort C, Part 1.	SAC
3.22.	Safety	LB17	Summary of Clinical Chemistry Values by Potential Clinical Importance – Part 1	This will not include Cohort C, Part 1.	SAC
3.23.	Safety	LB17	Summary of Clinical Chemistry Values by Potential Clinical Importance – Part 2		SAC
3.24.	Bystander Safety (Part 1, Cohort C)	LB17	Summary of Clinical Chemistry Values by Potential Clinical Importance – Bystander	Only for Cohort C, Part 1.	SAC
Laboratory: Hematology					
3.25.	Safety	LB1	Summary of Haematology Changes from Baseline by Visit – Part 1	This will not include Cohort C, Part 1.	SAC
3.26.	Safety	LB1	Summary of Haematology Changes from Baseline by Visit – Part 2		SAC
3.27.	Bystander Safety (Part 1, Cohort C)	LB1	Summary of Haematology Changes from Baseline by Visit – Bystander	Only for Cohort C, Part 1.	SAC
3.28.	Safety	LB17	Summary of Hematology Values by Potential Clinical Importance – Part 1	This will not include Cohort C, Part 1.	SAC
3.29.	Safety	LB17	Summary of Hematology Values by Potential Clinical Importance – Part 2		SAC
3.30.	Bystander Safety (Part 1, Cohort C)	LB17	Summary of Hematology Values by Potential Clinical Importance – Bystander	Only for Cohort C, Part 1.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Coagulation					
3.31.	Safety	LB1	Summary of Coagulation Changes from Baseline by Visit – Part 1	Only for Cohorts B, Part 1.	SAC
3.32.	Safety	LB1	Summary of Coagulation Changes from Baseline by Visit – Part 2	Only for Cohorts B, Part 2.	SAC
Telemetry					
3.33.	Safety	Non-standard SAFE_T2	Summary of Telemetry Findings – Part 1	This will not include Cohort C, Part 1.	SAC
3.34.	Safety	Non-standard SAFE_T2	Summary of Telemetry Findings – Part 2		SAC
Spirometry					
3.35.	Safety	Non-standard SAFE_T3	Summary of Spirometry Data – Part 1	This will not include Cohort C, Part 1.	SAC
3.36.	Safety	Non-standard SAFE_T3	Summary of Spirometry Data – Part 2		SAC
ECG					
3.37.	Safety	EG1	Summary of ECG Findings by Visit – Part 1	This will not include Cohort C, Part 1.	SAC
3.38.	Safety	EG1	Summary of ECG Findings by Visit – Part 2		SAC
3.39.	Bystander Safety (Part 1, Cohort C)	EG1	Summary of ECG Findings by Visit – Bystander	Only for Cohort C, Part 1.	SAC
3.40.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit – Part 1	This will not include Cohort C, Part 1.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.41.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit – Part 2		SAC
3.42.	Bystander Safety (Part 1, Cohort C)	EG2	Summary of Change from Baseline in ECG Values by Visit – Bystander	Only for Cohort C, Part 1.	SAC
3.43.	Safety	Non-standard SAFE_T7	Frequency of Maximum ECG Values by PCI Category – Part 1	Compute and display Maximum by day.	SAC
3.44.	Safety	Non-standard SAFE_T7	Frequency of Maximum ECG Values by PCI Category – Part 2		SAC
3.45.	Bystander Safety (Part 1, Cohort C)	Non-standard SAFE_T7	Frequency of Maximum ECG Values by PCI Category – Bystander	Compute and display Maximum by day. Only for Cohort C, Part 1.	SAC
3.46.	Safety	Non-standard SAFE_T8	Frequency of Worst Change from Baseline Values of QTcB and QTcF by PCI Category – Part 1	Compute and display Maximum by day.	SAC
3.47.	Safety	Non-standard SAFE_T8	Frequency of Worst Change from Baseline Values of QTcB and QTcF by PCI Category – Part 2		SAC
3.48.	Bystander Safety (Part 1, Cohort C)	Non-standard SAFE_T8	Frequency of Worst Change from Baseline Values of QTcB and QTcF by PCI Category – Bystander	Compute and display Maximum by day. Only for Cohort C, Part 1.	SAC
Vital Signs					
3.49.	Safety	VS1	Summary of Vital Signs by Visit – Part 1	This will not include Cohort C, Part 1.	SAC
3.50.	Safety	VS1	Summary of Vital Signs by Visit – Part 2		SAC
3.51.	Bystander Safety (Part 1, Cohort C)	VS1	Summary of Vital Signs by Visit – Bystander	Only for Cohort C, Part 1.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.52.	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit – Part 1	This will not include Cohort C, Part 1.	SAC
3.53.	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit – Part 2		SAC
3.54.	Bystander Safety (Part 1, Cohort C)	VS1	Summary of Change from Baseline in Vital Signs by Visit – Bystander	Only for Cohort C, Part 1.	SAC
3.55.	Safety	VS2	Summary of Vital Signs by PCI – Part 1	This will not include Cohort C, Part 1.	SAC
3.56.	Safety	VS2	Summary of Vital Signs by PCI – Part 2		SAC
3.57.	Bystander Safety (Part 1, Cohort C)	VS2	Summary of Vital Signs by PCI - Bystander	Only for Cohort C, Part 1.	SAC
Exposure and Treatment Compliance					
3.58	Safety	Non-standard SAFE_T5	Summary of Extent of Exposure to Study Treatment – Part 1	This will not include Cohort C, Part 1.	SAC
3.59	Safety	Non-standard SAFE_T5	Summary of Extent of Exposure to Study Treatment – Part 2		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.60	Bystander Safety (Part 1, Cohort C)	Non-standard SAFE_T5	Summary of Extent of Exposure to Study Treatment – Bystander		SAC

11.10.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	Systemic PK	PK01	Summary of CCI15106 Plasma Pharmacokinetic Concentration-Time Data [ng/mL] by Cohort and Visit		SAC
4.2.	Systemic PK	PK01	Summary of plasma CCI15106 Concentration Data at Follow Up visit [ng/mL] by Cohort	This will not include Cohort C, Part 1.	SAC
4.3.	BAL PK	PK01	Summary of Lung ELF CCI15106 Concentration Data [ng/mL] by Cohort		SAC
PK Derived Parameters					
4.4.	Systemic PK	PK03	Summary of Derived CCI15106 Plasma Pharmacokinetic Parameters by Cohort and Visit	This will not include Cohort C, Part 1.	SAC
4.5.	Systemic PK	Non-Standard PK_T1	Summary of Assessment of Dose Proportionality (Part 1 and Part 2)	Only for Cohorts A, Part 1 and Part 2.	SAC
4.6.	Systemic PK	Non-Standard PK_T2	Summary of Assessment of Steady State (Part 1 and Part 2)	This will not include Cohort C, Part 1.	SAC
4.7.	Systemic PK	Non-Standard PK_T3	Summary of Assessment of Accumulation (Part 1 and Part 2)	For Cohort A, Cohort B, Part 1, and Cohort B, Part 2.	SAC

11.10.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Mean/Median Concentration Plots					
4.1.	Systemic PK	PK17	Mean (+SD) CCI15106 Plasma Concentration-Time Plot (Linear and Semi-log) (Part 1)	For Part 1, Overlay all cohorts and doses on same page, plot time upto 1) 72 hours post dose 2) 12 hours post dose [excluding the data after the 2nd dose following the BD doses for both 1] & 2] to see better the earlier timepoitns. 3) plot to overlay day 1 and day 14 after the 30mg BD	SAC
4.2.	Systemic PK	PK17	Mean (+SD) CCI15106 Plasma Concentration-Time Plot (Linear and Semi-log) (Part 2)	For Part 2, 1) overlay day 1 and day 14 for each cohort (doses); 2) overlay all cohorts (doses) on same page for each full PK sampling day, Day 1 and Day 14	SAC
4.3.	Systemic PK	PK17	Mean (+SD) CCI15106 Trough Plasma Concentration by study day (Linear and Semi-log) (Part 1 and Part 2)	Overlay the all cohorts on same page	SAC
4.4.	Systemic PK	PK17	Mean (+SD) CCI15106 Plasma Concentration-Time Plot by Cohort (to compare between HV and COPD) (Linear and Semi-log)	1) plot to overlay only data after 60mg SD (part 1 cohort A and part 2 cohort A) 2) plot to overlay data after 60mg BD (part 1 cohort B and part 2 cohort B), overlay all full PK sampling day (day 1 and day 14) as well as population on same page	SAC
4.5.	Systemic PK		Boxplot of pre-BAL plasma concentration by cohort (Linear and Semi-log)	Create a legend mentioning: Cohort B, Part 1 – Healthy Cohort B Part 2 - COPD	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.6.	BAL PK		Boxplot of Lung ELF CCI15106 concentration by cohort (Linear and Semi-log)		SAC
Individual Concentration Plots					
4.7.	Systemic PK	PK16a	Individual CCI15106 Plasma Concentration-Time Plot (Linear and Semi-log) (Part 1)	For Cohort A, overlay profiles after the 60mg, 120mg, and overlay profiles on day 1 and day 14 (after 30mg BD) on the same plot For Cohort B, overlay profiles on day 1 and day 14 on the same plot	SAC
4.8.	Systemic PK	PK16a	Individual CCI15106 Plasma Concentration-Time Plot (Linear and Semi-log) (Part 2)	For Cohort B, also overlay profiles on day 1 and day 14 on the same plot (ignore pre-dose PK from day 2 to day 12, and day 15)	SAC
4.9.	Systemic PK	Non-Standard PK_F1	CCI15106 trough Plasma Concentration versus Study Day (Part 1 and Part 2)	Use line plot, All pre-dose from Day 2 following the BD regimens onwards Linear scale only	SAC
4.10.	Systemic PK	Non-Standard PK_F1	CCI15106 Plasma Concentration at follow up visit versus Subject ID (Part 1 and Part 2)	Scatter Plot	SAC
4.11.	BAL PK	Non-Standard PK_F2	Scatter Plot of Lung Drug Concentration versus Subject ID (Part 1 and Part 2)	X Axis: Subject ID Y-Axis: ELF Values	SAC
4.12.	BAL PK	Non-Standard PK_F2	Scatter Plot of Lung Drug Concentration versus Plasma Drug Concentration (BAL cohorts in Part 1 and Part 2)	data for all patients on same page separate colours for healthy and COPD patients Cohorts B for both parts The template is similar to PK_F2, only change the X-axis to plasma drug concentration.	SAC

11.10.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomization					
1.	Safety	TA1	Listing of Randomized and Actual Treatments – Part 1	This will not include Cohort C, Part 1.	SAC
2.	Safety	TA1	Listing of Randomized and Actual Treatments – Part 2		SAC
Subject Disposition					
3.	Safety	ES2	Listing of Reasons for Study Withdrawal – Part 1	This will not include Cohort C, Part 1.	SAC
4.	Safety	ES2	Listing of Reasons for Study Withdrawal – Part 2		SAC
5.	Bystander Safety (Part 1, Cohort C)	ES2	Listing of Reasons for Study Withdrawal – Bystander	Only for Cohort C, Part 1.	SAC
6.	All Participants Screened	ES7	Listing of Reasons for Screen Failure – Part 1	This will not include Cohort C, Part 1.	SAC
7.	All Participants Screened	ES7	Listing of Reasons for Screen Failure – Part 2		SAC
8.	Bystander Safety (Part 1, Cohort C)	ES7	Listing of Reasons for Screen Failure – Bystander	Only for Cohort C, Part 1.	SAC
9.	Safety	SD2	Listing of Subjects with Study Drug Stopping Record – Part 1	This will not include Cohort C, Part 1.	SAC
10.	Safety	SD2	Listing of Subjects with Study Drug Stopping Record – Part 2		SAC
Protocol Deviations					
11.	Safety	DV2	Listing of Important Protocol Deviations – Part 1	This will not include Cohort C, Part 1.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	Safety	DV2	Listing of Important Protocol Deviations – Part 2		SAC
13.	Bystander Safety (Part 1, Cohort C)	DV2	Listing of Important Protocol Deviations – Bystander	Only for Cohort C, Part 1.	SAC
14.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations – Part 1	This will not include Cohort C, Part 1.	SAC
15.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations – Part 2		SAC
16.	Bystander Safety (Part 1, Cohort C)	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations – Bystander	Only for Cohort C, Part 1.	SAC
Demographic and Baseline Characteristics					
17.	Safety	DM2	Listing of Demographic Characteristics – Part 1	This will not include Cohort C, Part 1.	SAC
18.	Safety	DM2	Listing of Demographic Characteristics – Part 2		SAC
19.	Bystander Safety (Part 1, Cohort C)	DM2	Listing of Demographic Characteristics – Bystander	Only for Cohort C, Part 1.	SAC
20.	Safety	DM9	Listing of Race – Part 1	This will not include Cohort C, Part 1.	SAC
21.	Safety	DM9	Listing of Race – Part 2		SAC
22.	Bystander Safety (Part 1, Cohort C)	DM9	Listing of Race - Bystander	Only for Cohort C, Part 1.	SAC
Prior and Concomitant Medications					
23.	Safety	CP_CM3	Listing of Concomitant Medications – Part 1	This will not include Cohort C, Part 1.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
24.	Safety	CP_CM3	Listing of Concomitant Medications – Part 2		SAC
25.	Bystander Safety (Part 1, Cohort C)	CP_CM3	Listing of Concomitant Medications – Bystander	Only for Cohort C, Part 1.	SAC
Exposure and Treatment Compliance					
26.	Safety	EX4	Listing of Exposure Data – Part 1	This will not include Cohort C, Part 1.	SAC
27.	Safety	EX4	Listing of Exposure Data – Part 2		SAC
28.	Bystander Safety (Part 1, Cohort C)	EX4	Listing of Exposure Data – Part 2		SAC
Adverse Events					
29.	Safety	AE9CP	Listing of All Adverse Events – Part 1	This will not include Cohort C, Part 1.	SAC
30.	Safety	AE9CP	Listing of All Adverse Events – Part 2		SAC
31.	Bystander Safety (Part 1, Cohort C)	AE9CP	Listing of All Adverse Events – Bystander	Only for Cohort C, Part 1.	SAC
32.	Safety	AE9CP	Listing of Serious Adverse Events – Part 1	This will not include Cohort C, Part 1.	SAC
33.	Safety	AE9CP	Listing of Serious Adverse Events – Part 2	This will not include Cohort C, Part 1.	SAC
34.	Bystander Safety (Part 1, Cohort C)	AE9CP	Listing of Serious Adverse Events – Bystander	Only for Cohort C, Part 1.	SAC
35.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment – Part 1	This will not include Cohort C, Part 1.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
36.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment – Part 2		SAC
37.	Bystander Safety (Part 1, Cohort C)	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment – Bystander	Only for Cohort C, Part 1.	SAC
All Laboratory					
38.	Safety	LB5	Listing of Haematology Laboratory Data – Part 1	This will not include Cohort C, Part 1.	SAC
39.	Safety	LB5	Listing of Haematology Laboratory Data – Part 2		SAC
40.	Bystander Safety (Part 1, Cohort C)	LB5	Listing of Haematology Laboratory Data – Bystander	Only for Cohort C, Part 1.	SAC
41.	Safety	LB5	Listing of Clinical Chemistry Laboratory Data – Part 1	This will not include Cohort C, Part 1.	SAC
42.	Safety	LB5	Listing of Clinical Chemistry Laboratory Data – Part 2		SAC
43.	Bystander Safety (Part 1, Cohort C)	LB5	Listing of Clinical Chemistry Laboratory Data – Bystander	Only for Cohort C, Part 1.	SAC
44.	Safety	LB5	Listing of Coagulation Laboratory Data – Part 1	This will not include Cohort A and Cohort C, Part 1.	SAC
45.	Safety	LB5	Listing of Coagulation Laboratory Data – Part 2	Only for Cohort B, Part 2.	SAC
46.	Safety	UR2a	Listing of Urinalysis Data – Part 1	This will not include Cohort C, Part 1.	SAC
47.	Safety	UR2a	Listing of Urinalysis Data – Part 2		SAC
48.	Bystander Safety (Part 1, Cohort C)	UR2a	Listing of Urinalysis Data – Bystander	Only for Cohort C, Part 1.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
49.	Safety	EG3	Listing of ECG Values – Part 1	This will not include Cohort C, Part 1.	SAC
50.	Safety	EG3	Listing of ECG Values – Part 2		SAC
51.	Bystander Safety (Part 1, Cohort C)	EG3	Listing of ECG Values - Bystander	Only for Cohort C, Part 1.	SAC
52.	Safety	EG5	Listing of ECG Findings – Part 1	This will not include Cohort C, Part 1.	SAC
53.	Safety	EG5	Listing of ECG Findings – Part 2		SAC
54.	Bystander Safety (Part 1, Cohort C)	EG5	Listing of ECG Findings – Bystander	Only for Cohort C, Part 1.	SAC
55.	Safety	EG3	Listing of All ECG Values for Subjects with Any Values of Potential Clinical Importance – Part 1	This will not include Cohort C, Part 1.	SAC
56.	Safety	EG3	Listing of All ECG Values for Subjects with Any Values of Potential Clinical Importance – Part 2		SAC
57.	Bystander Safety (Part 1, Cohort C)	EG3	Listing of All ECG Values for Subjects with Any Values of Potential Clinical Importance – Bystander	Only for Cohort C, Part 1.	SAC
Spirometry					
58.	Safety	Non-Standard SAFE_L1	Listing of Spirometry Values – Part 1	This will not include Cohort C, Part 1.	SAC
59.	Safety	Non-Standard SAFE_L1	Listing of Spirometry Values – Part 2		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Telemetry					
60.	Safety	Non-Standard SAFE_L2	Listing of Telemetry Values – Part 1	This will not include Cohort C, Part 1.	SAC
61.	Safety	Non-Standard SAFE_L2	Listing of Telemetry Values – Part 1		SAC
Vital Signs					
62.	Safety	VS4	Listing of Vital Signs – Part 1	This will not include Cohort C, Part 1.	SAC
63.	Safety	VS4	Listing of Vital Signs – Part 2		SAC
64.	Bystander Safety (Part 1, Cohort C)	VS4	Listing of Vital Signs - Bystander	Only for Cohort C, Part 1.	SAC
65.	Safety	VS4	Listing of All Vital Signs for Subjects with Any values of Potential Clinical Importance – Part 1	This will not include Cohort C, Part 1.	SAC
66.	Safety	VS4	Listing of All Vital Signs for Subjects with Any values of Potential Clinical Importance – Part 2		SAC
67.	Bystander Safety (Part 1, Cohort C)	VS4	Listing of All Vital Signs for Subjects with Any values of Potential Clinical Importance – Bystander	Only for Cohort C, Part 1.	SAC

11.10.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetics					
68.	Systemic PK	PK08	Listing of CCI15106 Plasma Pharmacokinetic Concentration-Time Data by Cohort and Study Day		SAC
69.	Systemic PK	PK14	Listing of Derived CCI15106 Plasma Pharmacokinetic Parameters Cohort and Study Day		SAC
Safety					
70.	Safety	MH2	Listing of Medical Conditions – Part 1	This will not include Cohort C, Part 1.	SAC
71.	Safety	MH2	Listing of Medical Conditions – Part 2		SAC
72.	Bystander Safety (Part 1, Cohort C)	MH2	Listing of Medical Conditions – Bystander	Only for Cohort C, Part 1.	SAC
73.	Safety	SU2	Listing of Substance Use – Part 1	This will not include Cohort C, Part 1.	SAC
74.	Safety	SU2	Listing of Substance Use – Part 2		SAC
75.	Bystander Safety (Part 1, Cohort C)	SU2	Listing of Substance Use – Bystander	Only for Cohort C, Part 1.	SAC
76.	All Screened Population	IE4	Listing of Study Eligibility – Part 1		SAC
77.	All Screened Population	IE4	Listing of Study Eligibility – Part 2		SAC

11.11. Appendix 11: Example Mock Shells for Data Displays

Example SAFE_T1
Protocol: 205822
Population: Safety

Table 1.61
Summary of Demographic Characteristics – Part 1

	Cohort A (N=6)	Cohort B (N=12)	Placebo (N=4)
Sex			
n	6	12	4
Male	6 (100%)	12 (100%)	4 (100%)
Female	0	0	0
Age (y)			
n	6	12	4
Mean	39.8	35.4	43.3
SD	9.75	11.18	9.54
Median	40.0	31.0	44.0
Min.	25	25	32
Max.	52	57	53
Ethnicity			
n	6	12	4
HISPANIC OR LATINO	0	1 (8%)	0
NOT HISPANIC OR LATINO	6 (100%)	11 (92%)	4 (100%)
Race			
n	6	12	4
WHITE - WHITE/CAUCASIAN/EUROPEAN HERITAGE	5 (83%)	9 (75%)	4 (100%)
AFRICAN AMERICAN/AFRICAN HERITAGE	1 (17%)	2 (17%)	0
Multiple	0	1 (8%)	0
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.			

Example SAFE_T2
Protocol: 205822

Population: Safety

Table X
Summary of Telemetry Findings – Part 1

	Cohort A (N=157)		Cohort B (N=160)		Placebo (N=160)	
Time Period 1						
n	156		160		160	
Normal	81	(52%)	90	(56%)	90	(56%)
Abnormal, not clinically significant	75	(48%)	69	(43%)	69	(43%)
Abnormal, clinically significant	0		1	(<1%)	1	(<1%)
Time Period 2						
n	117		123		123	
Normal	50	(43%)	67	(54%)	67	(54%)
Abnormal, not clinically significant	64	(55%)	55	(45%)	55	(45%)
Abnormal, clinically significant	2	(2%)	1	(<1%)	1	(<1%)

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Example SAFE_T3
Protocol: 205822

Population: Safety

Table X
Summary of Spirometry Results – Part 1

	CCI15106 60mg SD (N=157)	CCI15106 120mg SD (N=160)	CCI15106 30mg BID (N=160)	Placebo (N=160)
Time Period 1				
n	156	160		160
%Predicted FEV1	52%	56%		56%
%Predicted FVC	55%	45%		45%
Time Period 2				
n	117	123		123
%Predicted FEV1	52%	56%		56%
%Predicted FVC	55%	45%		45%
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% Predicted FEV1 = (Max FEV1/Predicted Normal FEV1)x100
% Predicted FVC = (Max FVC/Predicted Normal FVC)x100

Example SAFE_T4
Protocol: 205822
Population: Safety

Table 3.51
Summary of All Serious Adverse Events - Part1

System Organ Class Preferred Term	CCI15106 60 mg SD	CCI15106 120 mg SD	CCI15106 30 mg BID	CCI15106 60 mg BID	Placebo
ANY EVENT	1 (17%)	0	4 (67%)	9 (75%)	1 (25%)
Blood and lymphatic system disorders					
Any event	0	0	0	1 (8%)	0
Lymphadenopathy	0	0	0	1 (8%)	0
Gastrointestinal disorders					
Any event	0	0	1 (17%)	2 (17%)	0
Diarrhoea	0	0	0	1 (8%)	0
Mouth ulceration	0	0	1 (17%)	0	0
Vomiting	0	0	0	2 (17%)	0
General disorders and administration site conditions					
Any event	0	0	0	5 (42%)	0
Asthenia	0	0	0	1 (8%)	0
Chest pain	0	0	0	1 (8%)	0
Feeling hot	0	0	0	2 (17%)	0
Influenza like illness	0	0	0	1 (8%)	0
Malaise	0	0	0	3 (25%)	0
Infections and infestations					
Any event	0	0	1 (17%)	1 (8%)	0
Nasopharyngitis	0	0	1 (17%)	0	0
Upper respiratory tract infection	0	0	0	1 (8%)	0
Injury, poisoning and procedural complications					
.....					

Example SAFE_T5
Protocol: 205822
Population: Safety

Table X
Summary of Extent of Exposure to Study Treatment - Part 1

	Period		CCI15106 SD 60mg(HV) (N=6)	CCI15106 SD 120mg(HV) (N=6)	CCI15106 BID 30mg(HV) (N=6)	CCI15106 BID 60mg(HV) (N=12)	Placebo(HV) (N=4)
Time on Study Treatment (days) [1]	PERIOD 1	n	x	x	x	xx	x
		Mean	x.x	x	x	xx.x	xx.x
		SD	x.xx	x	x	x.xx	xx.xx
		Median	x.x	x	x	xx.x	xx.x
		Min.	x	x	x	xx	x
		Max.	x	x	x	xx	xx
	PERIOD 2	n	x	x	x	x	x
		Mean	x	x.x	x	x	x.x
		SD	x	x.xx	x	x	x.xx
		Median	x	x.x	x	x	x.x
		Min.	x	x	x	x	x
		Max.	x	x	x	x	x
	PERIOD 3	n	x	x	x	x	x
		Mean	x	x	xx.x	x	xx.x
		SD	x	x	x.xx	x	x.xx
		Median	x	x	xx.x	x	xx.x
		Min.	x	x	xx	x	xx
		Max.	x	x	xx	x	xx
Subject Daily Dose (mg) [2]	PERIOD 1	n	x	x	x	xx	x
		Mean	xx.x	x	x	xx.x	x.x
		SD	x.xx	x	x	x.xx	x.xx

		Median	xx.x	x	x	xx.x	x.x
		Min.	xx	x	x	xx	x
		Max.	xx	x	x	xx	x
	PERIOD 2	n	x	x	x	x	x
		Mean	x	xx.x	x	x	x.x
		SD	x	x.xx	x	x	x.xx
		Median	x	xx.x	x	x	x.x
		Min.	x	x	x	x	x
		Max.	x	xx	x	x	x
	PERIOD 3	n	x	x	x	x	x
		Mean	x	x	xx.x	x	x.x
		SD	x	x	x.xx	x	x.xx
		Median	x	x	x.x	x	x.x
		Min.	x	x	xx	x	x
		Max.	x	x	xx	x	x
Cumulative Actual Dose (mg)	PERIOD 1	n	x	x	x	xx	x
		Mean	xx.x	x	x	x.x	x.x
		SD	x.xx	x	x	x.xx	x.xx
		Median	xx.x	x	x	x.x	x.x
		Min.	x	x	x	xx	x
		Max.	xx	x	x	xx	x
	PERIOD 2	n	x	x	x	x	x
		Mean	x	x.x	x	x	x.x
		SD	x	x.xx	x	x	x.xx
		Median	x	x.x	x	x	x.x
		Min.	x	xx	x	x	x
		Max.	x	xx	x	x	x
	PERIOD 3	n	x	x	x	x	x
		Mean	x	x	xx.x	x	x.x
		SD	x	x	x.x	x	x.xx
		Median	x	x	xx.x	x	x.x
		Min.	x	x	xx	x	x
		Max.	x	x	xx	x	x

Note: [1]The time on study drug does not exclude dose interruptions.
[2]The subject daily dose (the cumulative actual dose divide by the duration of exposure) is calculated for each subject first and the summary statistics are calculated based on the subject average daily dose.

Example SAFE_T6
Protocol: 205822
Population: Safety

Table X
Frequency of Worst Change from Baseline Values of QTcB and QTcF by PCI Category

ECG Test	Visit	Category	Placebo (N=12)	CCI15106-CFI - 1 capsule - Single Dose (N=6)	CCI15106-CFI - 2 capsules - Single Dose (N=6)
QTcB Interval, Aggregate (msec)	BASELINE	n	12	6	6
	Worst Post Baseline	n	12	6	6
		Increase<=30	12(100%)	6(100%)	6(100%)
		30<Increase<=60	0	0	0
		Increase>60	0	0	0
QTcF Interval, Aggregate (msec)	Baseline	n	12	6	6
	Worst Post Baseline	n	12	6	6
		Increase<=30	12(100%)	6(100%)	6(100%)
		30<Increase<=60	0	0	0
		Increase>60	0	0	0

Example SAFE_T7
Protocol: 205822
Population: Safety

Table X
Frequency of Maximum ECG Values by PCI Category

ECG Test	Visit	Category	Placebo (N=12)	CCI15106-CFI - 1 capsule - Single Dose (N=6)	CCI15106-CFI - 2 capsules - Single Dose (N=6)
PR Interval, Aggregate (msec)	BASELINE	n	12	6	6
		Value<110	0	0	0
		110<=Value<=220	12(100%)	6(100%)	6(100%)
		Value>220	0	0	0
	WORST POST BASELINE	n	12	6	6
		Value<110	0	0	0
		110<=Value<=220	12(100%)	6(100%)	6(100%)
		Value>220	0	0	0
QRS Duration, Aggregate (msec)	SCREENING	n	12	6	6
		Value<75	0	0	0
		75<=Value<=110	11(92%)	6(100%)	6(100%)
		Value>110	1(8%)	0	0
	WORST POST BASELINE	n	12	6	6
		Value<75	0	0	0
		75<=Value<=110	11(92%)	6(100%)	6(100%)
		Value>110	1(8%)	0	0
QTcB Interval, Aggregate (msec)	SCREENING	n	12	6	6

	Value<=450	11(92%)	6(100%)	6(100%)
	450<Value<480	1(8%)	0	0
	480<=Value<500	0	0	0
	Value>=500	0	0	0
WORST POST	n	12	6	6
BASELINE	Value<=450	11(92%)	5(83%)	6(100%)
	450<Value<480	1(8%)	1(17%)	0
	480<=Value<500	0	0	0
	Value>=500	0	0	0

Repeat for QTcF

Note: Percentages may not add up to 100 for QRS Duration and PR Interval as there is a possibility of a patient being counted under both low and high categories.

Example : PK_T1
Protocol : 205822
Population : Systemic PK

Table 3.1.13
Summary of Assessment of Dose Proportionality (Part 1 and Part 2)

Parameter	Study Day	n	Slope			Intercept			Coefficient of Determination
			Estimate	SE	90% CI	Estimate	SE	90% CI	

Note(s): CI = confidence interval; SE = standard error.
Source: SAS Output XX

Example : PK_T2
Protocol : 205822
Population : Systemic PK

Table 3.1.16
Summary of Assessment of Steady State (Part 1 and Part 2)

		Slope		
Parameter	n	Estimate	SE	90% CI

Note(s): CI = confidence interval; SE = standard error.
Source: SAS Output XX

Example : PK_T3
Protocol : 205822
Population : Systemic PK

Table 3.1.17
Summary of Assessment of Accumulation (Part 1 and Part 2)

Dose Level	Parameter (unit)	Study Day	n	Geometric LS Mean	Geometric LS Mean 95% CI	Ratio of Geometric Means	90% CI	p-value

Note(s): LS = least squares; CI = confidence interval.
Accumulation was assessed using a linear mixed effects model with day as a fixed effect and subject as a random effect.

Source: SAS Output XX

Example : SAFE_L1 Page 1 of n
Protocol : 205822
Population : Safety (Part 1)

Listing 59
Listing of Spirometry Values – Part 1

			Spirometry						
Cohort / Subj.	Visit / Study Day	Visit date	Test	Time of first exhalation	Reading 1	Reading 2	Reading 3	Highest reading	%predicted

Source: SAS Output XX

Example : SAFE_L2
Protocol : 205822
Population : Safety (Part 1)

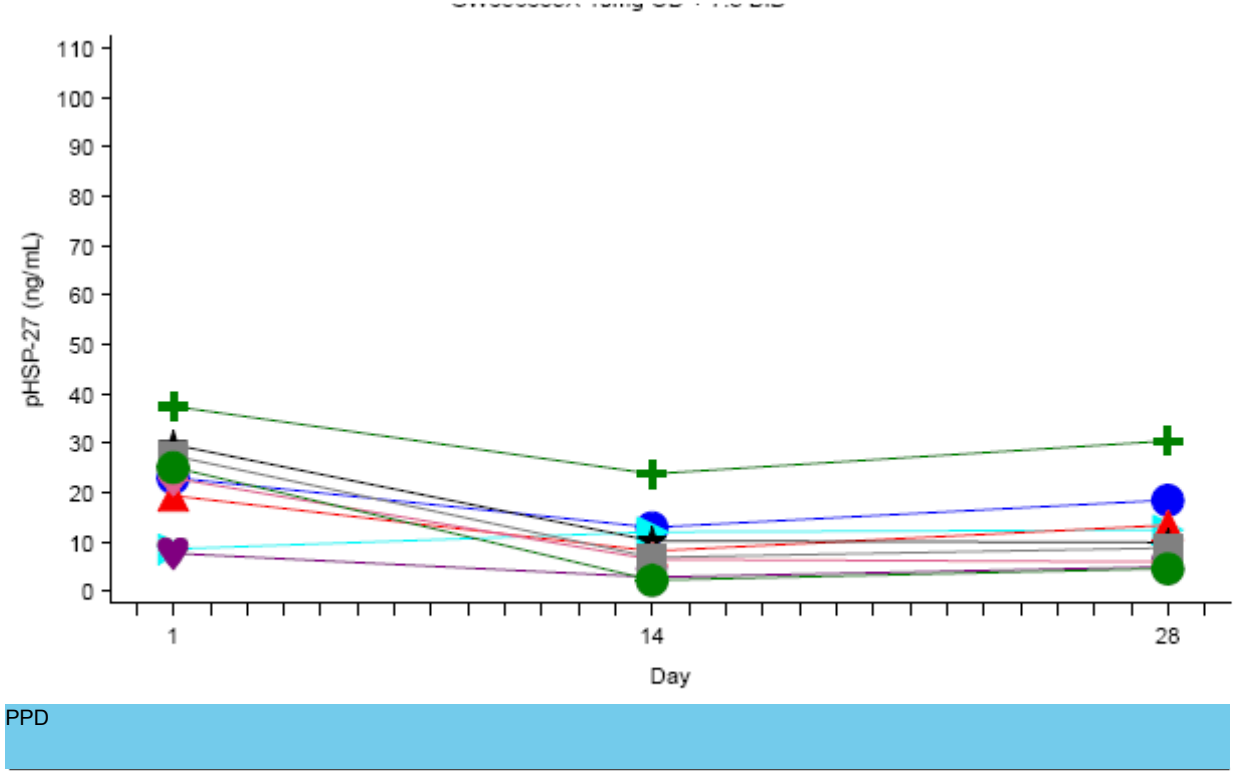
Listing 62
Listing of Telemetry Values – Part 1

			Telemetry				
Cohort / Subj.	Visit / Study Day	Visit date	Date started	Time started	Date stopped	Time stopped	Telemetry Result

Example : PK_F1

Protocol : 205822
Population : Systemic PK

Figure xxx: CCI15106 trough Plasma Concentration versus Study Day (Part 2)



Example : PK_F2

Protocol : 205822
Population : BAL PK

Figure XXX Scatter Plot of Lung Drug Concentration versus Subject ID (Part 1 and Part 2)