TITLE PAGE

Protocol 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.

Protocol Number: 205822

Short Title: Study of safety and drug levels of CCI15106 inhalation powder in healthy adults and adults with moderate chronic obstructive pulmonary disease. Study of CCI15106 levels in people standing near the person inhaling the drug.

Compound Number: CCI15106

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

20 APR 2017

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1. SYNOPSIS

Protocol 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). A concomitant study to evaluate environmental and healthy bystander exposure levels during dosing.

Short Title: Study of safety and drug levels of CCI15106 inhalation powder in healthy adults and adults with moderate chronic obstructive pulmonary disease. Study of CCI15106 levels in people standing near the person inhaling the drug.

Rationale:

This study is the first administration of CCI15106 inhalation powder hard capsules (CCI15106:polyvinyl alcohol 99:1 w/w 0.9x1 μm cylinder shape crystalline particles presented in capsules, from here on referred to as CCI15106-IP) to humans. This study will evaluate the safety, tolerability, and lung and systemic pharmacokinetics (PK) of CCI15106-IP delivered using Monodose RS01 device in healthy participants and in participants with moderate COPD.

The intention of this study is to provide sufficient confidence in the safety of the molecule delivered by inhalation to inform progression to further repeat dose and proof of concept studies.

A different formulation of CCI15106 (CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape particles) has been previously administered to humans in the first time in human study (FTiH) 202031.

Marketed CCI15106 is classified as teratogenic and is contra-indicated in women who are pregnant and in male partners of pregnant women and it is important to understand whether bystanders may be exposed to CCI15106 when it is used by patients in a dry powder, inhaled form. This study will evaluate the levels of CCI15106 in room air and in the plasma of bystanders. The study aims to replicate the real-life scenarios of dosing as close as possible. Real-life scenarios may include dosing of multiple patients in a single room in a nursing home or dosing of a single patient at home. A realistic worst-case scenario for bystanders is dosing of multiple patients in a standard size room in a nursing home.

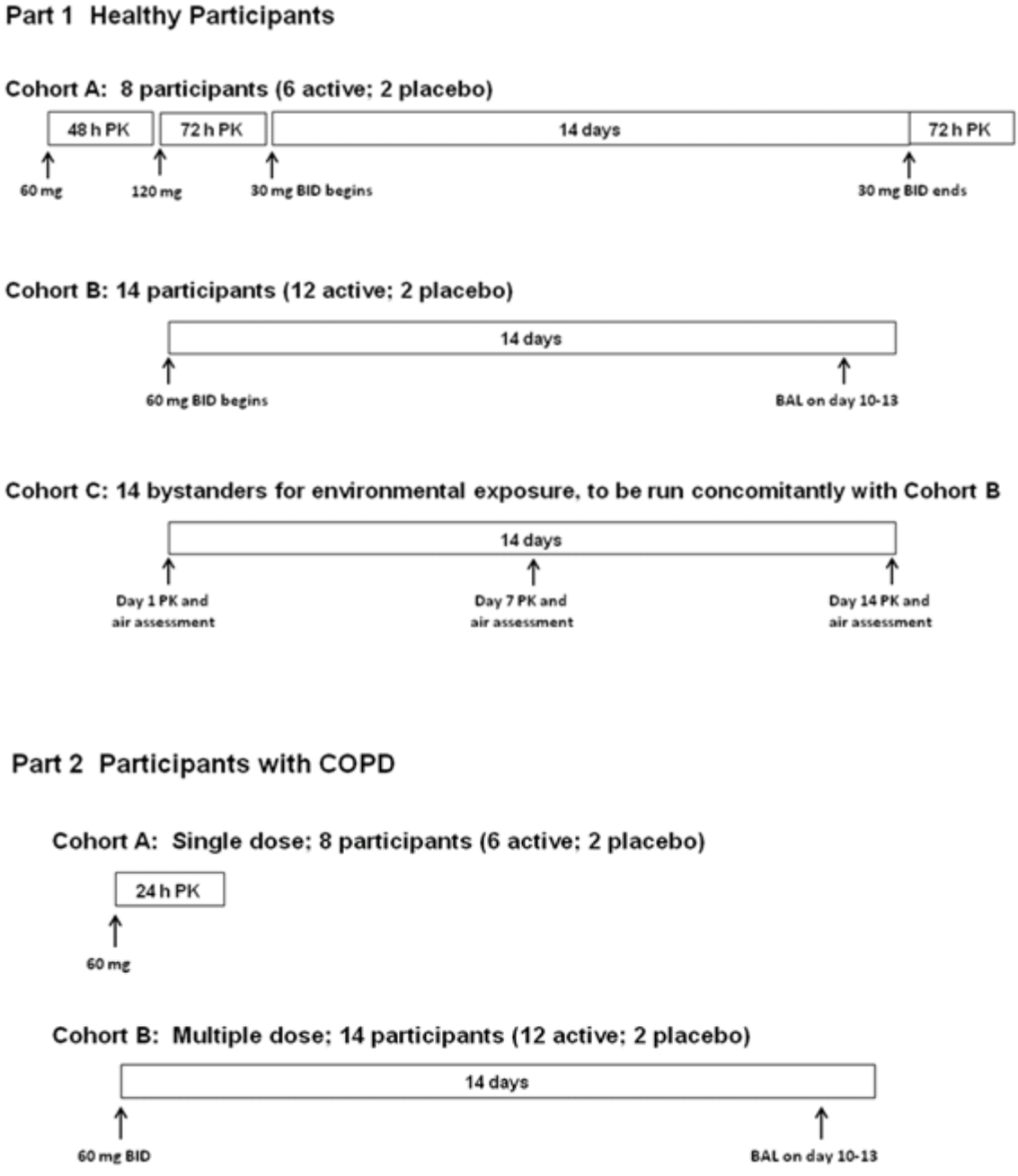
Objectives and Endpoints:

Objectives	Endpoints
Primary	
• 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 CCI15106 during self-administered dosing of participants.	• Concentration of CCI15106 in plasma of bystanders 15-20 minutes (min) after dosing (at predicted tmax) and 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	
• 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.
• 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.

Overall Design:

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.

Study schematic is presented below:



Number of Participants:

Approximately 36 healthy participants and approximately 22 participants with COPD will be randomized in this study for dosing.

Treatment Groups and Duration:

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. Doses administered and treatment duration for participants in each specific cohort will be as defined in the study schematic above. Participants will return for the follow-up visit approximately 30 days after discharge.

The total study duration will be approximately 82 days for Cohort A Part 1; approximately 75 days for Cohort B Part 1 and Cohort C Part 1; approximately 77 days for Cohort A Part 2; and approximately 90 days for Cohort B Part 2.

2. SCHEDULE OF ACTIVITIES (SOA)

If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order pre-dose:

1. Telemetry start
2. spirometry
3. 12-lead electrocardiogram (ECG)
4. vital signs
5. blood draws

and in the following order post-dose:

1. 12-lead ECG
2. vital signs
3. blood draws
4. spirometry

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Any change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GlaxoSmithKline (GSK) study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

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	XXX	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

3. INTRODUCTION

3.1. Study Rationale

This study is the first administration of CCI15106-IP (CCI15106:polyvinyl alcohol 99:1 w/w 0.9x1 μm cylinder shape crystalline particles produced using Liquidia's Particle Replication In Non-wetting Templates [PRINT] technology) to humans. The study will evaluate the safety, tolerability, and lung and systemic pharmacokinetics (PK) of single and repeat ascending doses of CCI15106-IP delivered by inhalation in healthy participants and in participants with moderate chronic obstructive pulmonary disease (COPD). The study will use a Monodose RS01 device for drug delivery by inhalation.

A different formulation of CCI15106 (CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape particles) has been previously administered to humans in the first time in human study (FTiH) 202031. That formulation was referred to as CCI15106 capsules for inhalation (CCI15106-CFI).

The intention of this study is to provide sufficient information regarding the safety of the molecule to inform progression to further repeat dose and proof of concept studies. The dose range proposed in this study is based on a starting dose previously investigated with the different formulation in the FTiH and escalating to a dose not to exceed the the no observed adverse effect level (NOAEL) in the most sensitive species (Section 5.5).

The other intention of this study is to investigate the level of CCI15106 that will be released into the air and may be found in the blood of the bystanders around participants inhaling CCI15106-IP.

3.2. Background

CCI15106 is ribavirin, which is a generic, broad spectrum nucleoside antiviral, discovered in the early 1970s, with both clinical and nonclinical data available, which is approved and used for oral administration in the treatment of chronic hepatitis C virus. It is also approved for respiratory syncytial virus (RSV) bronchiolitis by pulmonary inhalation in paediatric patients. CCI15106 is active versus RSV, human metapneumovirus, parainfluenza, influenza, adenovirus, and human rhinovirus (HRV), although HRV is 4-15-fold less susceptible than the others (GlaxoSmithKline Document Number 2015N249287_00). Based upon published data coronaviruses could also be susceptible without co-administration of interferon [Kurai, 2013, Morgenstern, 2005]. CCI15106 is not considered to be the active form, rather it is actively transported into target organs/cells and converted to ribavirin triphosphate (RTP) believed to be the active form against the viruses [Thomas, 2012]. The major limitation of the use of CCI15106 is hemolytic anemia due to accumulation of RTP in red blood cells and teratogenicity.

Liquidia's Particle Replication In Non-wetting Templates (PRINT) technology uses lithographic etching processes to produce particles with highly defined size and shape. CCI15106 plus the excipient, polyvinyl alcohol, are combined in a ratio of 99:1 w:w using Liquidia's technology to produce CCI15106-IP, a highly dispersible powder of uniform 0.9x1 μm cylinder shape particles which has afforded a 24-fold increase in lung

concentration at maximum (Cmax) relative to micronised CCI15106:Lactose formulation in a solid dose inhaled rat PK study (GlaxoSmithKline Document Number 2015N242219_00 [N20691-39]). The size and uniformity of the Liquidia particles provides an opportunity to improve the efficiency of CCI15106 administration to the lung while limiting systemic exposure that has the potential to limit hemolytic anemia and teratogenicity.

Acute exacerbations of COPD are a significant cause of morbidity and mortality [Vestbo, 2013; Kurai, 2013]. Multiple studies show that viral and/or bacterial respiratory infections are the most commonly associated triggers of COPD exacerbations. Respiratory viruses are detected in 20-60% of acute exacerbations of COPD [Kurai, 2013].

High efficiency lung delivery of broad spectrum CCI15106-containing engineered particles will establish an antiviral state in the lung. This has the potential to prevent the establishment or spread of the virus in the lower respiratory tract from the upper respiratory tract and/or increase the viral clearance translating to prevention of an exacerbation or a decrease in exacerbation severity and/or duration.

CCI15106 has been previously administered to humans in a different formulation, CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape PRINT particles (CCI15106 capsules for inhalation, referred to as CCI15106-CFI). Forty eight healthy participants have been administered a single dose of that formulation in one FTiH study 202031 and 12 participants received placebo. This study was planned as a double-blind (sponsor unblind), randomized, placebo-controlled, single and repeat escalating dose study to investigate the safety, tolerability, and pharmacokinetics of CCI15106-CFI in healthy participants and participants with moderate chronic obstructive pulmonary disease (COPD). In the single dose part of the study, CCI15106-CFI was administered by inhalation using Modified Air Inlet Rotahaler device at doses of 7.5 mg, 15 mg, 30 mg, and 60 mg. Overall, no clinically meaningful changes in vital signs or electrocardiograms (ECGs) were observed. There were no serious adverse events (SAEs) reported. Of the 60 subjects in the study, 25 reported adverse events (AEs) and 12 reported possibly drug-related AEs. The most common AEs were headache and cough (11 and 3 subjects, respectively). The comprehensive review conducted after single dose cohorts revealed acceptable safety profile, but lung epithelial lining fluid (ELF) levels of CCI15106 measured with 30 or 60 mg dose were below the levels predicted by pre-clinical evaluations and the increase in dose from 30 to 60 mg did not appear to result in a substantial increase in the lung concentration. Development of the CCI15106-CFI formulation was terminated before dosing repeat dose or COPD cohorts as a new formulation (CCI15106-IP) was developed that has higher ratio of active pharmaceutical ingredient to inactive ingredients per unit of powder and allows achieving the same dose in 1 capsule instead of 4. This is expected to lead to a higher lung ELF Cmax. The decision to terminate was not based on safety data.

Marketed formulations of CCI15106 are classified as teratogenic and is contra-indicated in women who are pregnant and in male partners of pregnant women. Currently approved aerosolised forms of CCI15106 are recommended to be administered in a negative pressure environment [Virazole USPI 2013]. It is important to understand whether bystanders may be exposed to CCI15106 when it is used by patients in a dry

powder, inhaled form. The most likely route of exposure of bystanders will be through inhalation of powder released during dosing. The study aims to replicate the real-life scenarios of dosing as close as possible. Real-life scenarios may include dosing of multiple patients in a single room in a nursing home or dosing of a single patient at home. A realistic worst-case scenario is dosing of multiple patients in a standard size room in a nursing home.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of CCI15106 may be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2015N250735_00]. Information specific to the approved formulations of CCI15106 can be found in the labels for oral CCI15106 approved for the treatment of hepatitis C and CCI15106 nebulizer approved for the treatment of respiratory syncytial infections in children [Rebetol SPC 2009; Virazole USPI 2013].

Based on pre-clinical safety assessment studies summarized in the IB and the clinical experience with CCI15106-CFI, as well as oral and inhaled (nebulised) CCI15106, the following clinical parameters will be monitored throughout the study in order to better characterize the safety and tolerability of CCI15106-IP (Section 3.3.1). Refer to SoA, Section 2, for the timing of all clinical assessments.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product, CCI15106-IP		
Teratogenicity and embryocidal effects	CCI15106 showed embryocidal and teratogenic effects in animals. The no observed adverse effect level (NOAEL) in oral embryofetal development studies in rats and rabbits was 0.3 mg/kg/day, considerably lower than the maximum proposed inhaled clinical dose of 120 mg/day CCI15106 (0.02-fold to 0.05-fold based on mg/m^2). In addition, human seminal fluid contains ~2-fold higher concentrations of CCI15106 compared to serum. There are limited data from the use of CCI15106 in pregnant women (5 cases of measles-pneumonia and 1 case of influenza-pneumonia)) [Virazole SPC, 2014]. Four pregnancies were completed and resulted in the birth of healthy children. A further 7 cases are known in which nurses administered Virazole dry substance during pregnancy (n=6) or just before conception (n=1). In 6 cases, healthy children were born. In one case, a chromosomal translocation was reported with mild developmental delay [Virazole SPC, 2014].	Women of child-bearing potential and male partners of women who are pregnant or breastfeeding will be excluded. Effective contraception for female partners of male participants will be required up to 7 months post study. Any pregnancies that occur during the study or up to 7 months post study will be reported by the investigator to the pregnancy registry. The informed consent form will describe these reproductive risks, as well as the risk to female partners of male participants. Systemic exposure for the target clinical dose of CCI15106 is expected to be lower than exposure for currently available oral and nebulized CCI15106. The maximum inhaled total daily single dose of CCI15106 in Protocol 205822 will be 120 mg and the maximum inhaled multiple daily doses will be 60 mg twice daily (BID). These proposed maximum clinical doses are significantly lower than the currently approved doses of CCI15106 (800-1400 mg for Copegus and Rebetol and 6 g for inhaled Virazole).
Mutagenicity	CCI15106 is clastogenic in vitro and in vivo but is Ames negative. The pattern of genotoxicity is consistent with that reported for other nucleoside analogues. Point of departure modelling (an accepted method of risk assessment for nucleoside analogues) indicates a negligible genotoxic concern. CCI15106 was not tumorigenic in lifetime rodent studies at doses up to 75 mg/kg/day in the mouse and 40 mg/kg/day in the rat (~3-fold the	The data indicate a negligible genotoxic concern, which is mitigated by the lower expected systemic and lung exposure compared with currently available oral and nebulized CCI15106 and shorter duration of clinical treatment (≤ 14 days). The maximum inhaled single total daily dose of 120 mg or multiple total daily doses of 60 mg

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	maximum proposed inhaled clinical dose of CCI15106-IP based on mg/m^2), or in the transgenic p53(±) mouse model at doses of up to 300 mg/kg/day.	BID for Protocol 205822 are significantly lower than the currently approved doses of CCI15106 (800-1400mg for Copegus and Rebetol and 6 g for inhaled Virazole).
Increased exposure in participants with severe renal impairment	As CCI15106/ribavirin is substantially excreted by the kidneys, exposure may be increased in those with pre-existing renal impairment CCI15106 is contraindicated in patients with chronic renal failure, patients with creatinine clearance < 50mL/min, and/or on hemodialysis [Rebetol SPC, 2009] However, the Copegus labels allow dose modifications for patients with CrCl <50 mL/min [Copegus USPI, 2015; Copegus SPC, 2015].	The maximum inhaled single total daily dose of 120 mg or multiple total daily doses of 60 mg BID proposed for Protocol 205822 are significantly lower than the currently approved doses of CCI15106 (800-1400mg for Copegus and Rebetol and 6 g for inhaled Virazole). COPD patients with impaired renal function (eGFR <30 cc/min, using CKD-EPI equation) will be excluded and renal function will be monitored.
Pulmonary effects	**GSK's formulations:** In toxicity studies conducted by GSK, no adverse pulmonary toxicity was observed following administration of either CCI15106:trehalose:trileucine particles or CCI15106-IP in GSK studies of 28 day duration at dose levels of ≤32.5 mg/kg in rat or ≤34.2 mg/kg in dog. The deposited lung doses at the NOAELs on the 28 day studies using CCI15106-IP were estimated 6- to 8-fold higher than in human at the maximum proposed clinical administration of CCI15106-IP of 120 mg/day (conservatively assuming 100% human lung deposition). Adverse lung pathology (including neutrophilic inflammatory cell infiltrates) and unscheduled deaths were observed in rats in a 14 day inhaled tolerability study with CCI15106-IP at an estimated dose of 68.7 mg/kg. Rat deaths and lung pathology have been reported during oral and inhalation toxicology programs for approved/marketed formulations of CCI15106 at systemic exposures and inhalation dose levels similar or less than those delivered in this study. As CCI15106-IP is dry powder, it has a reduced risk of acute lung effects compared to low osmolarity nebulised solution. No bronchospasms were observed in the FTIH study 202031; however there were occurrences of non-serious cough and dyspnoea. Maximal amounts of powder administered were higher in the FTIH study than those planned for the	Repeat dosing will be evaluated in healthy participants in this study prior to dosing in participants with COPD. Patients with poorly controlled COPD will be excluded (see Section 6.2.2). Lung function will be monitored with frequent spirometry and physical examinations will be conducted. If they become medically necessary, short-acting bronchodilators may be administered as needed by the clinical staff. Oxygen and resuscitation measures will be available in the unit in the event they would be needed. The trial is to be conducted in a dedicated phase I unit with supplementary (Medicines & Healthcare Products Regulatory Agency) accreditation and experience in the conduct of Phase I studies.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	current study. **Labels of approved formulations:** Virazole SPC (13 November 2014) includes the following: • Sudden deterioration in pulmonary function associated with aerosolized CCI15106/ ribavirin has been observed in children, and significant deterioration in pulmonary function has been observed in patients with asthma and chronic obstructive pulmonary disease (COPD) during CCI15106/ribavirin treatment. • Bronchospasm has been reported following CCI15106/ribavirin use by patients with COPD and asthma. Pulmonary adverse reactions reported in clinical studies or in postmarketing use of aerosolized CCI15106/ribavirin include bacterial pneumonia, pneumothorax, laryngitis, pharyngitis, dyspnoea, cough, hypo- and hyperventilation, apnoea, and bronchospasm.	
Haemolytic anaemia	The primary toxicity of approved formulations of CCI15106 is haemolytic anemia, which was observed in 10% of oral CCI15106 plus interferon alpha2b combination-treated participants and occurs within 1 to 2 weeks of start of therapy [Rebetol USPI, 2015]. Haemolytic anemia associated with CCI15106 may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarction. CCI15106 is known to accumulate in the red blood cells and may cause hemolysis, which may result in increased uric acid [De Franceschi, 2000]. Anemia has been shown to occur frequently with experimental oral and intravenous CCI15106 in humans [Virazole USPI, 2013]. Haemolytic anaemia is monitorable and reversible with reduction / cessation of treatment [Rebetol USPI, 2015]. **GSK formulations:** In toxicity studies conducted by GSK, mild anaemia was seen in 4 week studies following inhalation administration of CCI15106:trehalose:trileucine particles (rat and dog) or CCI15106-IP (rat only).	Participants will be monitored regularly with complete blood counts and hematocrit, as per SoA (Section 2). Participants with hemoglobinopathies will be excluded. Due to the short dose and duration and the red blood cell count monitoring in place, laboratory monitoring for hemolysis is not warranted in this study. Participants will have an ECG assessment prior to and during the study. Cardiac monitoring, including assessment of blood pressure and heart rate, along with 12-lead electrocardiograms (ECGs) will be performed, per protocol. If cardiac status deteriorates on therapy, study medication should be suspended and/or discontinued.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiac effects	**GSK formulations:** Heart toxicity was not observed in definitive 4 week toxicity studies in rats and dogs following inhalation administration of CCI15106:trehalose:trileucine particles or CCI15106-IP. Minimal lymphocytic/mononuclear or mixed inflammatory cell infiltrate in the myocardium was observed following inhalation administrations of 68.7 mg/kg/day as CCI15106-IP at higher dose levels during a 14 day tolerability study ($AUC_{0\text{-}24h}$ was 5-fold higher than the human $AUC_{0\text{-}24h}$ estimated at 120 mg CCI15106-IP). These findings were also observed following oral and inhalation administrations of approved/marketed formulations of CCI15106-IP and do not, therefore, present at a greater risk compared to marketed/approved CCI15106 formulations which are approved for administration at higher inhaled and oral dose levels/ systemic exposures and administered for longer treatment durations than those proposed for CCI15106-IP. There were no cardiac events reported in the FTIH study of CCI15106-CFI. The following cardiovascular adverse reactions have been reported in clinical studies and in the postmarketing setting of CCI15106, which included severely ill infants with life-threatening underlying disease: cardiac arrest, hypotension, bradycardia, and digitalis toxicity [Virazole USPI, 2013]. Bigeminy, bradycardia, and tachycardia, have been described in patients with underlying cardiac disease.	Participants will have ECG prior to dosing and will be assessed prior to and during therapy by 12-lead ECG and telemetry. If cardiac status deteriorates on therapy, study medication should be suspended and/or discontinued. Participants with uncontrolled or unstable cardiac diseases will be excluded.
Photosensitization	Photosensitivity reaction has been reported commonly in clinical trials and in the postmarketing setting for CCI15106 [Rebetol SPC, 2009]. Photoallergic reaction with CCI15106 has been described in the literature [Stryjek-Kaminska, 1999].	Physical examination to include skin exams will be performed and documented as per SoA (Section 2). Any findings suggesting photosensitivity reaction will be promptly addressed according to appropriate standard of care and followed up for resolution.
Oral erosions	Ulcerative stomatitis, stomatitis, mouth ulceration are undesirable effects associated with CCI15106 [Rebetol SPC, 2009]. Nasal erosions were	Physical examination to include oral exam will be performed and documented as per SoA (Section 2). Any

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	observed in the squamous epithelium of the nasal turbinates of a proportion of dogs (but not rats) receiving the high dose (25.1 mg/kg/day) following administration of CCI15106-CFI and ≥16.3 mg/kg following administration CCI15106-IP for 4 weeks. These effects were considered non adverse and unlikely to be clinically relevant since CCI15106 will be administered to humans by oral inhalation, compared with oro-nasal administration (over 60 minutes) in the dog study, thereby minimising the potential for nasal exposure. Histopathological findings in rats included epithelial changes in the larynx (squamous metaplasia) in animals given the control article and CCI15106 formulation over 4 weeks. These changes were low in incidence and severity and showed full recovery following completion of the off-dose period. The findings were consistent with low grade non-specific irritation and, being an adaptive change of low severity, are considered non-adverse [Kaufmann, 2009] and a poor predictor of irritancy in humans given that the rat larynx is known to be particularly sensitive to inhaled irritants [Lewis, 1991].	findings suggesting oral erosion will be promptly addressed according to appropriate standard of care and followed up for resolution.
Testicular toxicity	**Testicular toxicity:** Testicular toxicity was seen in mice treated orally with CCI15106 for 3 to 6 months at doses of 15 mg/kg/day and [Rebetol SPC, 2009]. Recovery occurred within one or two spermatogenic cycles. No stage specific or cell specific abnormalities of spermatogenesis were observed in GSK studies which were conducted on the testes of rats (CCI15106:trehalose:trileucine particles and CCI15106-IP) and dogs (CCI15106-IP only) during definitive 4 week inhalation toxicity studies.	Given the shorter duration of clinical treatment (≤ 14 days) and lower expected exposure compared with currently available oral and nebulized CCI15106, the risk of testicular toxicity is considered to be low.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
BAL procedure	BAL requires bronchoscopy and sedation. Bronchoscopy can be performed safely on an outpatient basis [Du Rand, 2013], however, serious complications occurred in 1.1% of patients, including mortality in 0.02% of patients in a retrospective series (n=20,986 patients). Common adverse events reported with bronchoscopy, included tachycardia/bradycardia, major and minor bleeding, bronchospasm, laryngospasm, cough, dyspnea, sore throat, apnea, seizure, desaturation, pneumothorax, and pulmonary edema.	BAL will be performed by an experienced pulmonologist in dedicated bronchoscopy suite with close monitoring in recovery area post procedure.
Other		
Bystander exposure, including healthcare workers	Detectible levels of CCI15196-IP may be present in the immediate inhalation area during routine care activities. Labels of approved formulations: The Virazole patient information leaflet (last revision August 2014) states the following: • Virazole is to be administered in a hospital setting only, by a doctor or a nurse. • The nebuliser through which Virazole is given should be turned off 5 to 10 minutes before visitors see the patient to minimise unnecessary exposure to Virazole. • Pregnant women, women who are trying to become pregnant, and sexually active men should avoid exposure to Virazole, because the risk of harm to an unborn baby is unknown. Breast-feeding women are also to avoid exposure to Virazole. Postmarketing surveillance of CCI15106 has revealed reports of adverse events in individuals providing direct care to infants receiving aerosolized CCI15106 [Virazole USPI 2013]. The most common signs and symptoms were headache, conjunctivitis, rhinitis, nausea, rash, dizziness, pharyngitis,	Levels in air and in bystanders will be assessed. Whenever study participants are dosed outside the negative pressure room, all hospital personnel will be asked to leave the room and will not re-enter until 15 min after dosing. Pregnant women or women of child-bearing potential will be warned of the potential risks. Training on the potential health hazard will be provided to study personnel, including protective equipment, monitoring, and waste disposal. No women of child-bearing potential will be enrolled as participants or as bystanders.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and lacrimation. Several cases of bronchospasm and/or chest pain have been reported, usually in individuals with reactive airways disease. Seven cases are known in which nurses administered Virazole dry substance during pregnancy (n=6) or just before conception (n=1). In 6 cases, healthy children were born. In one case, a chromosomal translocation was reported with mild developmental delay.	

Exposure risk for additional medications administered in the study (Salbutamol):

See package leaflet (https://www.medicines.org.uk/emc/PIL.22837.latest.pdf).

3.3.2. Benefit Assessment

As this Phase I study is being conducted to assess the safety and PK in healthy participants and participants with COPD, there is no direct clinical benefit to study participants. Participation in this study may contribute to the process of developing new therapies in an area of unmet need.

3.3.3. Overall Benefit:Risk Conclusion

CCI15106 is an approved product as an oral agent in combination with interferon α or β (pegylated and non-pegylated) for chronic hepatitis C in patients 3 years of age and older with compensated liver disease (Copegus, Rebetol), and is approved in the nebulised form for use in infants and young children with severe respiratory syncytial virus infections (Virazole). CCI15106-CFI has been administered to healthy participants in single doses up to 60 mg with acceptable safety and tolerability profile. The risk of adverse effects is minimized for the population being investigated in the proposed study by careful selection of participants for the study, the relatively short duration of exposure, and the extent of safety monitoring incorporated into the study. The highest dose planned in this study (single dose of 120 mg or multiple doses of 60 mg BID) is significantly lower than the currently approved doses of CCI15106 (800-1400 mg for Copegus and Rebetol and 6 g for aerosolized Virazole). The risk to study staff will be managed by occupational precautions.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• 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 CCI15106 during self-administered dosing of participants.	• Concentration of CCI15106 in plasma of bystanders 15-20 minutes (min) after dosing (at predicted tmax) and 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	
• 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.

Objectives	Endpoints
Tertiary/Exploratory	
• 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)

5. STUDY DESIGN

5.1. Overall Design

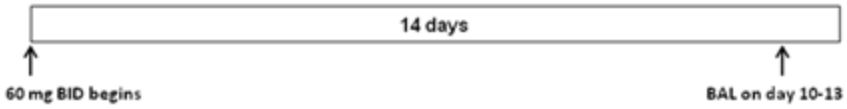
This is a two-part, double-blind (sponsor unblind), randomized, placebo-controlled, single and repeat escalating dose study. Investigator and participants will be blinded to treatment type (active or placebo), but will know what dose of the medication is being administered. Part 1 will investigate single 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.

Study schematic is presented below:

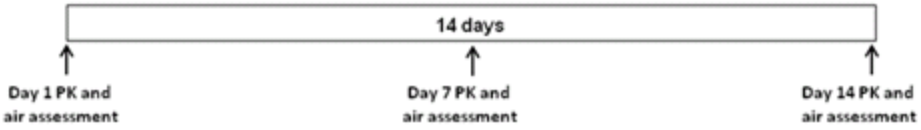
Part 1 Healthy Participants

Cohort A: 8 participants (6 active; 2 placebo)

Cohort B: 14 participants (12 active; 2 placebo)

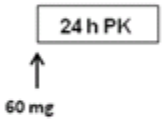


Cohort C: 14 bystanders for environmental exposure, to be run concomitantly with Cohort B



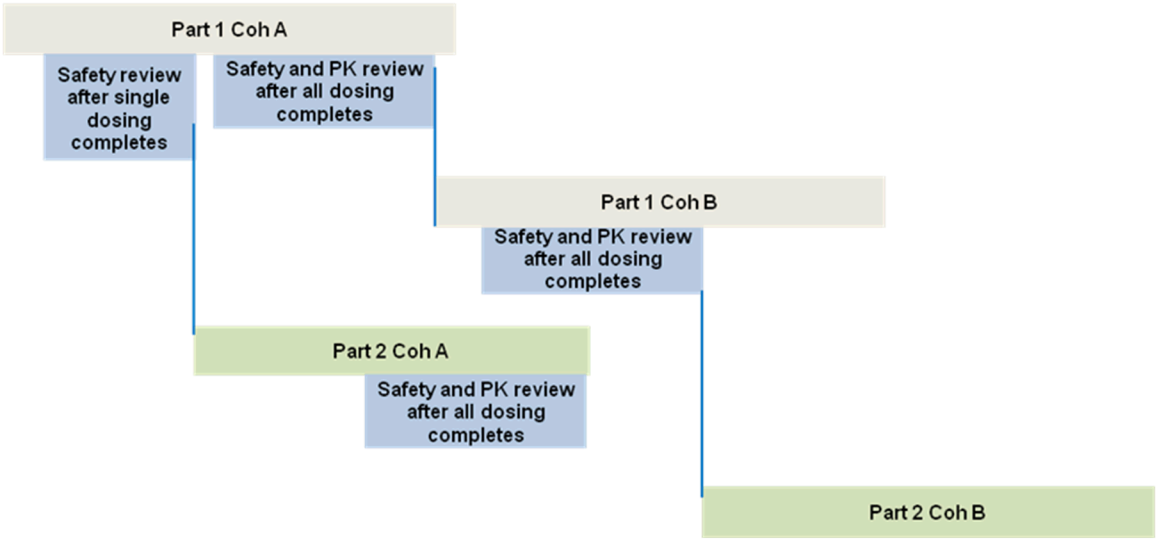
Part 2 Participants with COPD

Cohort A: Single dose; 8 participants (6 active; 2 placebo)



Cohort B: Multiple dose; 14 participants (12 active; 2 placebo)

The following reviews will be conducted during the study progression:



- In Part 1, Cohort B dosing can begin only after review of safety/tolerability and PK of all dosing in Part 1 Cohort A (see Section 7.2 for composition of the review team).
- In Part2, Cohort A dosing can begin only after review of safety/tolerability for a single dose administration of 60 and 120 mg in all participants in Part 1 Cohort A (see Section 7.2 for composition of the review team).
- In Part 2, Cohort B dosing can begin only after the comprehensive review of all data obtained in Part 1, including safety and systemic PK and lung PK, if available (see Section 7.2 for composition of the review team) and after review of safety/tolerability of Part 2 Cohort A.
- Environmental and bystander exposure review may be conducted at any time after the data are collected. Until this review is completed and exposure found acceptable, all subsequent cohorts will be dosed in the negative pressure environment.
- The planned doses may be modified, repeated or cancelled based upon safety/tolerability/ and/or PK from preceding cohorts (See Section 7.2 for more information). Single doses will not exceed 120 mg and repeat doses 60 mg BID.
- The planned dose frequency or duration may be modified based on emerging safety/tolerability and PK data from previous cohorts. The total daily dose will not exceed 120 mg.
- The number of cohorts may be reduced or expanded if needed.
- All participants in Part 1 Cohort B and in Part 2 Cohort B (60 mg BID dose for both Cohorts) will undergo BAL once during the study on days 10, 11, 12, or 13 after the first (morning) dose. Based on the lung ELF concentrations of CCI15106 observed, additional double-blinded, single-blinded or open-label repeat dose cohort(s) may be added at a dose not to exceed 120 mg daily. The total number of participants will not exceed that specified in Section 5.2.

- BAL may be used in the additional cohorts to obtain a more accurate estimation of the dose to lung exposure ratio and provide data for future dose predictions.

There will be approximately 3 cohorts of healthy participants in this study and approximately 2 cohorts of participants with moderate COPD. Participants in the dosing cohorts will be randomized to receive either CCI15106-IP or matching Liquidia particles without the active ingredient (lactose:polyvinyl alcohol 98:2 w/w 0.9x1 μm cylinder shape amorphous particles, referred to as placebo). Participants in Cohort C will be assigned to participants in Cohort B on a one to one basis for the entire duration of the study.

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.

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. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). Participants will be dosed the following morning on Day 1 followed by post-dose assessments. Blood for PK assessments will be collected for the next 48 hours (h). On Day 3 (after collection of 48 h PK time point), participants will receive a single dose of 120 mg followed by post-dose assessments and PK assessments for the next 72 h. Repeat dosing will begin on the morning of Day 6 (after collection of 72 h PK time point) and will continue for 14 days BID. Participants will remain in the unit for additional 2 days until 72 h PK timepoint is collected. Dosing frequency and duration may be adjusted based on emerging safety and tolerability data.

For Cohort B Part 1, Repeat Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). 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. BAL procedure will be performed as soon as possible (within 1 h) after the first (morning) dose on one of the following days: 10, 11, 12, or 13. Participants will be discharged on Day 15 following completion of all post-dose assessments after the last dose, or later if additional PK collection or other assessments are required. Participants will return for the follow-up visit approximately 30 days after discharge.

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. Bystanders will report to the unit on Day -1 and will remain for all 14 days of dosing of Cohort B. They will be positioned in the room with the dosing participants for every dose taken, as described in Section 9.4.8. Air sampling and bystander PK evaluation will be conducted on days 1, 7, and 14 as described in Section 9.4.8. Bystanders will be discharged on Day 15 following completion of all post-dose assessments after the last dose. Bystanders will return for the follow-up visit approximately 30 days after discharge.

For Cohort A Part 2, Single Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization

(randomization can also be done on Day 1, prior to dosing). They will be dosed the following morning on Day 1 followed by post-dose assessments. Participants will be discharged following completion of the post-dose assessments the next day (Day 2). They will return for the follow-up visit approximately 30 days after discharge.

For Cohort B Part 2, Repeat Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). 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. BAL procedure will be performed as soon as possible (within 1 h) after the first (morning) dose on one of the following days: 10, 11, 12, or 13. Participants will be discharged on Day 15 following completion of all post-dose assessments after the last dose, or later if additional PK collection or other assessments are required. Participants will return for the follow-up visit approximately 30 days after discharge.

The total study duration will be approximately 82 days for Cohort A Part 1; approximately 75 days for Cohort B Part 1 and Cohort C Part 1; approximately 77 days for Cohort A Part 2; and approximately 90 days for Cohort B Part 2.

5.2. Number of Participants

Approximately 36 healthy participants and approximately 22 participants with COPD will be randomized in this study for dosing.

Evaluable participants will be defined in the Reporting and Analysis Plan (RAP).

Additional participants or cohorts may be enrolled to allow for evaluation of additional dose levels or to increase numbers on prior doses or to increase the number of bystanders. The total number of participants in this study will not exceed 86 and the total number of cohorts will not exceed 7, including the bystander cohort(s).

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

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

5.4. Scientific Rationale for Study Design

Participants and all site personnel, with the exception of the study pharmacist or designee, will be blinded to participant randomization throughout the study. The GSK study team participating in the dose escalation meetings will review blinded data and will be un-blinded on a need to know basis only if necessary to facilitate review of the safety,

tolerability and PK data as appropriate in real time to inform dose escalation decisions. The GSK study team or personnel at any contract research organization that may be involved in data management or in statistics and programming will not reveal the treatment assignments to the site personnel or participants.

In repeat dosing cohorts, CCI15106-IP will be administered for 14 days to mimic the expected duration of treatment in target patient populations.

Inclusion of Bronchoscopy

BAL will be performed on 14 healthy participants (Cohort B Part 1) and 14 participants with COPD (Cohort B Part 2) to evaluate levels of CCI15106 in the ELF. BAL will be performed once, as soon as possible (within 1h) after the first (morning) dose. This will allow assessment of CCI15106 levels at around tmax in the ELF. The timing of BAL in Part 2 Cohort B may be adjusted based on BAL results obtained in Part 1. Available models [Weber, 2017] predict that the level of CCI15106 in the bronchoalveolar fluid following 14 days of 60 mg BID dosing may be achieved above 200 μM around T_{max} which is above the EC50 for all respiratory viruses including HRV and expected to prevent or minimise the migration of an upper respiratory tract viral infection to the lower respiratory tract. These data will enable a more accurate estimation of the dose to lung exposure ratio and provide valuable information for future dose predictions.

Inclusion of Participants with COPD Cohort

Due to potential exposure differences as a function of COPD-induced lung damage, participants with moderate COPD will be included to aid in dose selection for the future proof of concept studies in participants with COPD. This cohort will also help obtain some safety and tolerability data in this patient population prior to a wider administration in the Proof of Concept study.

Inclusion of Bystander Cohort

Due to known teratogenic potential of CCI15106, we need to evaluate how much of it gets into the environment around the dosing participant to ensure that no potentially pregnant bystanders are put at-risk due to secondary exposure. Participants dosed in the Cohort used to evaluate environmental and bystander exposure will be dosed outside a negative pressure enclosure. All other participants will be dosed inside the enclosure. When participants dose outside the enclosure, all personnel will leave the room and not re-enter until 15 min after dosing. During this time, participants will be observed through a window in the door.

5.5. Dose Justification

The dose proposed for Part 1 Cohort A is based on the data from 202031 where CCI15106-CFI up to 60 mg single dose has been evaluated, and no SAEs or severe AEs were observed, as well as the investigation of the four week toxicity and toxicokinetics in rats and dogs in which the NOAEL was determined [GSK Document Number 2017N312240_00 and GSK Document Number 2017N312247_00].

Table 1 below shows the safety margins in terms of lung and systemic exposure with respect to the NOAEL obtained from the pre-clinical studies, and the folder cover with respect to the systemic exposure following oral administration of the marketed dose (1200 mg/day) in humans for the doses proposed in this study. These data indicated reasonable safety margins for Cohort A in Parts 1 and 2, where single dose of CCI15106-IP will be administered.

The selection of appropriate dose for Part 1 Cohort B will be performed upon consideration of available safety, tolerability and systemic PK data from Part 1 cohort A. The review data set for this selection will, at minimum, consist of: any adverse events, liver function test results, vital signs, ECG, spirometry data, and laboratory findings, and any available systemic PK results.

The selection of appropriate dose for Part 2 Cohort A will be performed upon consideration of available safety and tolerability data following the single doses (60 and 120 mg) in all participants in Cohort A of Part 1.

The selection of appropriate dose for Part 2 Cohort B will be performed upon consideration of available safety, tolerability, systemic PK and lung concentration data from Part 1 Cohort B.

The dose level in any cohort may be titrated up or down based on emerging safety, tolerability, and systemic PK and lung data where available. The maximum dose will not exceed 120 mg per day.

Table 1 Prediction of Human Systemic and Lung Exposure and Safety Margins of CCI15106

Dose Frequency	Proposed human dose per day (mg)	Human Lung Dose (mg/g)	Lung Safety Margin (Rats)	Lung Safety Margin (Dogs)	Human Systemic expoure AUC(0-24) (ng.h/mL) *	Systemic Safety Margin (Rats)	Systemic Safety Margin (Dogs)	Systemic Safety Margin (human Oral Ribavirin)
Assume 100% lung deposition in humans								
SD	60	0.06	12	16				
SD	120	0.12	6	8				
Assume 59% lung deposition in humans								
SD	60	0.04	20	26	552	17	40	92
SD	120	0.07	10	13	1104	8	20	46
BD**	30	0.04	20	26	3080	3	7	16
BD	60	0.07	10	13	6150	2	4	8

Assumptions:

human: body weight 70 kg, lung weight 1000 g; 100% or 59% inhaled dose into lungs are assumed

59% was predicted from the MPPD for lung deposition of the device

rat: mean body weight 0.244kg, mean lung weight 1.145 g, 10% inhaled dose into lungs;

dog: mean body weight 8 kg, mean lung weight 73.1 g, 25% inhaled dose into lungs.

Rat NOAEL dose = 32.5 mg/kg, AUC=9.34 μg.h/mL (whole study means)

Dog NOAEL dose = 34.2 mg/kg, AUC=22.2 μg.h/mL (whole study means)

Human oral AUC(0-24) =2xAUC0-12=50.722 μg.h/mL (Steady state) [Copegus USPI, 2015]

* human systemic AUC(0-24) is predicted from a mechanistic model [Weber, 2017]

** BD - twice daily dosing; AUC(0-24) on Day 14

6. STUDY POPULATION

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

6.1. Inclusion Criteria

6.1.1. Inclusion Criteria for Healthy Participants and Bystanders

Participants are eligible to be included in the study only if all of the following criteria apply. Rescreening is allowed only if approved by the Medical Monitor.

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator (in consultation with the Medical Monitor if required) decide and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

4. Body weight ≥50 kg for males and 45 kg for females and body mass index (BMI) within the range 19 to 31 kg/m^2 (inclusive) for males and 17 to 31 kg/m^2 (inclusive) for females.

Sex

5. Male OR Female

   a. Male participants:

   A male participant with female partner of child bearing potential must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 7 months after the last dose of study treatment and refrain from donating sperm during this period.

b. Female participants:

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

Informed Consent

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

6.1.2. Inclusion Criteria for Participants with COPD

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

Age

1. Participant must be 40 to 75 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosed with moderate COPD (GOLD class II) by a qualified physician as defined by the GOLD guidelines (http://www.goldcopd.org/).
3. The participant has spirometry at screening, conducted 15-30 minutes after administration of 400 microgram (µg) salbutamol via metered dose inhaler showing:
    - post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% and <80% predicted normal [Quanjer, 2012] and
    - post-bronchodilator FEV_1/ forced vital capacity (FVC)<0.7, where FEV_1 is forced expiratory volume in 1 second and FVC is forced vital capacity.
4. Participant is a smoker or an ex-smoker with a smoking history of at least 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent).
5. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor if required agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

6. Body weight ≥ 45 kg and BMI within the range 17 – 32 kg/m^2 (inclusive).

Sex

7. Male OR Female

   a. Male participants:

   A male participant with female partner of child bearing potential must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 7 months after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

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

Informed Consent

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

6.2. Exclusion Criteria

6.2.1. Exclusion Criteria for Healthy Participants and Bystanders

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

Medical Conditions

1. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
4. QTc > 450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate (HR) according to Fridericia's formula (QTcF), machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
   - For purposes of data analysis, QTcF will be used as specified in the RAP.

5. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<40 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcF interval	>450 msec	

6. Any clinically significant central nervous system (e.g., seizures), cardiac, pulmonary, metabolic, renal, hepatic or gastrointestinal conditions or history of such conditions that, in the opinion of the investigator may place the participant at an unacceptable risk as a participant in this trial or may interfere with the absorption, distribution, metabolism or excretion of drugs.

Prior/Concomitant Therapy

7. Past or intended use of over-the-counter or prescription medication (including herbal medications) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study. Specific medications listed in Section 7.7 may be allowed.

Prior/Concurrent Clinical Study Experience

8. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 month period.
9. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
10. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Diagnostic assessments

11. Hemoglobin (Hgb) below the lower level of the normal range with one repeat testing allowed, or known hemoglobinopathies.
12. Known severe hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme.
13. Presence of Hepatitis B surface antigen (HBsAg) at screening, Positive Hepatitis C antibody test result at screening.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

14. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

15. Positive pre-study drug/alcohol screen
16. Positive HIV antibody test
17. Regular use of known drugs of abuse

Other Exclusions

18. Male partners of women who are pregnant or lactating
19. Regular alcohol consumption within 3 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
20. Breath test indicative of smoking at day -1.
21. History of sensitivity to any of the study medications, including CCI15106 or components thereof and, for cohorts that will undergo BAL, those that may be used in association with the BAL procedure or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
22. For cohorts that will undergo BAL, contraindications to bronchoalveolar lavage including hypercapnia >50 mm Hg, abnormal blood coagulation parameters, known or suspected intolerance of medications necessary for bronchoscopy, refractory hypoxemia, reactive airway disease or asthma, unstable angina or acute myocardial infarction.
23. Documented lactose allergy/intolerance for dosing cohorts.

6.2.2. Exclusion Criteria for Participants with COPD

1. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. QTc > 450 msec or QTc > 480 msec in participants with Bundle Branch Block

   NOTES:

   - The QTc is the QT interval corrected for HR according to Fridericia's formula (QTcF), machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used

to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

- For purposes of data analysis, QTcF will be used as specified in the RAP.

5. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<40 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcF interval	>450 msec	

6. Participant has poorly controlled COPD, defined as the occurrence of **either** of the following:
   - Acute worsening of COPD requiring use of antibiotics or systemic corticosteroids in the 6 weeks prior to screening visit **OR**
   - More than 2 exacerbations of COPD requiring treatment with oral steroids in the preceding year or hospitalization for the treatment of COPD within 3 months of screening or more than twice during the preceding year.
7. History of an upper or lower respiratory tract infection requiring antibiotics in the 4 weeks prior to screening
8. Participant has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the Investigator, compromise the safety of the participant or affect the interpretation of the results.
9. Unstable or uncontrolled cardiac disease.
10. Participants who have past or current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect participant safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension) ARE permitted to be entered into the study).

Prior/Concomitant Therapy

11. Participants are not allowed to take oral corticosteroids from 4 weeks prior to screening and for the duration of the study.
12. Participants taking medications for any chronic conditions have to be on stable doses for 4 weeks prior to screening and until after completion of the treatment period. This includes COPD maintenance therapies (e.g. inhaled corticosteroids, long-acting beta-agonists, long-acting muscarinic agonists).
13. Didanosine and azathioprine are not allowed.
14. Use of short-acting inhaled bronchodilators is allowed, but participants must be able to discontinue their medications several times during the study as described in Section 7.7.

15. Use of long-acting bronchodilators is allowed, but participants must be able to modify the schedule of their medications twice during the study as defined in Section 7.7.

Prior/Concurrent Clinical Study Experience

16. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months.
17. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
18. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

Diagnostic assessments

19. Impaired renal function (eGFR <30 cc/min, using CKD-EPI equation).
20. Known severe hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme.
21. Hgb below the lower level of the normal range with one repeat testing allowed or known hemoglobinopathies.
22. Presence of Hepatitis B surface antigen (HBsAg) at screening, Positive Hepatitis C antibody test result at screening.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

23. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

24. Positive pre-study drug/alcohol screen
25. Positive human immunodeficiency virus (HIV) antibody test
26. Regular use of known drugs of abuse

Other Exclusions

27. Male partners of women who are pregnant or lactating
28. Regular alcohol consumption within 3 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
29. Unable to refrain from smoking for 2 h prior to dosing and until all assessments are complete for 4 h after dosing and also for 1 h prior to any vital signs and ECG assessments.

30. History of sensitivity to any of the study medications, including CCI15106 or components thereof and, for cohorts that will undergo BAL, those that may be used in association with the BAL procedure or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
31. For cohorts that will undergo BAL, contraindications to bronchoalveolar lavage including hypercapnia >50 mm Hg, abnormal blood coagulation parameters, known or suspected intolerance of medications necessary for bronchoscopy, refractory hypoxemia, reactive airway disease or asthma, unstable angina or acute myocardial infarction.
32. Documented lactose allergy/intolerance.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will be allowed soft drinks without caffeine starting from 2 h after dosing, including both AM and PM doses. Standardized meals will be provided while the participant is confined to the clinical research unit, as outlined below.
- Participants will report to the clinic fasting (for at least 8 h) for screening visit, Day -1 of treatment periods and for follow-up visit.
- At all mealtimes, food will be served only after completion of protocol specified procedures scheduled at or around the same time.
- The morning dose of the CCI15106-IP will be given after fasting (for at least 8 h). The evening dose of the CCI15106-IP will be given at least 2 h after food. The doses will be approximately 12 h apart. For the first dose for any participant in the study, water should not be allowed for 2 h prior to dosing. For all other doses, water will be allowed freely.
- Participants should not eat for 2 h after dose administration for the single dose cohorts and after the first dose of the multiple dose cohorts.
- Breakfast will not be provided on the mornings of the BAL, however a snack is permitted on this day after the end of the procedure, as long as it does not interfere with any study related procedures.
- All other meals and snacks may be provided as per the clinics schedule. Should a mealtime interfere with a study procedure such as BAL, the investigator in consultation with the sponsor, may modify the meal times to ensure safety of the participants. Also, the fasting requirements may be modified or removed at any time during the study at the discretion of the sponsor in consultation with the investigator.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 h prior to the start of dosing until the participants leave the clinical unit.
- During each dosing session, participants will abstain from alcohol for 24 h prior to the start of dosing until the participants leave the clinical unit.
- For healthy participants, use of tobacco products is not allowed from screening until after participants leave the clinical unit.
- Participants with COPD who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the Clinical Unit. Participants with COPD will be escorted by staff for smoking breaks except during the period for 2 h prior to dosing and until all assessments are complete for 4 h after dosing.

6.3.3. Activity

- Participants will abstain from strenuous exercise from screening until follow-up visit. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study may be rescreened only upon approval of Medical Monitor. Rescreened participants should be assigned a different screening number.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	CCI15106-IP	Placebo
Dosage formulation:	1 capsule	1 capsule
Unit dose strength(s)/Dosage level(s):	30 mg of CCI15106 As 30.3 mg of CCI15106: polyvinyl alcohol 99:1 w/w PRINT 0.9x1 μm cylinder shape crystalline particles	30.3 mg of lactose: polyvinyl alcohol 98:2 w/w PRINT 0.9x1 μm cylinder shape amorphous particles
Route of Administration	By inhalation	By inhalation
Dosing instructions:	Each inhalation will follow instructions provided with the device. The number of inhalations will depend on the dose. The morning dose to be taken fasting (at least 8 h). For repeat dose cohorts, the evening dose to be taken at least 2 h after food. For repeat dose cohort(s) with bystander exposure monitoring, a ±1.5 h window is allowed.	Each inhalation will follow instructions provided with the device. The number of inhalations will depend on the dose. The morning dose to be taken fasting (at least 8 h). For repeat dose cohorts, the evening dose to be taken at least 2 h after food. For repeat dose cohorts with bystander exposure monitoring, a ±1.5 h window is allowed.
Packaging and Labeling	Study Treatment will be provided in a HDPE (high density polyethylene) bottle. Each bottle contains 2 capsules and a desiccant canister. Each bottle is overwrapped in a foil pouch containing a desiccant sachet. Each bottle and each pouch will be labelled as required per country requirement.	Study Treatment will be provided in a HDPE bottle. Each bottle contains 2 capsules and a desiccant canister. Each bottle is overwrapped in a foil pouch containing a desiccant sachet. Each bottle and each pouch will be labelled as required per country requirement.
Device	Monodose RS01	Monodose RS01
Manufacturer	Plastiape S.p.A.	Plastiape S.p.A.

7.1.1. Medical Devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are Monodose RS01.
- Instructions for medical device use are provided in the Study Reference Manual (SRM).
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 9.2).

7.2. Dose Modification

- This protocol allows some alteration from the currently outlined dosing schedule. The maximum daily dose administered will not exceed 120 mg per day either as a single dose or as 60 mg BID.
- The decision to proceed to Part 1 Cohort B will be made by the GSK Study Team comprised at a minimum of the team leader, medical monitor, Global Clinical Safety and Pharmacovigilance scientist or physician (Clinical Pharmacokineticist, Statistician and Preclinical Safety Assessment as necessary), and the Investigator or delegate based on safety and tolerability data obtained in all participants at the prior dose levels in Part 1. The actual doses to be administered may be adjusted based on safety, tolerability, and preliminary PK data if appropriate, at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose. The highest dose in the study will not exceed 120 mg per day either as a single dose or as 60 mg BID.
- The decision to proceed to participants with COPD will be made by the GSK Study Team comprised at a minimum of the team leader, medical monitor, Global Clinical Safety and Pharmacovigilance scientist or physician (Clinical Pharmacokineticist, Statistician and Preclinical Safety Assessment as necessary), and the Investigator or delegate based on safety and tolerability data obtained after single dosing completes in healthy participants in Part 1 Cohort A.
- The actual doses to be administered may be adjusted based on safety, tolerability, and preliminary PK data if appropriate, at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.
- The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety and PK findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional participant(s) or cohort(s) will be the same as that described for other study participants.

7.3. Method of Treatment Assignment

No treatment assignment will be performed for bystander cohort(s).

For all other cohorts, participants will be centrally randomized using an Interactive Web Response System.

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.

Study treatment will be dispensed at all times indicated in the SoA (Section 2).

7.4. Blinding

This will be a double-blind (sponsor unblinded) study. The GSK study team participating in the dose escalation meetings will be blinded to the participant's treatment assignment and will be un-blinded only if necessary to facilitate review of the safety, tolerability and PK data as appropriate in real time to inform dose escalation decisions.

However, the study team performing the analyses to support dose escalation decisions will be unblinded to allow accurate assessment of the data, including the study pharmacokineticists, statisticians, programmers and data managers, who will have access to the randomization codes for analysis purposes. If additional contract research organizations are involved in data analysis or in statistical analysis and programming, the same will apply to their staff as well.

Participants will be randomized to receive study treatment. Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study treatment and will ensure that there are no differences in time taken to dispense following randomization.

This 3rd party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study treatment with the investigator or with other participants.

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

Additional double-blinded, single-blinded or open-label repeat dose cohort(s) may be added at a dose not to exceed 120 mg daily.

- The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- Investigators have direct access to the participant's individual study treatment.

- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding.
- The date and reason for the unblinding must be fully documented.

A participant may continue in the study if that participant's treatment assignment is unblinded, upon discussion with the medical monitor.

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

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- Capsules should be kept refrigerated (2-8°C) in their sealed packaging, protected from moisture.
- Monodose RS01 devices will be supplied in bulk. After use, the devices will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date. Devices will be disposed of at site after reconciliation is verified by study monitor.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM or equivalent.
- Precaution will be taken to avoid direct contact with the study treatment. No women of child-bearing potential will administer study treatment. Staff administering the study treatment will wear protective gown and gloves. A Material Safety Data Sheet describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

Dosing Procedure for Cohorts not Used for Environmental Exposure Monitoring

- Participants will inhale the dose from the Monodose RS01 device inside a negative pressure room or enclosure.
- The investigator/designee will remove the capsule from the bottle and load it into the Monodose RS01 device one at a time in a safety cabinet. One device will be used per capsule. The investigator/designee will be trained to load the capsule into the device and pierce the capsule ready for inhalation (empty capsules will be used for training).
- The participant will inhale the dose, and staff will observe participant doing it. Staff will be trained to listen for a rattle that the device makes during successful dosing. After dosing, the Monodose RS01 device will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date.
- The participant will be trained to use a "fast and deep" inspiration technique per inhalation, to achieve rapidly consecutive maximal inhalations (empty capsules will be used for training). This will ensure optimal and consistent treatment delivery. For participants, the training session will be on either Day -1 or on Day 1, prior to administration of the first dose. Subsequent assessment of Monodose RS01 device technique, and repeat device training where deemed necessary by the investigator/designee, will take place immediately before administration of each dose.

Dosing Procedure for Cohorts Used for Environmental Exposure Monitoring

- Participants will inhale the dose from the Monodose RS01 device in a room designated for dosing. All investigators/designees will leave the room and observe dosing participants and bystanders through a glass in the door. Only participants inhaling the dose and designated bystanders are allowed in the room during inhalation of the dose.
- The bystander will remove the capsule from the bottle and load it into the Monodose RS01 device one at a time. One device will be used per dose (2 capsules in this cohort). The bystander will be trained to load the capsule into the device and pierce the capsule ready for inhalation (empty capsules will be used for training).
- The bystander will pass loaded and charged device to the dosing participant.
- The participant will inhale the dose, and staff will observe participant doing it through a glass in the door. The bystander will be trained to listen for a rattle that the device makes during successful dosing. After dosing, the participant will pass the device back to the bystander.
- The bystander will open the device, remove the capsule and place it on the table between the dosing participant and the bystander. The bystander will then load the second capsule into the same device, pierce the capsule and pass the loaded device back to the dosing participant.
- The participant will inhale the second dose, the bystander will listen for a rattle that the device makes during successful dosing and staff will observe participant doing it

through a glass in the door. After dosing, the participant will pass the device back to the bystander.

- The bystander will open the device, remove the second capsule, and place the open device with both capsules on the table between the dosing participant and the bystander.
- The bystander and participant will remain seated around the table for 15 min. After this time, the bystander will place the Monodose RS01 device and both used capsules into the plastic bag labelled with the participant number, day of dosing, and date. After that is done, bystander and participant can leave the room. The bystander will need to wash their hands prior to leaving the room.
- The participant will be trained to use a "fast and deep" inspiration technique per inhalation, to achieve rapidly consecutive maximal inhalations (empty capsules will be used for training). This will ensure optimal and consistent treatment delivery. For participants and bystanders, the training session will be on either Day -1 or on Day 1, prior to administration of the first dose. Subsequent assessment of Monodose RS01 device technique, and repeat device training where deemed necessary by the investigator/designee, will take place immediately before administration of each dose.

7.6. Treatment Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

The participants will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

If failure of the capsule actuation is suspected (i.e. due to failure to pierce the capsule during device priming), the investigator is permitted to rechallenge the individual with a maximum of two further administrations at the same dose. If dosing failure is suspected for any other reason, the participant may have to be excluded after consultation with the Medical Monitor.

The Monodose RS01 devices will be under the supervision of the study organisers at all times during the clinical trial.

7.7. Concomitant Therapy

7.7.1. Permitted Medications and Non-Drug Therapies

Paracetamol or Acetaminophen, at doses of ≤2 grams/day is permitted.

Medications associated with the BAL procedure are permitted, but these medications are to be disclosed to the Sponsor prior to dosing any participants.

Participants with COPD taking medications for any chronic conditions have to be on stable doses for 4 weeks prior to screening and until after completion of the treatment period.

Salbutamol is administered 15 to 30 min prior to spirometry at screening for diagnostic purposes. Short-acting bronchodilators should not be used from 6 h prior to each morning dose administration until 4 h after that dose. If they become medically necessary during that time, short-acting bronchodilators may be administered as needed by the clinical staff only and their use must be documented.

For participants with COPD, use of long-acting bronchodilators is allowed, but their use must be modified twice during the study as follows: at screening and on Day 1, they must not be taken for at least 2 h prior to spirometry.

Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor.

7.7.2. Prohibited Medications and Non-Drug Therapies

Participants are not allowed to take oral corticosteroids from 4 weeks prior to screening and for the duration of the study.

For participants with COPD, self administration of short-acting inhaled bronchodilators is not allowed at screening, from 4 h prior to spirometry until spirometry is completed. Self administration of short-acting inhaled bronchodilators is not allowed during treatment period from 6 h prior to each morning dose administration until 4 h after that dose.

Didanosine and azathioprine are not allowed.

Except as permitted in Section 7.7.1, participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because most of the participants are healthy and the indication being studied is not life threatening.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

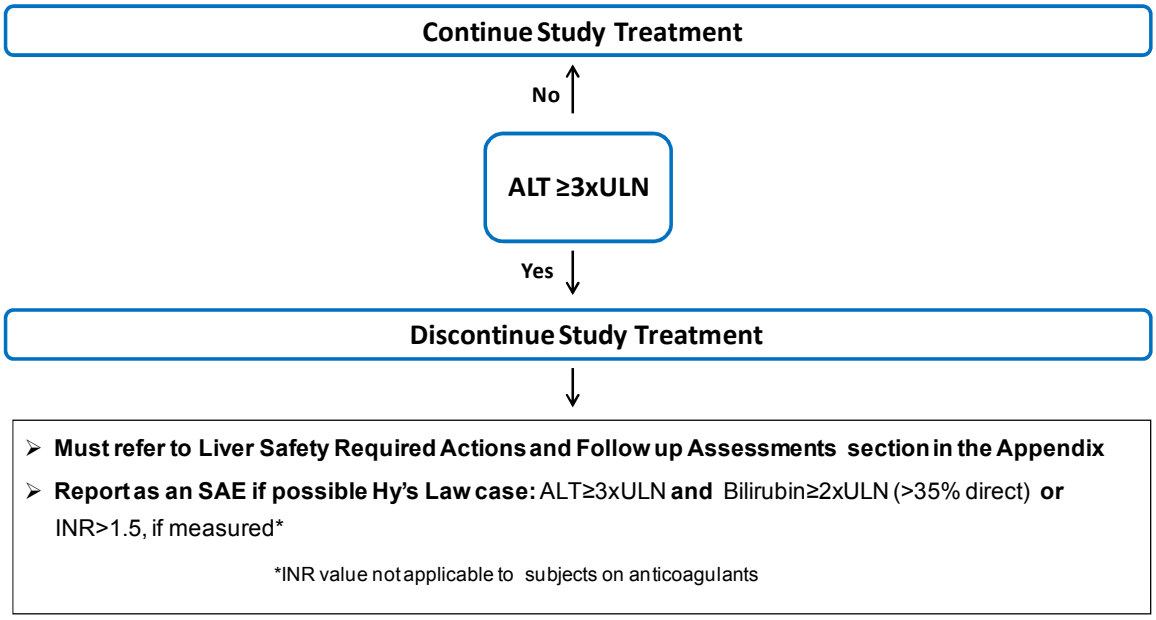
8.1. Discontinuation of Study Treatment

If participant is withdrawn from study treatment, this constitutes withdrawal from study. Participants will have to be followed up for safety reasons as deemed necessary by the Investigator and should be encouraged to return for a follow-up visit as specified in the SoA (Section 2). If this is not possible, procedures specified for the follow-up visit can be performed at the last visit that the participant attends.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined above

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.2. QTc Stopping Criteria

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

- QTc, QTcF >500 msec,
- Change from baseline: QTc >60 msec

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

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

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

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Other Stopping Criteria

Data will be reviewed by the investigator and sponsor for consideration of potential study pausing or stopping if:

Two (2) or more subjects, within a dose-level, receiving study treatment experience grade 3 respiratory adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience a grade 3 hematologic adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience severe hypersensitivity related adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience a grade 3 vital signs (heart rate and/ or blood pressure) adverse event that are deemed possibly or probably related to study drug by the investigator.

One (1) or more subjects receiving study treatment experience anaphylaxis that is deemed possibly or probably related to study drug by the investigator.

In case of dose limiting toxicities at a given dose level, dose escalation will be stopped and a lower or intermediate dose may be introduced.

8.1.4. Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (Section 2) for data to be collected at follow-up and for any further evaluations that need to be completed.
- Participants will have to be followed up for safety reasons as deemed necessary by the Investigator and should be encouraged to return for a follow-up visit as specified in the SoA (Section 2). If this is not possible, procedures specified for the follow-up visit can be performed at the last visit that the participant attends.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The following time window tolerances apply to all protocol assessments:

Predose	- 60 to 0 min (- 60 to -15 min for spirometry)
0h - 4h post	- 5 / + 10 min
5h – 24h post	- 10 / + 10 min

9.1. Efficacy Assessments

There are no efficacy assessments in this study.

9.2. Adverse Events

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

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

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and no later than in 24 h, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

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

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The Cardiovascular CRFs are presented as queries in response to reporting of certain Cardiovascular MedDRA terms. The Cardiovascular information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a Cardiovascular Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Pregnancy

- Female participants of child bearing potential are excluded from this study
- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until 7 months after the last dose of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.7. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for inhalation. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2.1, Section 9.2.2, Section 9.2.3, Section 9.2.4 and Appendix 4 of the protocol.

9.2.7.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 7.

9.2.7.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2.1, Section 9.2.2, Section 9.2.3, and Section 9.2.4). This applies to all participants, including those who discontinue study treatment or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.7.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor by facsimile transmission. If facsimile transmission is unavailable, then notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.2.7.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.3. Treatment of Overdose

For this study, any dose of CCI15106-IP greater than the dose specified for the treatment period within a 24 h time period [±4 h] will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until CCI15106 can no longer be detected systemically (at least 30±2 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Screening Assessments

Cardiovascular medical history/risk factors will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

9.4.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems, and skin. Height and weight will also be measured and recorded. Oral exam will be performed.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Oral exam will also be performed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.3. Vital Signs

- Vital signs will be measured in semi-supine position and will include oral or tympanic temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure. The same method of temperature assessment should be used throughout the study.
- For BAL, vital signs will also include oxygen saturation and will be evaluated and recorded before, every 5 minutes during the procedure, at the end of, and between 30 and 60 minutes after the bronchoscopy.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Three readings of blood pressure and pulse rate will be taken where indicated as triplicate in SoA (Section 2) and all three readings will be recorded.

9.4.4. Electrocardiograms

- Triplicate OR single 12-lead ECG will be obtained in semi-supine position after 5 minutes rest as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- Continuous cardiac telemetry will be performed where indicated in SoA (Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the participant's source documents.

9.4.5. Spirometry

- Spirometry (FEV1 and FVC) will be performed at time points specified in the SoA (Section 2). Further tests should be performed, at the discretion of the investigator, if the participant has symptoms that could suggest bronchospasm.
- Spirometry manoeuvres will be conducted according to ATS/ERS 2005 spirometry standards [Miller, 2005]. The greatest FEV1 and the greatest FVC from 3 technically acceptable and reproducible manoeuvres will be recorded.
- For participants with COPD, at screening, 400 µg salbutamol will be administered 15-30 minutes prior to performing spirometry. FEV1 and FVC percent predicted values will be derived using the Global Lung Function Initiative reference values [Quanjer, 2012].

9.4.6. Capillary pCO2

The pCO2 levels will be measured at the times indicated in SoA (Section 2). The participant's hand will be heated in warm water (42 degrees) for about 10 minutes and a capillary blood sample will be collected by skin puncture using a lancet or automated incision device.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30±2 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 2).

9.4.8. Environmental and Bystander Exposure Evaluation

Exposure monitoring will be conducted in accordance with the principles outlined in prEN 689:2016, the draft European standard for workplace exposure assessment to airborne contaminants [prEN 689:2016].

9.4.8.1. Air Monitoring

During and after the first daily dose on Days 1, 7 and 14 in Cohort B Part 1, static air samples will be collected on filters within air pumps positioned in two locations in the room. The air disturbance caused by the pumps is negligible and would not be expected to alter the normal air flow patterns in the room. Marks may be placed on the floor to indicate position of the participant and positions of pumps to ensure consistency throughout the study. Samples will be run over 20 and 60 min following dosing in each location. An additional set of samples over 60 min will be taken before the start of dosing on Day 1 to provide a background benchmark for reference.

On days when static air sampling is performed, the dosing sessions will have to be separated by the time necessary to collect the 60 min air sample.

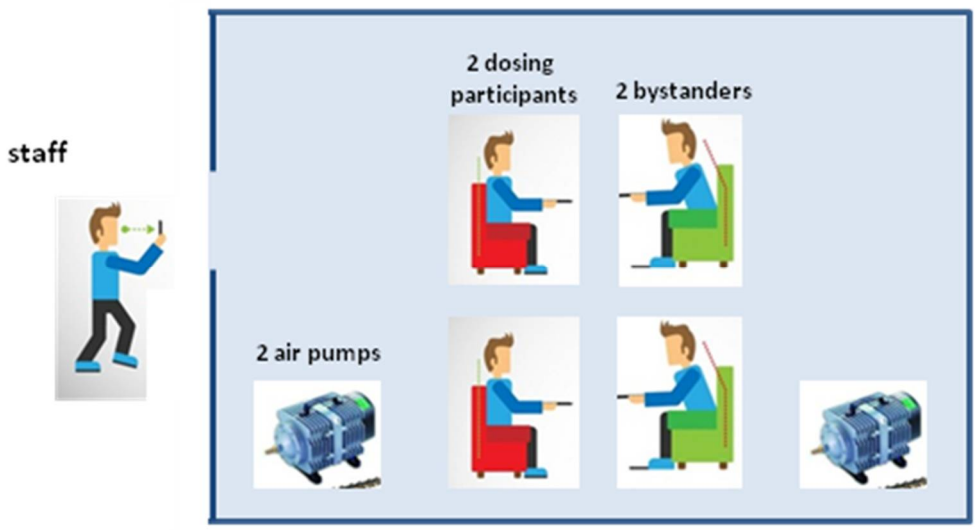
Sampling devices (Institute of Occupational Medicine [IOM] sampling heads connected to sampling pumps) shall be used to measure CCI15106 concentration. The IOM filter cassette assembly will be prepared using an immersion-extraction procedure to avoid any errors through wall deposition. Whenever possible, the Hygienist will observe the room through a glass in the door for the duration of sampling to make observations and note relevant contextual information to assist in the interpretation of the exposure measurements.

Air sample analysis will be performed by the Bureau Veritas laboratory (Bureau Veritas North America Inc, 95 Oakwood Road, Lake Zurich, IL, 60047). For air sampling, field blanks (filters which have been handled during the survey but not had air pulled through them) will be submitted with samples to check for accidental contamination during sample handling and storage. An average of one blank for every ten field samples will be sent for analysis.

9.4.8.2. Bystander Monitoring

Please refer to Figure 1 for the illustration of the design. Each dosing participant will be assigned a designated bystander for the duration of dosing. Two participants will dose at the same time in sitting position. The designated bystander will be seated facing their dosing participant within approximately 1 m of him/her. The first dosing participant will inhale the dose (both capsules), and then the second dosing participant will inhale the dose (both capsules). Please refer to Section 7.5 for detailed instructions on dosing. Each participant and their bystander will stay seated for the next 15 min, after which they will leave the dosing room. The staff will exit the room prior to bystander loading the capsule into the device (see Section 7.5) and remain outside the room for at least 15 min after dosing observing through a glass door.

Figure 1 Bystander and participant design illustration



The next two bystanders will be positioned near the next 2 dosing participants, and so on until all dosing is completed. This procedure will be followed for all doses in Cohort B Part 1, with the same bystanders positioned next to the same inhaling participant. After the first daily dose on days 1, 7 and 14, blood will be collected from bystanders 15 min after dosing (at ~tmax for CCI15106). Additionally, personal exposure air samples will be collected on filters placed on each bystander after the first daily dose on days 1, 7 and 14. The filters will be worn during dosing and for 15-minute period after dosing. Static air monitoring will be performed at the same time during and after the first daily dose on days 1, 7 and 14. During these dosing sessions, each set of two dosing participants will be separated by the time necessary to collect the 60 min air sample.

The filters used for personal exposure (IOM sampling heads connected to sampling pumps) shall be used to measure CCI15106 concentration in the person's breathing zone. The IOM filter cassette assembly will be prepared using an immersion-extraction procedure to avoid any errors through wall deposition. Whenever possible, the Hygienist will observe the room through a glass in the door for the duration of sampling to make

observations and note relevant contextual information to assist in the interpretation of the exposure measurements.

See Section 9.5 for PK assessments of bystanders.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection

Blood samples for PK analysis of CCI15106 in plasma will be collected at the time points indicated in SoA (Section 2). One 3 mL blood sample will be collected at each time point and the actual date and time of each sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the SRM OR equivalent.

9.5.2. BAL Sample Collection

BAL samples for ELF concentration analysis of CCI15106, urea, and cell counts will be collected at the time points indicated in SoA (Section 2). The actual date and time of each BAL sample collection will be recorded.

Details of BAL sample collection, processing, storage, and shipping procedures are provided in the SRM OR equivalent.

Due to the analysis methodology, any cells present in the ELF will be disrupted and their content released and analyzed together with the supernatant.

9.5.3. Urea Blood Sample

A 2 mL blood sample will be collected into Lithium Heparin tubes as soon as practically possible before the BAL samples.

Processing for plasma, storage and shipping procedures will be provided in the SRM or equivalent.

9.5.4. Sample Analysis

BAL and plasma analysis will be performed under the control of PTS-DMPK, GSK, the details of which will be included in the SRM OR equivalent. Concentrations of CCI15106 will be determined in plasma and BAL samples using the currently approved bioanalytical methodology. Plasma and BAL urea concentrations will be determined by Clinical Pathology, Safety Assessment, GSK. Raw data will be stored in the Good Laboratory Practices archives, GSK.

For bystander exposure, a plasma concentration of less than 0.5 ng/mL (the Limit Of Quantification of the method) represents an acceptable exposure since this is 29-fold lower than the highest plasma concentration measured at the no effect dose level for teratogenicity in the most sensitive species (rat [Rebetol SPC, 2009]).

Once the plasma and BAL samples have been analyzed for CCI15106, any remaining plasma or BAL may be used for other compound-related metabolites analyses, microbiome analysis, or other exploratory analyses that inform the effect of the drug on the body or the disease, the results of which will be reported under a separate protocol.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

Sample size is based on feasibility and though no formal power calculations are performed, the sample size is deemed adequate to provide a preliminary assessment of safety prior to progression to the next study.

Part 1

In Part 1, the study plans to enrol healthy participants in 3 cohorts. In Cohort A, there will be 6 participants on active and 2 on placebo, in cohort B, there will be 12 on active and 2 on placebo. In cohort C, there will be 14 subjects who will participate as bystanders and they will be associated with the dosing subjects in Cohort B on a one to one basis for the entire duration of dosing. All subjects in Cohort B will also undergo BAL.

Part 2:

In Part 2, 22 participants with COPD are planned to be enrolled. Cohort A will have 6 participants on active dose and 2 on placebo and Cohort B will have 12 participants on active and 2 on placebo. Fourteen participants (12 active and 2 placebo) enrolled in Cohort B Part 2 will also undergo BAL.

Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of seeing adverse events. For example, in Parts 1 and 2, in

treatment groups where 6 patients will receive the active drug, if the true adverse outcome rate is 5%, the chance of seeing at least one adverse outcome at a given dose is 26%. Similarly, if the true adverse outcome rate is 20%, the chance of seeing at least one adverse outcome at a given dose is 73%. For the treatment groups with 12 subjects receiving the active treatment, if the true adverse outcome rate is 5%, the chance of seeing at least one adverse outcome at a given dose is 46%. Similarly, if the true adverse outcome rate is 20%, the chance of seeing at least one adverse outcome at a given dose is 93%. This level of predictability is deemed adequate within this Phase 1 setting prior to commencement of the next study.

10.1.1. Sample Size Sensitivity

As sample size is based on feasibility, no sample size sensitivity was performed.

10.1.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Definition / Criteria	Analyses Evaluated
All Participants Screened	• Comprise of all participants who consent to participate in the clinical study. • Defined separately for Part 1 and Part 2.	
Safety	• Comprise of all participants who receive at least one dose of study treatment. • This population will be based on the treatment the participant actually received. • Defined separately for Part 1 (excluding Cohort C) and Part 2.	• Safety • Study Population
Systemic Pharmacokinetic Concentration	• Participants who receive at least one dose of study treatment and who undergo plasma PK sampling and have at least one postdose 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. • Defined separately for Part 1 (excluding Cohort C) and Part 2.	• PK
Lung ELF Concentration Population	• Participants who receive at least one dose of study treatment and who undergo BAL sampling and have postdose lung ELF CCI15106 and urea concentration result.	• BAL

Population	Definition / Criteria	Analyses Evaluated
	• 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. • Defined separately for Part 1 and Part 2	
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

10.3. Statistical Analyses

The analysis and reporting of Part 1 may be conducted prior to the completion of Part 2. For all parts, the analysis and reporting will be performed after the datasets are authorized and released for reporting.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by cohort, participant and time; summaries will be presented by cohort, treatment, and time.

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, n and percent will be used as summary statistics for categorical variables.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings.

Complete details will be documented in the RAP.

10.3.1. Safety Analyses

All safety analyses will be based on the Safety Population.

Endpoint	Statistical Analysis Methods
Adverse events (AEs)	The proportion of participants reporting AEs will be tabulated by treatment and by cohort. AEs will also be tabulated by severity and relationship.
Clinical laboratory	Laboratory results will be included in the reporting of this study for hematology, clinical chemistry, and urinalysis. 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 will also be tabulated.
Electrocardiogram (ECG)	The ECG parameters of PR, QRS, QT, QTc, QTcF and HR (bpm) will be reported. Overall assessment of ECG (Investigator's judgment) will be recorded as Normal, Abnormal - Not Clinically Significant and Abnormal - Clinically Significant. Summary statistics for change from baseline will also be tabulated.
Telemetry	Overall assessment of Telemetry (Investigator's judgment) will be recorded as Normal, Abnormal - Not Clinically Significant and Abnormal - Clinically Significant.
Spirometry	% Predicted forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) values will be tabulated for each timepoint.
Vital signs assessments	The following Vital Signs measurements will be tabulated: supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature. Summary statistics for change from baseline will also be tabulated.
Monodose RS01 Device safety	Safety incidents reported from use of medical device will be tabulated.

10.3.2. Pharmacokinetic Analyses

PK analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation Department (CPMS) within GSK. Plasma CCI15106 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.3 and above. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters may be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-last) and AUC(0-∞) where data

permit for single dose, and AUC(0-τ) for repeat dose], elimination half-life (t1/2), and clearance (CL/F) as data permit.

AUC(0-24), or AUC(0-48), or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality.

Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined from Cohorts B of Part 1 and Part 2.

PK data will be presented in graphical and/or tabular form and will be summarized descriptively. A population PK model (POP PK) may be developed with all available data as appropriate and may be reported separately. Further details of the analysis plan and methods will be detailed within the RAP and data analysis plan OR equivalent.

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.

All pharmacokinetic data will be stored in the Archives, GSK Pharmaceuticals, R&D.

PK exploratory analyses will be described in the reporting and analysis plan. The population PK analysis if conducted, will be presented separately from the main clinical study report.

10.3.3. Bystander and Environmental exposure Analyses

The plasma concentration data from bystanders will be summarised descriptively and listed. The amount of CCI15106 obtained from filters will be tabulated and reported. Additional analyses, where deemed necessary, will be described in the RAP.

If data permit, the plasma concentration measured from bystanders may be plotted against the data collected from the air filters.

10.3.4. Interim Analyses

No formal interim analyses are planned for this study. Safety and tolerability will be evaluated as described in Section 5.1. Systemic and, where available, lung PK may also be evaluated.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

%CV	Coefficient of variation
%CVb	Between-subject coefficient of variation
μg	Microgram
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	AUC from time zero to end of dosing interval
AUC(0-∞)	AUC from time zero to infinity
AUC(0-24)	AUC from time zero to 24 hours
AUC(0-t)	AUC from time zero to the time of last quantifiable concentration
BAL	Bronchoalveolar lavage
BMI	Body mass index
CCI15106-CFI	CCI15106 capsules for inhalation
CI	Confidence interval
CL/F	clearance
Cmax	Concentration at maximum
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case report form
ECG	Electrocardiogram
ELF	Epithelial lining fluid
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FTIH	First time in human
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B surface antigen
Hep B	Hepatitis B
Hep C	Hepatitis C
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
HRV	Human rhinovirus

IB	Investigator brochure
ICH	International conference on harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
Kg	Kilogram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
mg	milligram
min	Minute
mL	Milliliter
mm Hg	Millimeter of mercury
NOAEL	No observed adverse effect level
PK	Pharmacokinetics
POP PK	Population PK
PRINT	Particle Replication In Non-wetting Templates
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RSV	respiratory syncytial virus
RTP	Ribavirin triphosphate
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SRM	Study Reference Manual
t1/2	Elimination half-life
Tmax	Time of maximum concentration
ULN	Upper limit of normal
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WBC	White blood cells
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	Red blood cells (RBC) Indices: Mean corpuscular hemoglobin (MCV) Mean corpuscular volume (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Fasting Glucose	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis			

Laboratory Assessments	Parameters
	C virus antibody) • Serum pregnancy test in women • Coagulation parameters in the BAL cohorts The results of each test must be entered into the CRF.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

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

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Agreement to definition of source data.

Study and Site Closure

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

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

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

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

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Guidance for Grading Adverse Events

Taken from the Food and Drug Administration (FDA) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

The purpose of this appendix is to provide guidance and it is to be used in conjunction with the investigator's judgment.

Guidance for Grading Vital Signs Adverse Events

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements
** Oral temperature; no recent hot or cold beverages or smoking
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing

Allergic Reactions

Grade 1 allergic reaction (Pruritis without rash):

Participants with Grade 1 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

- Temperature >38.5°C

- Eosinophilia
- Respiratory involvement including brochospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 1 allergic reaction may continue the study drug at the discretion of the investigator. The participant should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK.

Grade 2 allergic reaction (Localized urticaria):
Participants with Grade 2 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

- Temperature >38.5°C
- Eosinophilia
- Respiratory involvement including brochospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 2 allergic reaction may continue the study drug at the discretion of the investigator. The participant should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK.

Grade 3 allergic reaction (Generalized urticaria or angioedema):
Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Grade 4 allergic reaction (Anaphylaxis):
Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Revised ACTG Toxicity Grade	Definition	Investigator action
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria Angioedema	Discontinue therapy
Grade 4	Anaphylaxis	Discontinue therapy

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events (CV)

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are

requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor and the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Male participants

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

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 3 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner are not eligible to participate.
- In addition male participants must refrain from donating sperm for duration of study and for 7 months after study completion or from last dose.

Table 3 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion

NOTES:

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

Female participants

Female participants of childbearing potential are not eligible to participate.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who can become pregnant are not eligible to participate

12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 h
• Record the liver event data, and complete an SAE data collection tool if the event also meets the criteria for an SAE2
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
• Do not restart or rechallenge participant with study treatment
MONITORING:
<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Blood sample for pharmacokinetic (PK) analysis, obtained within 48 h of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event</td></tr>
</table>

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James,2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Collect Liver Imaging and/or Liver Biopsy data.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally,if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**,indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excludingstudies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

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

12.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.1 for the list of GSK medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

TITLE PAGE

Protocol 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.

Protocol Number: 205822 /01

Short Title: Study of safety and drug levels of CCI15106 inhalation powder in healthy adults and adults with moderate chronic obstructive pulmonary disease. Study of CCI15106 levels in people standing near the person inhaling the drug.

Compound Number: CCI15106

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): EudraCT **2017-001070-42**

Approval Date: 31-MAY-2017

SPONSOR SIGNATORY:

PPD

31 MAY 2017

Date

PPD

PPD Etienne Dumont
Director, Clinical Development

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	31-May-2017
Original Protocol	20-Apr-2017

Amendment 01 31-May-2017

Overall Rationale for the Amendment: Changes requested after regulatory reviews

Section # and Name	**Description of Change**	**Brief Rationale**
8.1.3 Other Stopping Criteria	Added additional stopping criteria	Enhancing safety parameters in the study
5.1 Overall Design	Added PK review to all reviews required to proceed between study cohorts	Enhancing review requirements between study cohorts
1. Synopsis 2. Schedule of Activities 5.1 Overall Design	Added requirement to call male participants approximately 7 months after study completion to ensure their partner is not pregnant	Enhancing safety monitoring

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1. SYNOPSIS

Protocol 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). A concomitant study to evaluate environmental and healthy bystander exposure levels during dosing.

Short Title: Study of safety and drug levels of CCI15106 inhalation powder in healthy adults and adults with moderate chronic obstructive pulmonary disease. Study of CCI15106 levels in people standing near the person inhaling the drug.

Rationale:

This study is the first administration of CCI15106 inhalation powder hard capsules (CCI15106:polyvinyl alcohol 99:1 w/w 0.9x1 μm cylinder shape crystalline particles presented in capsules, from here on referred to as CCI15106-IP) to humans. This study will evaluate the safety, tolerability, and lung and systemic pharmacokinetics (PK) of CCI15106-IP delivered using Monodose RS01 device in healthy participants and in participants with moderate COPD.

The intention of this study is to provide sufficient confidence in the safety of the molecule delivered by inhalation to inform progression to further repeat dose and proof of concept studies.

A different formulation of CCI15106 (CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape particles) has been previously administered to humans in the first time in human study (FTiH) 202031.

Marketed CCI15106 is classified as teratogenic and is contra-indicated in women who are pregnant and in male partners of pregnant women and it is important to understand whether bystanders may be exposed to CCI15106 when it is used by patients in a dry powder, inhaled form. This study will evaluate the levels of CCI15106 in room air and in the plasma of bystanders. The study aims to replicate the real-life scenarios of dosing as close as possible. Real-life scenarios may include dosing of multiple patients in a single room in a nursing home or dosing of a single patient at home. A realistic worst-case scenario for bystanders is dosing of multiple patients in a standard size room in a nursing home.

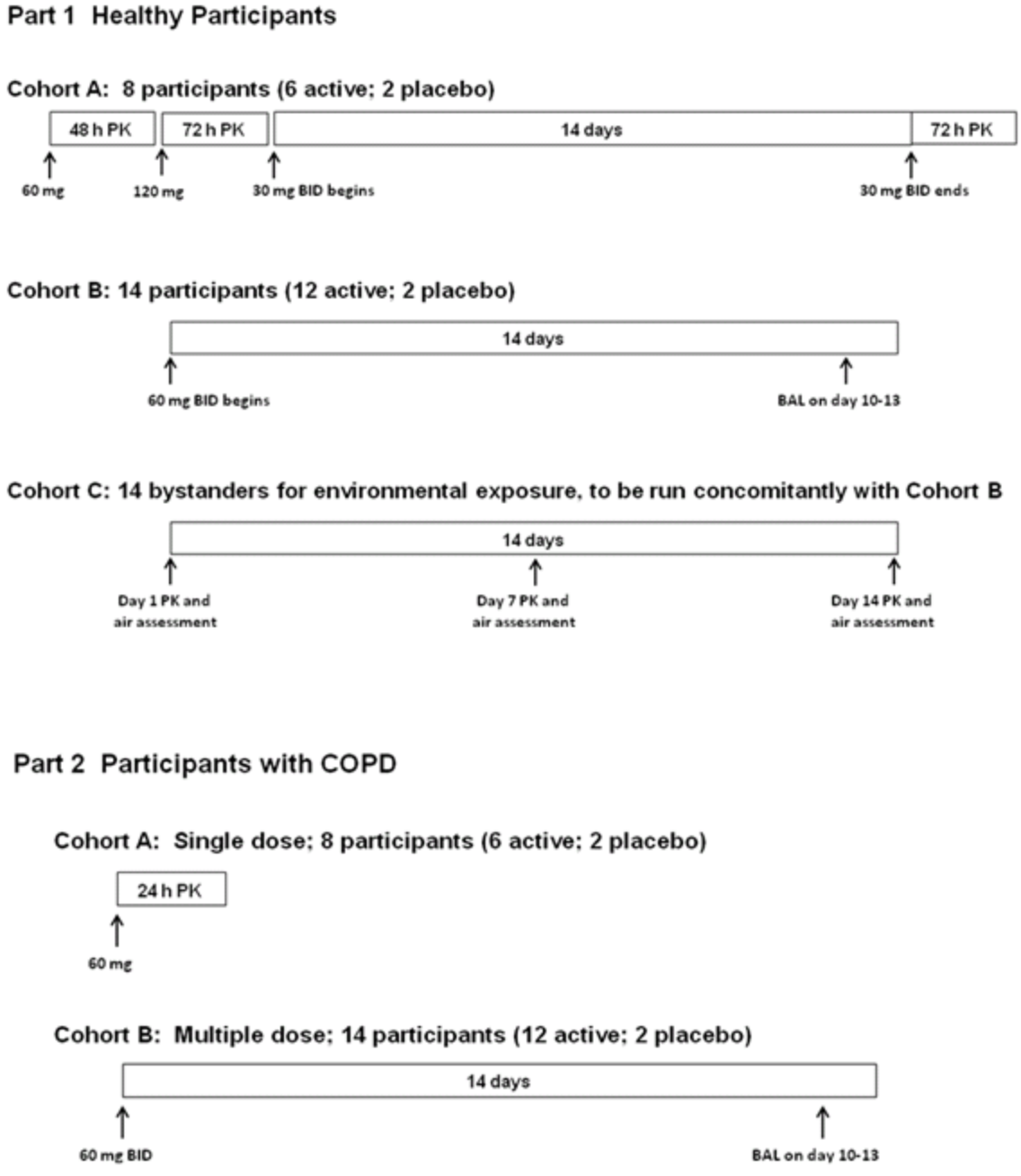
Objectives and Endpoints:

Objectives	Endpoints
Primary	
• 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 CCI15106 during self-administered dosing of participants.	• Concentration of CCI15106 in plasma of bystanders 15-20 minutes (min) after dosing (at predicted tmax) and 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	
• 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.
• 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.

Overall Design:

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.

Study schematic is presented below:



Number of Participants:

Approximately 36 healthy participants and approximately 22 participants with COPD will be randomized in this study for dosing.

Treatment Groups and Duration:

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. Doses administered and treatment duration for participants in each specific cohort will be as defined in the study schematic above. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

The total study duration will be approximately 82 days for Cohort A Part 1; approximately 75 days for Cohort B Part 1 and Cohort C Part 1; approximately 77 days for Cohort A Part 2; and approximately 90 days for Cohort B Part 2.

2. SCHEDULE OF ACTIVITIES (SOA)

If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order pre-dose:

1. Telemetry start
2. spirometry
3. 12-lead electrocardiogram (ECG)
4. vital signs
5. blood draws

and in the following order post-dose:

1. 12-lead ECG
2. vital signs
3. blood draws
4. spirometry

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Any change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GlaxoSmithKline (GSK) study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

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[2]	Notes
Informed consent	X		1. Screening assessments can be performed over multiple screening visits 2. All male participants will be called approximately 7 months after the follow-up visit to ensure no partner pregnancy 3. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required 4. To be drawn fasting (for at least 8 h) 5. To be administered to participants with COPD only, 15-30 minutes prior to spirometry 6. To be done at screening for participants with COPD only, following salbutamol dosing 7. To be performed in the bronchoalveolar lavage (BAL) cohorts only to confirm participant eligibility 8. 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[3]	X		
Haematology, clinical chemistry and urinalysis (include liver chemistries)[4]	X	X	
Salbutamol administration[5]	X		
Spirometry[6]	X		
12-lead ECG and vital signs	X	X	
Coagulation parameters[7]	X		
Capillary pCO_2[8]	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	XXX	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

3. INTRODUCTION

3.1. Study Rationale

This study is the first administration of CCI15106-IP (CCI15106:polyvinyl alcohol 99:1 w/w 0.9x1 μm cylinder shape crystalline particles produced using Liquidia's Particle Replication In Non-wetting Templates [PRINT] technology) to humans. The study will evaluate the safety, tolerability, and lung and systemic pharmacokinetics (PK) of single and repeat ascending doses of CCI15106-IP delivered by inhalation in healthy participants and in participants with moderate chronic obstructive pulmonary disease (COPD). The study will use a Monodose RS01 device for drug delivery by inhalation.

A different formulation of CCI15106 (CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape particles) has been previously administered to humans in the first time in human study (FTiH) 202031. That formulation was referred to as CCI15106 capsules for inhalation (CCI15106-CFI).

The intention of this study is to provide sufficient information regarding the safety of the molecule to inform progression to further repeat dose and proof of concept studies. The dose range proposed in this study is based on a starting dose previously investigated with the different formulation in the FTiH and escalating to a dose not to exceed the the no observed adverse effect level (NOAEL) in the most sensitive species (Section 5.5).

The other intention of this study is to investigate the level of CCI15106 that will be released into the air and may be found in the blood of the bystanders around participants inhaling CCI15106-IP.

3.2. Background

CCI15106 is ribavirin, which is a generic, broad spectrum nucleoside antiviral, discovered in the early 1970s, with both clinical and nonclinical data available, which is approved and used for oral administration in the treatment of chronic hepatitis C virus. It is also approved for respiratory syncytial virus (RSV) bronchiolitis by pulmonary inhalation in paediatric patients. CCI15106 is active versus RSV, human metapneumovirus, parainfluenza, influenza, adenovirus, and human rhinovirus (HRV), although HRV is 4-15-fold less susceptible than the others (GlaxoSmithKline Document Number 2015N249287_00). Based upon published data coronaviruses could also be susceptible without co-administration of interferon [Kurai, 2013, Morgenstern, 2005]. CCI15106 is not considered to be the active form, rather it is actively transported into target organs/cells and converted to ribavirin triphosphate (RTP) believed to be the active form against the viruses [Thomas, 2012]. The major limitation of the use of CCI15106 is hemolytic anemia due to accumulation of RTP in red blood cells and teratogenicity.

Liquidia's Particle Replication In Non-wetting Templates (PRINT) technology uses lithographic etching processes to produce particles with highly defined size and shape. CCI15106 plus the excipient, polyvinyl alcohol, are combined in a ratio of 99:1 w:w using Liquidia's technology to produce CCI15106-IP, a highly dispersible powder of uniform 0.9x1 μm cylinder shape particles which has afforded a 24-fold increase in lung

concentration at maximum (Cmax) relative to micronised CCI15106:Lactose formulation in a solid dose inhaled rat PK study (GlaxoSmithKline Document Number 2015N242219_00 [N20691-39]). The size and uniformity of the Liquidia particles provides an opportunity to improve the efficiency of CCI15106 administration to the lung while limiting systemic exposure that has the potential to limit hemolytic anemia and teratogenicity.

Acute exacerbations of COPD are a significant cause of morbidity and mortality [Vestbo, 2013; Kurai, 2013]. Multiple studies show that viral and/or bacterial respiratory infections are the most commonly associated triggers of COPD exacerbations. Respiratory viruses are detected in 20-60% of acute exacerbations of COPD [Kurai, 2013].

High efficiency lung delivery of broad spectrum CCI15106-containing engineered particles will establish an antiviral state in the lung. This has the potential to prevent the establishment or spread of the virus in the lower respiratory tract from the upper respiratory tract and/or increase the viral clearance translating to prevention of an exacerbation or a decrease in exacerbation severity and/or duration.

CCI15106 has been previously administered to humans in a different formulation, CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape PRINT particles (CCI15106 capsules for inhalation, referred to as CCI15106-CFI). Forty eight healthy participants have been administered a single dose of that formulation in one FTiH study 202031 and 12 participants received placebo. This study was planned as a double-blind (sponsor unblind), randomized, placebo-controlled, single and repeat escalating dose study to investigate the safety, tolerability, and pharmacokinetics of CCI15106-CFI in healthy participants and participants with moderate chronic obstructive pulmonary disease (COPD). In the single dose part of the study, CCI15106-CFI was administered by inhalation using Modified Air Inlet Rotahaler device at doses of 7.5 mg, 15 mg, 30 mg, and 60 mg. Overall, no clinically meaningful changes in vital signs or electrocardiograms (ECGs) were observed. There were no serious adverse events (SAEs) reported. Of the 60 subjects in the study, 25 reported adverse events (AEs) and 12 reported possibly drug-related AEs. The most common AEs were headache and cough (11 and 3 subjects, respectively). The comprehensive review conducted after single dose cohorts revealed acceptable safety profile, but lung epithelial lining fluid (ELF) levels of CCI15106 measured with 30 or 60 mg dose were below the levels predicted by pre-clinical evaluations and the increase in dose from 30 to 60 mg did not appear to result in a substantial increase in the lung concentration. Development of the CCI15106-CFI formulation was terminated before dosing repeat dose or COPD cohorts as a new formulation (CCI15106-IP) was developed that has higher ratio of active pharmaceutical ingredient to inactive ingredients per unit of powder and allows achieving the same dose in 1 capsule instead of 4. This is expected to lead to a higher lung ELF Cmax. The decision to terminate was not based on safety data.

Marketed formulations of CCI15106 are classified as teratogenic and is contra-indicated in women who are pregnant and in male partners of pregnant women. Currently approved aerosolised forms of CCI15106 are recommended to be administered in a negative pressure environment [Virazole USPI 2013]. It is important to understand whether bystanders may be exposed to CCI15106 when it is used by patients in a dry

powder, inhaled form. The most likely route of exposure of bystanders will be through inhalation of powder released during dosing. The study aims to replicate the real-life scenarios of dosing as close as possible. Real-life scenarios may include dosing of multiple patients in a single room in a nursing home or dosing of a single patient at home. A realistic worst-case scenario is dosing of multiple patients in a standard size room in a nursing home.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of CCI15106 may be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2015N250735_02]. Information specific to the approved formulations of CCI15106 can be found in the labels for oral CCI15106 approved for the treatment of hepatitis C and CCI15106 nebulizer approved for the treatment of respiratory syncytial infections in children [Rebetol SPC 2009; Virazole USPI 2013].

Based on pre-clinical safety assessment studies summarized in the IB and the clinical experience with CCI15106-CFI, as well as oral and inhaled (nebulised) CCI15106, the following clinical parameters will be monitored throughout the study in order to better characterize the safety and tolerability of CCI15106-IP (Section 3.3.1). Refer to SoA, Section 2, for the timing of all clinical assessments.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product, CCI15106-IP		
Teratogenicity and embryocidal effects	CCI15106 showed embryocidal and teratogenic effects in animals. The no observed adverse effect level (NOAEL) in oral embryofetal development studies in rats and rabbits was 0.3 mg/kg/day, considerably lower than the maximum proposed inhaled clinical dose of 120 mg/day CCI15106 (0.02-fold to 0.05-fold based on mg/m^2). In addition, human seminal fluid contains ~2-fold higher concentrations of CCI15106 compared to serum. There are limited data from the use of CCI15106 in pregnant women (5 cases of measles-pneumonia and 1 case of influenza-pneumonia)) [Virazole SPC, 2014]. Four pregnancies were completed and resulted in the birth of healthy children. A further 7 cases are known in which nurses administered Virazole dry substance during pregnancy (n=6) or just before conception (n=1). In 6 cases, healthy children were born. In one case, a chromosomal translocation was reported with mild developmental delay [Virazole SPC, 2014].	Women of child-bearing potential and male partners of women who are pregnant or breastfeeding will be excluded. Effective contraception for female partners of male participants will be required up to 7 months post study. Any pregnancies that occur during the study or up to 7 months post study will be reported by the investigator to the pregnancy registry. The informed consent form will describe these reproductive risks, as well as the risk to female partners of male participants. Systemic exposure for the target clinical dose of CCI15106 is expected to be lower than exposure for currently available oral and nebulized CCI15106. The maximum inhaled total daily single dose of CCI15106 in Protocol 205822 will be 120 mg and the maximum inhaled multiple daily doses will be 60 mg twice daily (BID). These proposed maximum clinical doses are significantly lower than the currently approved doses of CCI15106 (800-1400 mg for Copegus and Rebetol and 6 g for inhaled Virazole).
Mutagenicity	CCI15106 is clastogenic in vitro and in vivo but is Ames negative. The pattern of genotoxicity is consistent with that reported for other nucleoside analogues. Point of departure modelling (an accepted method of risk assessment for nucleoside analogues) indicates a negligible genotoxic concern. CCI15106 was not tumorigenic in lifetime rodent studies at doses up to 75 mg/kg/day in the mouse and 40 mg/kg/day in the rat (~3-fold the	The data indicate a negligible genotoxic concern, which is mitigated by the lower expected systemic and lung exposure compared with currently available oral and nebulized CCI15106 and shorter duration of clinical treatment (≤ 14 days). The maximum inhaled single total daily dose of 120 mg or multiple total daily doses of 60 mg

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	maximum proposed inhaled clinical dose of CCI15106-IP based on mg/m^2), or in the transgenic p53(±) mouse model at doses of up to 300 mg/kg/day.	BID for Protocol 205822 are significantly lower than the currently approved doses of CCI15106 (800-1400mg for Copegus and Rebetol and 6 g for inhaled Virazole).
Increased exposure in participants with severe renal impairment	As CCI15106/ribavirin is substantially excreted by the kidneys, exposure may be increased in those with pre-existing renal impairment CCI15106 is contraindicated in patients with chronic renal failure, patients with creatinine clearance < 50mL/min, and/or on hemodialysis [Rebetol SPC, 2009] However, the Copegus labels allow dose modifications for patients with CrCl <50 mL/min [Copegus USPI, 2015; Copegus SPC, 2015].	The maximum inhaled single total daily dose of 120 mg or multiple total daily doses of 60 mg BID proposed for Protocol 205822 are significantly lower than the currently approved doses of CCI15106 (800-1400mg for Copegus and Rebetol and 6 g for inhaled Virazole). COPD patients with impaired renal function (eGFR <30 cc/min, using CKD-EPI equation) will be excluded and renal function will be monitored.
Pulmonary effects	**GSK's formulations:** In toxicity studies conducted by GSK, no adverse pulmonary toxicity was observed following administration of either CCI15106:trehalose:trileucine particles or CCI15106-IP in GSK studies of 28 day duration at dose levels of ≤32.5 mg/kg in rat or ≤34.2 mg/kg in dog. The deposited lung doses at the NOAELs on the 28 day studies using CCI15106-IP were estimated 6- to 8-fold higher than in human at the maximum proposed clinical administration of CCI15106-IP of 120 mg/day (conservatively assuming 100% human lung deposition). Adverse lung pathology (including neutrophilic inflammatory cell infiltrates) and unscheduled deaths were observed in rats in a 14 day inhaled tolerability study with CCI15106-IP at an estimated dose of 68.7 mg/kg. Rat deaths and lung pathology have been reported during oral and inhalation toxicology programs for approved/marketed formulations of CCI15106 at systemic exposures and inhalation dose levels similar or less than those delivered in this study. As CCI15106-IP is dry powder, it has a reduced risk of acute lung effects compared to low osmolarity nebulised solution. No bronchospasms were observed in the FTIH study 202031; however there were occurrences of non-serious cough and dyspnoea. Maximal amounts of powder administered were higher in the FTIH study than those planned for the	Repeat dosing will be evaluated in healthy participants in this study prior to dosing in participants with COPD. Patients with poorly controlled COPD will be excluded (see Section 6.2.2). Lung function will be monitored with frequent spirometry and physical examinations will be conducted. If they become medically necessary, short-acting bronchodilators may be administered as needed by the clinical staff. Oxygen and resuscitation measures will be available in the unit in the event they would be needed. The trial is to be conducted in a dedicated phase I unit with supplementary (Medicines & Healthcare Products Regulatory Agency) accreditation and experience in the conduct of Phase I studies.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	current study. **Labels of approved formulations:** Virazole SPC (13 November 2014) includes the following: • Sudden deterioration in pulmonary function associated with aerosolized CCI15106/ ribavirin has been observed in children, and significant deterioration in pulmonary function has been observed in patients with asthma and chronic obstructive pulmonary disease (COPD) during CCI15106/ribavirin treatment. • Bronchospasm has been reported following CCI15106/ribavirin use by patients with COPD and asthma. Pulmonary adverse reactions reported in clinical studies or in postmarketing use of aerosolized CCI15106/ribavirin include bacterial pneumonia, pneumothorax, laryngitis, pharyngitis, dyspnoea, cough, hypo- and hyperventilation, apnoea, and bronchospasm.	
Haemolytic anaemia	The primary toxicity of approved formulations of CCI15106 is haemolytic anemia, which was observed in 10% of oral CCI15106 plus interferon alpha2b combination-treated participants and occurs within 1 to 2 weeks of start of therapy [Rebetol USPI, 2015]. Haemolytic anemia associated with CCI15106 may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarction. CCI15106 is known to accumulate in the red blood cells and may cause hemolysis, which may result in increased uric acid [De Franceschi, 2000]. Anemia has been shown to occur frequently with experimental oral and intravenous CCI15106 in humans [Virazole USPI, 2013]. Haemolytic anaemia is monitorable and reversible with reduction / cessation of treatment [Rebetol USPI, 2015]. **GSK formulations:** In toxicity studies conducted by GSK, mild anaemia was seen in 4 week studies following inhalation administration of CCI15106:trehalose:trileucine particles (rat and dog) or CCI15106-IP (rat only).	Participants will be monitored regularly with complete blood counts and hematocrit, as per SoA (Section 2). Participants with hemoglobinopathies will be excluded. Due to the short dose and duration and the red blood cell count monitoring in place, laboratory monitoring for hemolysis is not warranted in this study. Participants will have an ECG assessment prior to and during the study. Cardiac monitoring, including assessment of blood pressure and heart rate, along with 12-lead electrocardiograms (ECGs) will be performed, per protocol. If cardiac status deteriorates on therapy, study medication should be suspended and/or discontinued.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiac effects	**GSK formulations:** Heart toxicity was not observed in definitive 4 week toxicity studies in rats and dogs following inhalation administration of CCI15106:trehalose:trileucine particles or CCI15106-IP. Minimal lymphocytic/mononuclear or mixed inflammatory cell infiltrate in the myocardium was observed following inhalation administrations of 68.7 mg/kg/day as CCI15106-IP at higher dose levels during a 14 day tolerability study ($AUC_{0\text{-}24h}$ was 5-fold higher than the human $AUC_{0\text{-}24h}$ estimated at 120 mg CCI15106-IP). These findings were also observed following oral and inhalation administrations of approved/marketed formulations of CCI15106-IP and do not, therefore, present at a greater risk compared to marketed/approved CCI15106 formulations which are approved for administration at higher inhaled and oral dose levels/ systemic exposures and administered for longer treatment durations than those proposed for CCI15106-IP. There were no cardiac events reported in the FTIH study of CCI15106-CFI. The following cardiovascular adverse reactions have been reported in clinical studies and in the postmarketing setting of CCI15106, which included severely ill infants with life-threatening underlying disease: cardiac arrest, hypotension, bradycardia, and digitalis toxicity [Virazole USPI, 2013]. Bigeminy, bradycardia, and tachycardia, have been described in patients with underlying cardiac disease.	Participants will have ECG prior to dosing and will be assessed prior to and during therapy by 12-lead ECG and telemetry. If cardiac status deteriorates on therapy, study medication should be suspended and/or discontinued. Participants with uncontrolled or unstable cardiac diseases will be excluded.
Photosensitization	Photosensitivity reaction has been reported commonly in clinical trials and in the postmarketing setting for CCI15106 [Rebetol SPC, 2009]. Photoallergic reaction with CCI15106 has been described in the literature [Stryjek-Kaminska, 1999].	Physical examination to include skin exams will be performed and documented as per SoA (Section 2). Any findings suggesting photosensitivity reaction will be promptly addressed according to appropriate standard of care and followed up for resolution.
Oral erosions	Ulcerative stomatitis, stomatitis, mouth ulceration are undesirable effects associated with CCI15106 [Rebetol SPC, 2009]. Nasal erosions were	Physical examination to include oral exam will be performed and documented as per SoA (Section 2). Any

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	observed in the squamous epithelium of the nasal turbinates of a proportion of dogs (but not rats) receiving the high dose (25.1 mg/kg/day) following administration of CCI15106-CFI and ≥16.3 mg/kg following administration CCI15106-IP for 4 weeks. These effects were considered non adverse and unlikely to be clinically relevant since CCI15106 will be administered to humans by oral inhalation, compared with oro-nasal administration (over 60 minutes) in the dog study, thereby minimising the potential for nasal exposure. Histopathological findings in rats included epithelial changes in the larynx (squamous metaplasia) in animals given the control article and CCI15106 formulation over 4 weeks. These changes were low in incidence and severity and showed full recovery following completion of the off-dose period. The findings were consistent with low grade non-specific irritation and, being an adaptive change of low severity, are considered non-adverse [Kaufmann, 2009] and a poor predictor of irritancy in humans given that the rat larynx is known to be particularly sensitive to inhaled irritants [Lewis, 1991].	findings suggesting oral erosion will be promptly addressed according to appropriate standard of care and followed up for resolution.
Testicular toxicity	**Testicular toxicity:** Testicular toxicity was seen in mice treated orally with CCI15106 for 3 to 6 months at doses of 15 mg/kg/day and [Rebetol SPC, 2009]. Recovery occurred within one or two spermatogenic cycles. No stage specific or cell specific abnormalities of spermatogenesis were observed in GSK studies which were conducted on the testes of rats (CCI15106:trehalose:trileucine particles and CCI15106-IP) and dogs (CCI15106-IP only) during definitive 4 week inhalation toxicity studies.	Given the shorter duration of clinical treatment (≤ 14 days) and lower expected exposure compared with currently available oral and nebulized CCI15106, the risk of testicular toxicity is considered to be low.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
BAL procedure	BAL requires bronchoscopy and sedation. Bronchoscopy can be performed safely on an outpatient basis [Du Rand, 2013], however, serious complications occurred in 1.1% of patients, including mortality in 0.02% of patients in a retrospective series (n=20,986 patients). Common adverse events reported with bronchoscopy, included tachycardia/bradycardia, major and minor bleeding, bronchospasm, laryngospasm, cough, dyspnea, sore throat, apnea, seizure, desaturation, pneumothorax, and pulmonary edema.	BAL will be performed by an experienced pulmonologist in dedicated bronchoscopy suite with close monitoring in recovery area post procedure.
Other		
Bystander exposure, including healthcare workers	Detectible levels of CCI15196-IP may be present in the immediate inhalation area during routine care activities. Labels of approved formulations: The Virazole patient information leaflet (last revision August 2014) states the following: • Virazole is to be administered in a hospital setting only, by a doctor or a nurse. • The nebuliser through which Virazole is given should be turned off 5 to 10 minutes before visitors see the patient to minimise unnecessary exposure to Virazole. • Pregnant women, women who are trying to become pregnant, and sexually active men should avoid exposure to Virazole, because the risk of harm to an unborn baby is unknown. Breast-feeding women are also to avoid exposure to Virazole. Postmarketing surveillance of CCI15106 has revealed reports of adverse events in individuals providing direct care to infants receiving aerosolized CCI15106 [Virazole USPI 2013]. The most common signs and symptoms were headache, conjunctivitis, rhinitis, nausea, rash, dizziness, pharyngitis,	Levels in air and in bystanders will be assessed. Whenever study participants are dosed outside the negative pressure room, all hospital personnel will be asked to leave the room and will not re-enter until 15 min after dosing. Pregnant women or women of child-bearing potential will be warned of the potential risks. Training on the potential health hazard will be provided to study personnel, including protective equipment, monitoring, and waste disposal. No women of child-bearing potential will be enrolled as participants or as bystanders.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and lacrimation. Several cases of bronchospasm and/or chest pain have been reported, usually in individuals with reactive airways disease. Seven cases are known in which nurses administered Virazole dry substance during pregnancy (n=6) or just before conception (n=1). In 6 cases, healthy children were born. In one case, a chromosomal translocation was reported with mild developmental delay.	

Exposure risk for additional medications administered in the study (Salbutamol):

See package leaflet (https://www.medicines.org.uk/emc/PIL.22837.latest.pdf).

3.3.2. Benefit Assessment

As this Phase I study is being conducted to assess the safety and PK in healthy participants and participants with COPD, there is no direct clinical benefit to study participants. Participation in this study may contribute to the process of developing new therapies in an area of unmet need.

3.3.3. Overall Benefit:Risk Conclusion

CCI15106 is an approved product as an oral agent in combination with interferon α or β (pegylated and non-pegylated) for chronic hepatitis C in patients 3 years of age and older with compensated liver disease (Copegus, Rebetol), and is approved in the nebulised form for use in infants and young children with severe respiratory syncytial virus infections (Virazole). CCI15106-CFI has been administered to healthy participants in single doses up to 60 mg with acceptable safety and tolerability profile. The risk of adverse effects is minimized for the population being investigated in the proposed study by careful selection of participants for the study, the relatively short duration of exposure, and the extent of safety monitoring incorporated into the study. The highest dose planned in this study (single dose of 120 mg or multiple doses of 60 mg BID) is significantly lower than the currently approved doses of CCI15106 (800-1400 mg for Copegus and Rebetol and 6 g for aerosolized Virazole). The risk to study staff will be managed by occupational precautions.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• 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 CCI15106 during self-administered dosing of participants.	• Concentration of CCI15106 in plasma of bystanders 15-20 minutes (min) after dosing (at predicted tmax) and 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	
• 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.

Objectives	Endpoints
Tertiary/Exploratory	
• 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)

5. STUDY DESIGN

5.1. Overall Design

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.

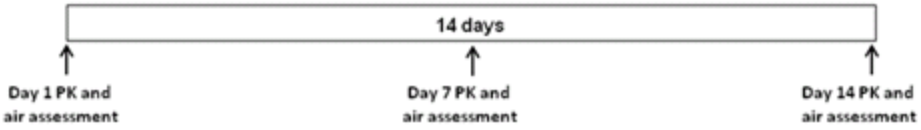
Study schematic is presented below:

Part 1 Healthy Participants

Cohort A: 8 participants (6 active; 2 placebo)

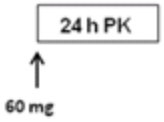
Cohort B: 14 participants (12 active; 2 placebo)

Cohort C: 14 bystanders for environmental exposure, to be run concomitantly with Cohort B



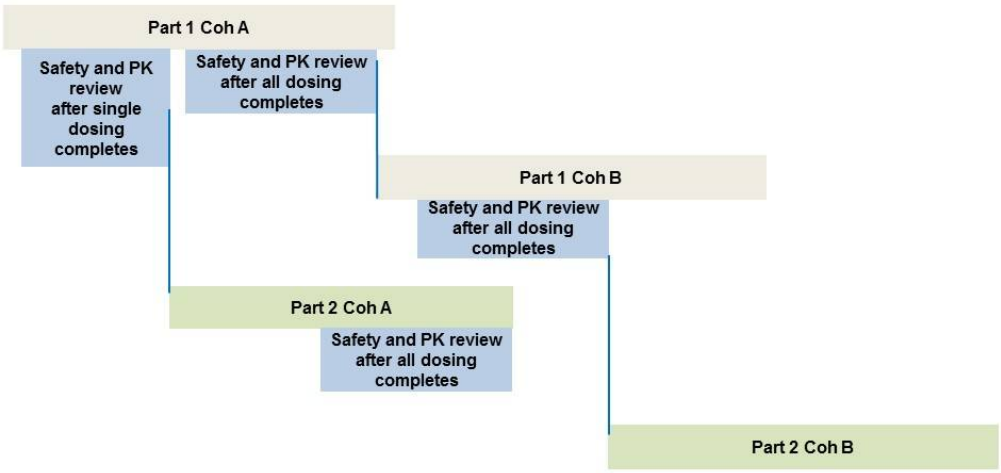
Part 2 Participants with COPD

Cohort A: Single dose; 8 participants (6 active; 2 placebo)



Cohort B: Multiple dose; 14 participants (12 active; 2 placebo)

The following reviews will be conducted during the study progression:



- In Part 1, Cohort B dosing can begin only after review of safety/tolerability and PK of all dosing in Part 1 Cohort A (see Section 7.2 for composition of the review team).
- In Part2, Cohort A dosing can begin only after review of safety/tolerability and PK for a single dose administration of 60 and 120 mg in all participants in Part 1 Cohort A (see Section 7.2 for composition of the review team).
- In Part 2, Cohort B dosing can begin only after the comprehensive review of all data obtained in Part 1, including safety and systemic PK, as well as lung PK where available (see Section 7.2 for composition of the review team) and after review of safety/tolerability of Part 2 Cohort A.
- Environmental and bystander exposure review may be conducted at any time after the data are collected. Until this review is completed and exposure found acceptable, all subsequent cohorts will be dosed in the negative pressure environment.
- The planned doses may be modified, repeated or cancelled based upon safety/tolerability/ and/or PK from preceding cohorts (See Section 7.2 for more information). Single doses will not exceed 120 mg and repeat doses 60 mg BID.
- The planned dose frequency or duration may be modified based on emerging safety/tolerability and PK data from previous cohorts. The total daily dose will not exceed 120 mg.
- The number of cohorts may be reduced or expanded if needed.

- All participants in Part 1 Cohort B and in Part 2 Cohort B (60 mg BID dose for both Cohorts) will undergo BAL once during the study on days 10, 11, 12, or 13 after the first (morning) dose. Based on the lung ELF concentrations of CCI15106 observed, additional double-blinded, single-blinded or open-label repeat dose cohort(s) may be added at a dose not to exceed 120 mg daily. The total number of participants will not exceed that specified in Section 5.2.
- BAL may be used in the additional cohorts to obtain a more accurate estimation of the dose to lung exposure ratio and provide data for future dose predictions.

There will be approximately 3 cohorts of healthy participants in this study and approximately 2 cohorts of participants with moderate COPD. Participants in the dosing cohorts will be randomized to receive either CCI15106-IP or matching Liquidia particles without the active ingredient (lactose:polyvinyl alcohol 98:2 w/w 0.9x1 μm cylinder shape amorphous particles, referred to as placebo). Participants in Cohort C will be assigned to participants in Cohort B on a one to one basis for the entire duration of the study.

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.

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. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). Participants will be dosed the following morning on Day 1 followed by post-dose assessments. Blood for PK assessments will be collected for the next 48 hours (h). On Day 3 (after collection of 48 h PK time point), participants will receive a single dose of 120 mg followed by post-dose assessments and PK assessments for the next 72 h. Repeat dosing will begin on the morning of Day 6 (after collection of 72 h PK time point) and will continue for 14 days BID. Participants will remain in the unit for additional 2 days until 72 h PK timepoint is collected. Dosing frequency and duration may be adjusted based on emerging safety and tolerability data. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

For Cohort B Part 1, Repeat Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). 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. BAL procedure will be performed as soon as possible (within 1 h) after the first (morning) dose on one of the following days: 10, 11, 12, or 13. Participants will be discharged on Day 15 following completion of all post-dose assessments after the last dose, or later if additional PK collection or other assessments are required. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

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. Bystanders will report to the unit on Day

-1 and will remain for all 14 days of dosing of Cohort B. They will be positioned in the room with the dosing participants for every dose taken, as described in Section 9.4.8. Air sampling and bystander PK evaluation will be conducted on days 1, 7, and 14 as described in Section 9.4.8. Bystanders will be discharged on Day 15 following completion of all post-dose assessments after the last dose. Bystanders will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

For Cohort A Part 2, Single Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). They will be dosed the following morning on Day 1 followed by post-dose assessments. Participants will be discharged following completion of the post-dose assessments the next day (Day 2). They will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

For Cohort B Part 2, Repeat Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). 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. BAL procedure will be performed as soon as possible (within 1 h) after the first (morning) dose on one of the following days: 10, 11, 12, or 13. Participants will be discharged on Day 15 following completion of all post-dose assessments after the last dose, or later if additional PK collection or other assessments are required. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

The total study duration will be approximately 82 days for Cohort A Part 1; approximately 75 days for Cohort B Part 1 and Cohort C Part 1; approximately 77 days for Cohort A Part 2; and approximately 90 days for Cohort B Part 2.

5.2. Number of Participants

Approximately 36 healthy participants and approximately 22 participants with COPD will be randomized in this study for dosing.

Evaluable participants will be defined in the Reporting and Analysis Plan (RAP).

Additional participants or cohorts may be enrolled to allow for evaluation of additional dose levels or to increase numbers on prior doses or to increase the number of bystanders. The total number of participants in this study will not exceed 86 and the total number of cohorts will not exceed 7, including the bystander cohort(s).

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

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

5.4. Scientific Rationale for Study Design

Participants and all site personnel, with the exception of the study pharmacist or designee, will be blinded to participant randomization throughout the study. The GSK study team participating in the dose escalation meetings will review blinded data and will be un-blinded on a need to know basis only if necessary to facilitate review of the safety, tolerability and PK data as appropriate in real time to inform dose escalation decisions. The GSK study team or personnel at any contract research organization that may be involved in data management or in statistics and programming will not reveal the treatment assignments to the site personnel or participants.

In repeat dosing cohorts, CCI15106-IP will be administered for 14 days to mimic the expected duration of treatment in target patient populations.

Inclusion of Bronchoscopy

BAL will be performed on 14 healthy participants (Cohort B Part 1) and 14 participants with COPD (Cohort B Part 2) to evaluate levels of CCI15106 in the ELF. BAL will be performed once, as soon as possible (within 1h) after the first (morning) dose. This will allow assessment of CCI15106 levels at around tmax in the ELF. The timing of BAL in Part 2 Cohort B may be adjusted based on BAL results obtained in Part 1. Available models [Weber, 2017] predict that the level of CCI15106 in the bronchoalveolar fluid following 14 days of 60 mg BID dosing may be achieved above 200 μM around T_{max} which is above the EC50 for all respiratory viruses including HRV and expected to prevent or minimise the migration of an upper respiratory tract viral infection to the lower respiratory tract. These data will enable a more accurate estimation of the dose to lung exposure ratio and provide valuable information for future dose predictions.

Inclusion of Participants with COPD Cohort

Due to potential exposure differences as a function of COPD-induced lung damage, participants with moderate COPD will be included to aid in dose selection for the future proof of concept studies in participants with COPD. This cohort will also help obtain some safety and tolerability data in this patient population prior to a wider administration in the Proof of Concept study.

Inclusion of Bystander Cohort

Due to known teratogenic potential of CCI15106, we need to evaluate how much of it gets into the environment around the dosing participant to ensure that no potentially pregnant bystanders are put at-risk due to secondary exposure. Participants dosed in the

Cohort used to evaluate environmental and bystander exposure will be dosed outside a negative pressure enclosure. All other participants will be dosed inside the enclosure. When participants dose outside the enclosure, all personnel will leave the room and not re-enter until 15 min after dosing. During this time, participants will be observed through a window in the door.

5.5. Dose Justification

The dose proposed for Part 1 Cohort A is based on the data from 202031 where CCI15106-CFI up to 60 mg single dose has been evaluated, and no SAEs or severe AEs were observed, as well as the investigation of the four week toxicity and toxicokinetics in rats and dogs in which the NOAEL was determined [GSK Document Number 2017N312240_00 and GSK Document Number 2017N312247_00].

Table 1 below shows the safety margins in terms of lung and systemic exposure with respect to the NOAEL obtained from the pre-clinical studies, and the folder cover with respect to the systemic exposure following oral administration of the marketed dose (1200 mg/day) in humans for the doses proposed in this study. These data indicated reasonable safety margins for Cohort A in Parts 1 and 2, where single dose of CCI15106-IP will be administered.

The selection of appropriate dose for Part 1 Cohort B will be performed upon consideration of available safety, tolerability and systemic PK data from Part 1 cohort A. The review data set for this selection will, at minimum, consist of: any adverse events, liver function test results, vital signs, ECG, spirometry data, and laboratory findings, and any available systemic PK results.

The selection of appropriate dose for Part 2 Cohort A will be performed upon consideration of available safety and tolerability data following the single doses (60 and 120 mg) in all participants in Cohort A of Part 1.

The selection of appropriate dose for Part 2 Cohort B will be performed upon consideration of available safety, tolerability, systemic PK and lung concentration data from Part 1 Cohort B.

The dose level in any cohort may be titrated up or down based on emerging safety, tolerability, and systemic PK and lung data where available. The maximum dose will not exceed 120 mg per day.

Table 1 Prediction of Human Systemic and Lung Exposure and Safety Margins of CCI15106

Dose Frequency	Proposed human dose per day (mg)	Human Lung Dose (mg/g)	Lung Safety Margin (Rats)	Lung Safety Margin (Dogs)	Human Systemic expoure AUC(0-24) (ng.h/mL) *	Systemic Safety Margin (Rats)	Systemic Safety Margin (Dogs)	Systemic Safety Margin (human Oral Ribavirin)
Assume 100% lung deposition in humans								
SD	60	0.06	12	16				
SD	120	0.12	6	8				
Assume 59% lung deposition in humans								
SD	60	0.04	20	26	552	17	40	92
SD	120	0.07	10	13	1104	8	20	46
BD**	30	0.04	20	26	3080	3	7	16
BD	60	0.07	10	13	6150	2	4	8

Assumptions:

human: body weight 70 kg, lung weight 1000 g; 100% or 59% inhaled dose into lungs are assumed

59% was predicted from the MPPD for lung deposition of the device

rat: mean body weight 0.244kg, mean lung weight 1.145 g, 10% inhaled dose into lungs;

dog: mean body weight 8 kg, mean lung weight 73.1 g, 25% inhaled dose into lungs.

Rat NOAEL dose = 32.5 mg/kg, AUC=9.34 μg.h/mL (whole study means)

Dog NOAEL dose = 34.2 mg/kg, AUC=22.2 μg.h/mL (whole study means)

Human oral AUC(0-24) =2xAUC0-12=50.722 μg.h/mL (Steady state) [Copegus USPI, 2015]

* human systemic AUC(0-24) is predicted from a mechanistic model [Weber, 2017]

** BD - twice daily dosing; AUC(0-24) on Day 14

6. STUDY POPULATION

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

6.1. Inclusion Criteria

6.1.1. Inclusion Criteria for Healthy Participants and Bystanders

Participants are eligible to be included in the study only if all of the following criteria apply. Rescreening is allowed only if approved by the Medical Monitor.

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator (in consultation with the Medical Monitor if required) decide and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

4. Body weight ≥50 kg for males and 45 kg for females and body mass index (BMI) within the range 19 to 31 kg/m^2 (inclusive) for males and 17 to 31 kg/m^2 (inclusive) for females.

Sex

5. Male OR Female

   a. Male participants:

   A male participant with female partner of child bearing potential must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 7 months after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

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

Informed Consent

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

6.1.2. Inclusion Criteria for Participants with COPD

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

Age

1. Participant must be 40 to 75 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosed with moderate COPD (GOLD class II) by a qualified physician as defined by the GOLD guidelines (http://www.goldcopd.org/).
3. The participant has spirometry at screening, conducted 15-30 minutes after administration of 400 microgram (μg) salbutamol via metered dose inhaler showing:
    - post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% and <80% predicted normal [Quanjer, 2012] and
    - post-bronchodilator FEV_1/ forced vital capacity (FVC)<0.7, where FEV_1 is forced expiratory volume in 1 second and FVC is forced vital capacity.
4. Participant is a smoker or an ex-smoker with a smoking history of at least 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent).
5. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor if required agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

6. Body weight ≥ 45 kg and BMI within the range 17 – 32 kg/m^2 (inclusive).

Sex

7. Male OR Female

    a. Male participants:

    A male participant with female partner of child bearing potential must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 7 months after the last dose of study treatment and refrain from donating sperm during this period.

    b. Female participants:

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

Informed Consent

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

6.2. Exclusion Criteria

6.2.1. Exclusion Criteria for Healthy Participants and Bystanders

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

Medical Conditions

1. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)

2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
4. QTc > 450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate (HR) according to Fridericia's formula (QTcF), machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
   - For purposes of data analysis, QTcF will be used as specified in the RAP.
5. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<40 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcF interval	>450 msec	

6. Any clinically significant central nervous system (e.g., seizures), cardiac, pulmonary, metabolic, renal, hepatic or gastrointestinal conditions or history of such conditions that, in the opinion of the investigator may place the participant at an unacceptable risk as a participant in this trial or may interfere with the absorption, distribution, metabolism or excretion of drugs.

Prior/Concomitant Therapy

7. Past or intended use of over-the-counter or prescription medication (including herbal medications) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study. Specific medications listed in Section 7.7 may be allowed.

Prior/Concurrent Clinical Study Experience

8. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 month period.
9. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.

10. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Diagnostic assessments

11. Hemoglobin (Hgb) below the lower level of the normal range with one repeat testing allowed, or known hemoglobinopathies.
12. Known severe hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme.
13. Presence of Hepatitis B surface antigen (HBsAg) at screening, Positive Hepatitis C antibody test result at screening.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

14. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

15. Positive pre-study drug/alcohol screen
16. Positive HIV antibody test
17. Regular use of known drugs of abuse

Other Exclusions

18. Male partners of women who are pregnant or lactating
19. Regular alcohol consumption within 3 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
20. Breath test indicative of smoking at day -1.
21. History of sensitivity to any of the study medications, including CCI15106 or components thereof and, for cohorts that will undergo BAL, those that may be used in association with the BAL procedure or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
22. For cohorts that will undergo BAL, contraindications to bronchoalveolar lavage including hypercapnia >50 mm Hg, abnormal blood coagulation parameters, known or suspected intolerance of medications necessary for bronchoscopy, refractory hypoxemia, reactive airway disease or asthma, unstable angina or acute myocardial infarction.
23. Documented lactose allergy/intolerance for dosing cohorts.

6.2.2. Exclusion Criteria for Participants with COPD

1. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. QTc > 450 msec or QTc > 480 msec in participants with Bundle Branch Block

   NOTES:

   - The QTc is the QT interval corrected for HR according to Fridericia's formula (QTcF), machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
   - For purposes of data analysis, QTcF will be used as specified in the RAP.
5. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<40 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcF interval	>450 msec	

6. Participant has poorly controlled COPD, defined as the occurrence of **either** of the following:
   - Acute worsening of COPD requiring use of antibiotics or systemic corticosteroids in the 6 weeks prior to screening visit **OR**
   - More than 2 exacerbations of COPD requiring treatment with oral steroids in the preceding year or hospitalization for the treatment of COPD within 3 months of screening or more than twice during the preceding year.
7. History of an upper or lower respiratory tract infection requiring antibiotics in the 4 weeks prior to screening
8. Participant has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the Investigator, compromise the safety of the participant or affect the interpretation of the results.
9. Unstable or uncontrolled cardiac disease.

10. Participants who have past or current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect participant safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension) ARE permitted to be entered into the study).

Prior/Concomitant Therapy

11. Participants are not allowed to take oral corticosteroids from 4 weeks prior to screening and for the duration of the study.
12. Participants taking medications for any chronic conditions have to be on stable doses for 4 weeks prior to screening and until after completion of the treatment period. This includes COPD maintenance therapies (e.g. inhaled corticosteroids, long-acting beta-agonists, long-acting muscarinic agonists).
13. Didanosine and azathioprine are not allowed.
14. Use of short-acting inhaled bronchodilators is allowed, but participants must be able to discontinue their medications several times during the study as described in Section 7.7.
15. Use of long-acting bronchodilators is allowed, but participants must be able to modify the schedule of their medications twice during the study as defined in Section 7.7.

Prior/Concurrent Clinical Study Experience

16. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months.
17. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
18. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

Diagnostic assessments

19. Impaired renal function (eGFR <30 cc/min, using CKD-EPI equation).
20. Known severe hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme.
21. Hgb below the lower level of the normal range with one repeat testing allowed or known hemoglobinopathies.
22. Presence of Hepatitis B surface antigen (HBsAg) at screening, Positive Hepatitis C antibody test result at screening.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

23. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

24. Positive pre-study drug/alcohol screen
25. Positive human immunodeficiency virus (HIV) antibody test
26. Regular use of known drugs of abuse

Other Exclusions

27. Male partners of women who are pregnant or lactating
28. Regular alcohol consumption within 3 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
29. Unable to refrain from smoking for 2 h prior to dosing and until all assessments are complete for 4 h after dosing and also for 1 h prior to any vital signs and ECG assessments.
30. History of sensitivity to any of the study medications, including CCI15106 or components thereof and, for cohorts that will undergo BAL, those that may be used in association with the BAL procedure or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
31. For cohorts that will undergo BAL, contraindications to bronchoalveolar lavage including hypercapnia >50 mm Hg, abnormal blood coagulation parameters, known or suspected intolerance of medications necessary for bronchoscopy, refractory hypoxemia, reactive airway disease or asthma, unstable angina or acute myocardial infarction.
32. Documented lactose allergy/intolerance.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will be allowed soft drinks without caffeine starting from 2 h after dosing, including both AM and PM doses. Standardized meals will be provided while the participant is confined to the clinical research unit, as outlined below.
- Participants will report to the clinic fasting (for at least 8 h) for screening visit, Day -1 of treatment periods and for follow-up visit.
- At all mealtimes, food will be served only after completion of protocol specified procedures scheduled at or around the same time.

- The morning dose of the CCI15106-IP will be given after fasting (for at least 8 h). The evening dose of the CCI15106-IP will be given at least 2 h after food. The doses will be approximately 12 h apart. For the first dose for any participant in the study, water should not be allowed for 2 h prior to dosing. For all other doses, water will be allowed freely.
- Participants should not eat for 2 h after dose administration for the single dose cohorts and after the first dose of the multiple dose cohorts.
- Breakfast will not be provided on the mornings of the BAL, however a snack is permitted on this day after the end of the procedure, as long as it does not interfere with any study related procedures.
- All other meals and snacks may be provided as per the clinics schedule. Should a mealtime interfere with a study procedure such as BAL, the investigator in consultation with the sponsor, may modify the meal times to ensure safety of the participants. Also, the fasting requirements may be modified or removed at any time during the study at the discretion of the sponsor in consultation with the investigator.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 h prior to the start of dosing until the participants leave the clinical unit.
- During each dosing session, participants will abstain from alcohol for 24 h prior to the start of dosing until the participants leave the clinical unit.
- For healthy participants, use of tobacco products is not allowed from screening until after participants leave the clinical unit.
- Participants with COPD who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the Clinical Unit. Participants with COPD will be escorted by staff for smoking breaks except during the period for 2 h prior to dosing and until all assessments are complete for 4 h after dosing.

6.3.3. Activity

- Participants will abstain from strenuous exercise from screening until follow-up visit. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study may be rescreened only upon approval of Medical Monitor. Rescreened participants should be assigned a different screening number.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	CCI15106-IP	Placebo
Dosage formulation:	1 capsule	1 capsule
Unit dose strength(s)/Dosage level(s):	30 mg of CCI15106 As 30.3 mg of CCI15106: polyvinyl alcohol 99:1 w/w PRINT 0.9x1 μm cylinder shape crystalline particles	30.3 mg of lactose: polyvinyl alcohol 98:2 w/w PRINT 0.9x1 μm cylinder shape amorphous particles
Route of Administration	By inhalation	By inhalation
Dosing instructions:	Each inhalation will follow instructions provided with the device. The number of inhalations will depend on the dose. The morning dose to be taken fasting (at least 8 h). For repeat dose cohorts, the evening dose to be taken at least 2 h after food. For repeat dose cohort(s) with bystander exposure monitoring, a ±1.5 h window is allowed.	Each inhalation will follow instructions provided with the device. The number of inhalations will depend on the dose. The morning dose to be taken fasting (at least 8 h). For repeat dose cohorts, the evening dose to be taken at least 2 h after food. For repeat dose cohorts with bystander exposure monitoring, a ±1.5 h window is allowed.
Packaging and Labeling	Study Treatment will be provided in a HDPE (high density polyethylene) bottle. Each bottle contains 2 capsules and a desiccant canister. Each bottle is overwrapped in a foil pouch containing a desiccant sachet. Each bottle and each pouch will be labelled as required per country requirement.	Study Treatment will be provided in a HDPE bottle. Each bottle contains 2 capsules and a desiccant canister. Each bottle is overwrapped in a foil pouch containing a desiccant sachet. Each bottle and each pouch will be labelled as required per country requirement.
Device	Monodose RS01	Monodose RS01
Manufacturer	Plastiape S.p.A.	Plastiape S.p.A.

7.1.1. Medical Devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are Monodose RS01.
- Instructions for medical device use are provided in the Study Reference Manual (SRM).
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 9.2).

7.2. Dose Modification

- This protocol allows some alteration from the currently outlined dosing schedule. The maximum daily dose administered will not exceed 120 mg per day either as a single dose or as 60 mg BID.
- The decision to proceed to Part 1 Cohort B will be made by the GSK Study Team comprised at a minimum of the team leader, medical monitor, Global Clinical Safety and Pharmacovigilance scientist or physician (Clinical Pharmacokineticist, Statistician and Preclinical Safety Assessment as necessary), and the Investigator or delegate based on safety and tolerability data obtained in all participants at the prior dose levels in Part 1. The actual doses to be administered may be adjusted based on safety, tolerability, and preliminary PK data if appropriate, at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose. The highest dose in the study will not exceed 120 mg per day either as a single dose or as 60 mg BID.
- The decision to proceed to participants with COPD will be made by the GSK Study Team comprised at a minimum of the team leader, medical monitor, Global Clinical Safety and Pharmacovigilance scientist or physician (Clinical Pharmacokineticist, Statistician and Preclinical Safety Assessment as necessary), and the Investigator or delegate based on safety and tolerability data obtained after single dosing completes in healthy participants in Part 1 Cohort A.
- The actual doses to be administered may be adjusted based on safety, tolerability, and preliminary PK data if appropriate, at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.
- The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety and PK findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional participant(s) or cohort(s) will be the same as that described for other study participants.

7.3. Method of Treatment Assignment

No treatment assignment will be performed for bystander cohort(s).

For all other cohorts, participants will be centrally randomized using an Interactive Web Response System.

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.

Study treatment will be dispensed at all times indicated in the SoA (Section 2).

7.4. Blinding

This will be a double-blind (sponsor unblinded) study. The GSK study team participating in the dose escalation meetings will be blinded to the participant's treatment assignment and will be un-blinded only if necessary to facilitate review of the safety, tolerability and PK data as appropriate in real time to inform dose escalation decisions.

However, the study team performing the analyses to support dose escalation decisions will be unblinded to allow accurate assessment of the data, including the study pharmacokineticists, statisticians, programmers and data managers, who will have access to the randomization codes for analysis purposes. If additional contract research organizations are involved in data analysis or in statistical analysis and programming, the same will apply to their staff as well.

Participants will be randomized to receive study treatment. Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study treatment and will ensure that there are no differences in time taken to dispense following randomization.

This 3rd party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study treatment with the investigator or with other participants.

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

Additional double-blinded, single-blinded or open-label repeat dose cohort(s) may be added at a dose not to exceed 120 mg daily.

- The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- Investigators have direct access to the participant's individual study treatment.

- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding.
- The date and reason for the unblinding must be fully documented.

A participant may continue in the study if that participant's treatment assignment is unblinded, upon discussion with the medical monitor.

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

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- Capsules should be kept refrigerated (2-8°C) in their sealed packaging, protected from moisture.
- Monodose RS01 devices will be supplied in bulk. After use, the devices will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date. Devices will be disposed of at site after reconciliation is verified by study monitor.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM or equivalent.
- Precaution will be taken to avoid direct contact with the study treatment. No women of child-bearing potential will administer study treatment. Staff administering the study treatment will wear protective gown and gloves. A Material Safety Data Sheet describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

Dosing Procedure for Cohorts not Used for Environmental Exposure Monitoring

- Participants will inhale the dose from the Monodose RS01 device inside a negative pressure room or enclosure.
- The investigator/designee will remove the capsule from the bottle and load it into the Monodose RS01 device one at a time in a safety cabinet. One device will be used per capsule. The investigator/designee will be trained to load the capsule into the device and pierce the capsule ready for inhalation (empty capsules will be used for training).
- The participant will inhale the dose, and staff will observe participant doing it. Staff will be trained to listen for a rattle that the device makes during successful dosing. After dosing, the Monodose RS01 device will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date.
- The participant will be trained to use a "fast and deep" inspiration technique per inhalation, to achieve rapidly consecutive maximal inhalations (empty capsules will be used for training). This will ensure optimal and consistent treatment delivery. For participants, the training session will be on either Day -1 or on Day 1, prior to administration of the first dose. Subsequent assessment of Monodose RS01 device technique, and repeat device training where deemed necessary by the investigator/designee, will take place immediately before administration of each dose.

Dosing Procedure for Cohorts Used for Environmental Exposure Monitoring

- Participants will inhale the dose from the Monodose RS01 device in a room designated for dosing. All investigators/designees will leave the room and observe dosing participants and bystanders through a glass in the door. Only participants inhaling the dose and designated bystanders are allowed in the room during inhalation of the dose.
- The bystander will remove the capsule from the bottle and load it into the Monodose RS01 device one at a time. One device will be used per dose (2 capsules in this cohort). The bystander will be trained to load the capsule into the device and pierce the capsule ready for inhalation (empty capsules will be used for training).
- The bystander will pass loaded and charged device to the dosing participant.
- The participant will inhale the dose, and staff will observe participant doing it through a glass in the door. The bystander will be trained to listen for a rattle that the device makes during successful dosing. After dosing, the participant will pass the device back to the bystander.
- The bystander will open the device, remove the capsule and place it on the table between the dosing participant and the bystander. The bystander will then load the second capsule into the same device, pierce the capsule and pass the loaded device back to the dosing participant.
- The participant will inhale the second dose, the bystander will listen for a rattle that the device makes during successful dosing and staff will observe participant doing it

through a glass in the door. After dosing, the participant will pass the device back to the bystander.

- The bystander will open the device, remove the second capsule, and place the open device with both capsules on the table between the dosing participant and the bystander.
- The bystander and participant will remain seated around the table for 15 min. After this time, the bystander will place the Monodose RS01 device and both used capsules into the plastic bag labelled with the participant number, day of dosing, and date. After that is done, bystander and participant can leave the room. The bystander will need to wash their hands prior to leaving the room.
- The participant will be trained to use a "fast and deep" inspiration technique per inhalation, to achieve rapidly consecutive maximal inhalations (empty capsules will be used for training). This will ensure optimal and consistent treatment delivery. For participants and bystanders, the training session will be on either Day -1 or on Day 1, prior to administration of the first dose. Subsequent assessment of Monodose RS01 device technique, and repeat device training where deemed necessary by the investigator/designee, will take place immediately before administration of each dose.

7.6. Treatment Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

The participants will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

If failure of the capsule actuation is suspected (i.e. due to failure to pierce the capsule during device priming), the investigator is permitted to rechallenge the individual with a maximum of two further administrations at the same dose. If dosing failure is suspected for any other reason, the participant may have to be excluded after consultation with the Medical Monitor.

The Monodose RS01 devices will be under the supervision of the study organisers at all times during the clinical trial.

7.7. Concomitant Therapy

7.7.1. Permitted Medications and Non-Drug Therapies

Paracetamol or Acetaminophen, at doses of ≤2 grams/day is permitted.

Medications associated with the BAL procedure are permitted, but these medications are to be disclosed to the Sponsor prior to dosing any participants.

Participants with COPD taking medications for any chronic conditions have to be on stable doses for 4 weeks prior to screening and until after completion of the treatment period.

Salbutamol is administered 15 to 30 min prior to spirometry at screening for diagnostic purposes. Short-acting bronchodilators should not be used from 6 h prior to each morning dose administration until 4 h after that dose. If they become medically necessary during that time, short-acting bronchodilators may be administered as needed by the clinical staff only and their use must be documented.

For participants with COPD, use of long-acting bronchodilators is allowed, but their use must be modified twice during the study as follows: at screening and on Day 1, they must not be taken for at least 2 h prior to spirometry.

Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor.

7.7.2. Prohibited Medications and Non-Drug Therapies

Participants are not allowed to take oral corticosteroids from 4 weeks prior to screening and for the duration of the study.

For participants with COPD, self administration of short-acting inhaled bronchodilators is not allowed at screening, from 4 h prior to spirometry until spirometry is completed. Self administration of short-acting inhaled bronchodilators is not allowed during treatment period from 6 h prior to each morning dose administration until 4 h after that dose.

Didanosine and azathioprine are not allowed.

Except as permitted in Section 7.7.1, participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because most of the participants are healthy and the indication being studied is not life threatening.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

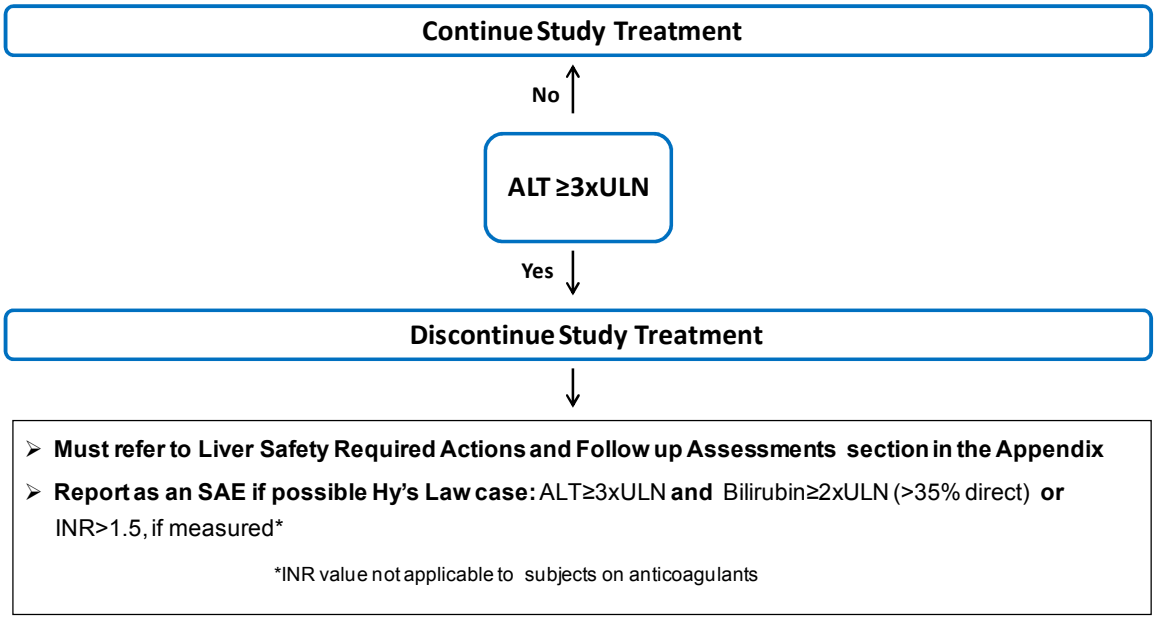
8.1. Discontinuation of Study Treatment

If participant is withdrawn from study treatment, this constitutes withdrawal from study. Participants will have to be followed up for safety reasons as deemed necessary by the Investigator and should be encouraged to return for a follow-up visit as specified in the SoA (Section 2). If this is not possible, procedures specified for the follow-up visit can be performed at the last visit that the participant attends.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined above

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.2. QTc Stopping Criteria

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

- QTc, QTcF >500 msec,
- Change from baseline: QTc >60 msec

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

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

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

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Other Stopping Criteria

Dosing will be stopped for any individual participant in case of SAEs and in case of any AEs which in the opinion of the investigator might jeopardise the health of the trial participant.

Additionally, dosing will be stopped and the study will be put on halt if any of the below scenarios occurred. If following an internal safety review the Sponsor deems it appropriate to restart the trial, this can be done following approval of a substantial amendment:

Two (2) or more subjects, within a dose-level, receiving study treatment experience grade 3 respiratory adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience a grade 3 hematologic adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience severe hypersensitivity related adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience a grade 3 vital signs (heart rate and/ or blood pressure) adverse event that are deemed possibly or probably related to study drug by the investigator.

One (1) or more subjects receiving study treatment experience anaphylaxis that is deemed possibly or probably related to study drug by the investigator.

8.1.4. Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (Section 2) for data to be collected at follow-up and for any further evaluations that need to be completed.
- Participants will have to be followed up for safety reasons as deemed necessary by the Investigator and should be encouraged to return for a follow-up visit as specified in the SoA (Section 2). If this is not possible, procedures specified for the follow-up visit can be performed at the last visit that the participant attends.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The following time window tolerances apply to all protocol assessments:

Predose	- 60 to 0 min (- 60 to -15 min for spirometry)
0h - 4h post	- 5 / + 10 min
5h – 24h post	- 10 / + 10 min

9.1. Efficacy Assessments

There are no efficacy assessments in this study.

9.2. Adverse Events

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

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

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and no later than in 24 h, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

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

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The Cardiovascular CRFs are presented as queries in response to reporting of certain Cardiovascular MedDRA terms. The Cardiovascular information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a Cardiovascular Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Pregnancy

- Female participants of child bearing potential are excluded from this study
- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until 7 months after the last dose of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.7. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for inhalation. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2.1, Section 9.2.2, Section 9.2.3, Section 9.2.4 and Appendix 4 of the protocol.

9.2.7.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 7.

9.2.7.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2.1, Section 9.2.2, Section 9.2.3, and Section 9.2.4). This applies to all participants, including those who discontinue study treatment or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.7.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor by facsimile transmission. If facsimile transmission is unavailable, then notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.2.7.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.3. Treatment of Overdose

For this study, any dose of CCI15106-IP greater than the dose specified for the treatment period within a 24 h time period [±4 h] will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until CCI15106 can no longer be detected systemically (at least 30±2 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Screening Assessments

Cardiovascular medical history/risk factors will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

9.4.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems, and skin. Height and weight will also be measured and recorded. Oral exam will be performed.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Oral exam will also be performed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.3. Vital Signs

- Vital signs will be measured in semi-supine position and will include oral or tympanic temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure. The same method of temperature assessment should be used throughout the study.
- For BAL, vital signs will also include oxygen saturation and will be evaluated and recorded before, every 5 minutes during the procedure, at the end of, and between 30 and 60 minutes after the bronchoscopy.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Three readings of blood pressure and pulse rate will be taken where indicated as triplicate in SoA (Section 2) and all three readings will be recorded.

9.4.4. Electrocardiograms

- Triplicate OR single 12-lead ECG will be obtained in semi-supine position after 5 minutes rest as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- Continuous cardiac telemetry will be performed where indicated in SoA (Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the participant's source documents.

9.4.5. Spirometry

- Spirometry (FEV1 and FVC) will be performed at time points specified in the SoA (Section 2). Further tests should be performed, at the discretion of the investigator, if the participant has symptoms that could suggest bronchospasm.
- Spirometry manoeuvres will be conducted according to ATS/ERS 2005 spirometry standards [Miller, 2005]. The greatest FEV1 and the greatest FVC from 3 technically acceptable and reproducible manoeuvres will be recorded.
- For participants with COPD, at screening, 400 µg salbutamol will be administered 15-30 minutes prior to performing spirometry. FEV1 and FVC percent predicted values will be derived using the Global Lung Function Initiative reference values [Quanjer, 2012].

9.4.6. Capillary pCO2

The pCO2 levels will be measured at the times indicated in SoA (Section 2). The participant's hand will be heated in warm water (42 degrees) for about 10 minutes and a capillary blood sample will be collected by skin puncture using a lancet or automated incision device.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30±2 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 2).

9.4.8. Environmental and Bystander Exposure Evaluation

Exposure monitoring will be conducted in accordance with the principles outlined in prEN 689:2016, the draft European standard for workplace exposure assessment to airborne contaminants [prEN 689:2016].

9.4.8.1. Air Monitoring

During and after the first daily dose on Days 1, 7 and 14 in Cohort B Part 1, static air samples will be collected on filters within air pumps positioned in two locations in the room. The air disturbance caused by the pumps is negligible and would not be expected to alter the normal air flow patterns in the room. Marks may be placed on the floor to indicate position of the participant and positions of pumps to ensure consistency throughout the study. Samples will be run over 20 and 60 min following dosing in each location. An additional set of samples over 60 min will be taken before the start of dosing on Day 1 to provide a background benchmark for reference.

On days when static air sampling is performed, the dosing sessions will have to be separated by the time necessary to collect the 60 min air sample.

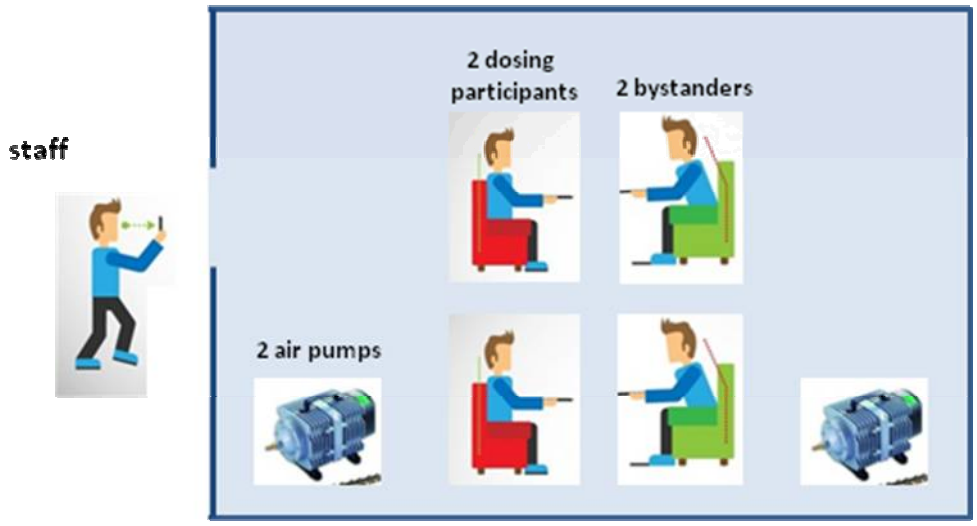
Sampling devices (Institute of Occupational Medicine [IOM] sampling heads connected to sampling pumps) shall be used to measure CCI15106 concentration. The IOM filter cassette assembly will be prepared using an immersion-extraction procedure to avoid any errors through wall deposition. Whenever possible, the Hygienist will observe the room through a glass in the door for the duration of sampling to make observations and note relevant contextual information to assist in the interpretation of the exposure measurements.

Air sample analysis will be performed by the Bureau Veritas laboratory (Bureau Veritas North America Inc, 95 Oakwood Road, Lake Zurich, IL, 60047). For air sampling, field blanks (filters which have been handled during the survey but not had air pulled through them) will be submitted with samples to check for accidental contamination during sample handling and storage. An average of one blank for every ten field samples will be sent for analysis.

9.4.8.2. Bystander Monitoring

Please refer to Figure 1 for the illustration of the design. Each dosing participant will be assigned a designated bystander for the duration of dosing. Two participants will dose at the same time in sitting position. The designated bystander will be seated facing their dosing participant within approximately 1 m of him/her. The first dosing participant will inhale the dose (both capsules), and then the second dosing participant will inhale the dose (both capsules). Please refer to Section 7.5 for detailed instructions on dosing. Each participant and their bystander will stay seated for the next 15 min, after which they will leave the dosing room. The staff will exit the room prior to bystander loading the capsule into the device (see Section 7.5) and remain outside the room for at least 15 min after dosing observing through a glass door.

Figure 1 Bystander and participant design illustration



The next two bystanders will be positioned near the next 2 dosing participants, and so on until all dosing is completed. This procedure will be followed for all doses in Cohort B Part 1, with the same bystanders positioned next to the same inhaling participant. After the first daily dose on days 1, 7 and 14, blood will be collected from bystanders 15 min after dosing (at ~tmax for CCI15106). Additionally, personal exposure air samples will be collected on filters placed on each bystander after the first daily dose on days 1, 7 and 14. The filters will be worn during dosing and for 15-minute period after dosing. Static air monitoring will be performed at the same time during and after the first daily dose on days 1, 7 and 14. During these dosing sessions, each set of two dosing participants will be separated by the time necessary to collect the 60 min air sample.

The filters used for personal exposure (IOM sampling heads connected to sampling pumps) shall be used to measure CCI15106 concentration in the person's breathing zone. The IOM filter cassette assembly will be prepared using an immersion-extraction procedure to avoid any errors through wall deposition. Whenever possible, the Hygienist will observe the room through a glass in the door for the duration of sampling to make

observations and note relevant contextual information to assist in the interpretation of the exposure measurements.

See Section 9.5 for PK assessments of bystanders.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection

Blood samples for PK analysis of CCI15106 in plasma will be collected at the time points indicated in SoA (Section 2). One 3 mL blood sample will be collected at each time point and the actual date and time of each sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the SRM OR equivalent.

9.5.2. BAL Sample Collection

BAL samples for ELF concentration analysis of CCI15106, urea, and cell counts will be collected at the time points indicated in SoA (Section 2). The actual date and time of each BAL sample collection will be recorded.

Details of BAL sample collection, processing, storage, and shipping procedures are provided in the SRM OR equivalent.

Due to the analysis methodology, any cells present in the ELF will be disrupted and their content released and analyzed together with the supernatant.

9.5.3. Urea Blood Sample

A 2 mL blood sample will be collected into Lithium Heparin tubes as soon as practically possible before the BAL samples.

Processing for plasma, storage and shipping procedures will be provided in the SRM or equivalent.

9.5.4. Sample Analysis

BAL and plasma analysis will be performed under the control of PTS-DMPK, GSK, the details of which will be included in the SRM OR equivalent. Concentrations of CCI15106 will be determined in plasma and BAL samples using the currently approved bioanalytical methodology. Plasma and BAL urea concentrations will be determined by Clinical Pathology, Safety Assessment, GSK. Raw data will be stored in the Good Laboratory Practices archives, GSK.

For bystander exposure, a plasma concentration of less than 0.5 ng/mL (the Limit Of Quantification of the method) represents an acceptable exposure since this is 29-fold lower than the highest plasma concentration measured at the no effect dose level for teratogenicity in the most sensitive species (rat [Rebetol SPC, 2009]).

Once the plasma and BAL samples have been analyzed for CCI15106, any remaining plasma or BAL may be used for other compound-related metabolites analyses, microbiome analysis, or other exploratory analyses that inform the effect of the drug on the body or the disease, the results of which will be reported under a separate protocol.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

Sample size is based on feasibility and though no formal power calculations are performed, the sample size is deemed adequate to provide a preliminary assessment of safety prior to progression to the next study.

Part 1

In Part 1, the study plans to enrol healthy participants in 3 cohorts. In Cohort A, there will be 6 participants on active and 2 on placebo, in cohort B, there will be 12 on active and 2 on placebo. In cohort C, there will be 14 subjects who will participate as bystanders and they will be associated with the dosing subjects in Cohort B on a one to one basis for the entire duration of dosing. All subjects in Cohort B will also undergo BAL.

Part 2:

In Part 2, 22 participants with COPD are planned to be enrolled. Cohort A will have 6 participants on active dose and 2 on placebo and Cohort B will have 12 participants on active and 2 on placebo. Fourteen participants (12 active and 2 placebo) enrolled in Cohort B Part 2 will also undergo BAL.

Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of seeing adverse events. For example, in Parts 1 and 2, in

treatment groups where 6 patients will receive the active drug, if the true adverse outcome rate is 5%, the chance of seeing at least one adverse outcome at a given dose is 26%. Similarly, if the true adverse outcome rate is 20%, the chance of seeing at least one adverse outcome at a given dose is 73%. For the treatment groups with 12 subjects receiving the active treatment, if the true adverse outcome rate is 5%, the chance of seeing at least one adverse outcome at a given dose is 46%. Similarly, if the true adverse outcome rate is 20%, the chance of seeing at least one adverse outcome at a given dose is 93%. This level of predictability is deemed adequate within this Phase 1 setting prior to commencement of the next study.

10.1.1. Sample Size Sensitivity

As sample size is based on feasibility, no sample size sensitivity was performed.

10.1.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Definition / Criteria	Analyses Evaluated
All Participants Screened	• Comprise of all participants who consent to participate in the clinical study. • Defined separately for Part 1 and Part 2.	
Safety	• Comprise of all participants who receive at least one dose of study treatment. • This population will be based on the treatment the participant actually received. • Defined separately for Part 1 (excluding Cohort C) and Part 2.	• Safety • Study Population
Systemic Pharmacokinetic Concentration	• Participants who receive at least one dose of study treatment and who undergo plasma PK sampling and have at least one postdose 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. • Defined separately for Part 1 (excluding Cohort C) and Part 2.	• PK
Lung ELF Concentration Population	• Participants who receive at least one dose of study treatment and who undergo BAL sampling and have postdose lung ELF CCI15106 and urea concentration result.	• BAL

Population	Definition / Criteria	Analyses Evaluated
	• 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. • Defined separately for Part 1 and Part 2	
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

10.3. Statistical Analyses

The analysis and reporting of Part 1 may be conducted prior to the completion of Part 2. For all parts, the analysis and reporting will be performed after the datasets are authorized and released for reporting.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by cohort, participant and time; summaries will be presented by cohort, treatment, and time.

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, n and percent will be used as summary statistics for categorical variables.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings.

Complete details will be documented in the RAP.

10.3.1. Safety Analyses

All safety analyses will be based on the Safety Population.

Endpoint	Statistical Analysis Methods
Adverse events (AEs)	The proportion of participants reporting AEs will be tabulated by treatment and by cohort. AEs will also be tabulated by severity and relationship.
Clinical laboratory	Laboratory results will be included in the reporting of this study for hematology, clinical chemistry, and urinalysis. 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 will also be tabulated.
Electrocardiogram (ECG)	The ECG parameters of PR, QRS, QT, QTc, QTcF and HR (bpm) will be reported. Overall assessment of ECG (Investigator's judgment) will be recorded as Normal, Abnormal - Not Clinically Significant and Abnormal - Clinically Significant. Summary statistics for change from baseline will also be tabulated.
Telemetry	Overall assessment of Telemetry (Investigator's judgment) will be recorded as Normal, Abnormal - Not Clinically Significant and Abnormal - Clinically Significant.
Spirometry	% Predicted forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) values will be tabulated for each timepoint.
Vital signs assessments	The following Vital Signs measurements will be tabulated: supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature. Summary statistics for change from baseline will also be tabulated.
Monodose RS01 Device safety	Safety incidents reported from use of medical device will be tabulated.

10.3.2. Pharmacokinetic Analyses

PK analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation Department (CPMS) within GSK. Plasma CCI15106 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.3 and above. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters may be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-last) and AUC(0-∞) where data

permit for single dose, and AUC(0-τ) for repeat dose], elimination half-life (t1/2), and clearance (CL/F) as data permit.

AUC(0-24), or AUC(0-48), or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality.

Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined from Cohorts B of Part 1 and Part 2.

PK data will be presented in graphical and/or tabular form and will be summarized descriptively. A population PK model (POP PK) may be developed with all available data as appropriate and may be reported separately. Further details of the analysis plan and methods will be detailed within the RAP and data analysis plan OR equivalent.

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.

All pharmacokinetic data will be stored in the Archives, GSK Pharmaceuticals, R&D.

PK exploratory analyses will be described in the reporting and analysis plan. The population PK analysis if conducted, will be presented separately from the main clinical study report.

10.3.3. Bystander and Environmental exposure Analyses

The plasma concentration data from bystanders will be summarised descriptively and listed. The amount of CCI15106 obtained from filters will be tabulated and reported. Additional analyses, where deemed necessary, will be described in the RAP.

If data permit, the plasma concentration measured from bystanders may be plotted against the data collected from the air filters.

10.3.4. Interim Analyses

No formal interim analyses are planned for this study. Safety and tolerability will be evaluated as described in Section 5.1. Systemic and, where available, lung PK may also be evaluated.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

%CV	Coefficient of variation
%CVb	Between-subject coefficient of variation
μg	Microgram
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	AUC from time zero to end of dosing interval
AUC(0-∞)	AUC from time zero to infinity
AUC(0-24)	AUC from time zero to 24 hours
AUC(0-t)	AUC from time zero to the time of last quantifiable concentration
BAL	Bronchoalveolar lavage
BMI	Body mass index
CCI15106-CFI	CCI15106 capsules for inhalation
CI	Confidence interval
CL/F	clearance
Cmax	Concentration at maximum
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case report form
ECG	Electrocardiogram
ELF	Epithelial lining fluid
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FTIH	First time in human
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B surface antigen
Hep B	Hepatitis B
Hep C	Hepatitis C
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
HRV	Human rhinovirus

IB	Investigator brochure
ICH	International conference on harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
Kg	Kilogram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
mg	milligram
min	Minute
mL	Milliliter
mm Hg	Millimeter of mercury
NOAEL	No observed adverse effect level
PK	Pharmacokinetics
POP PK	Population PK
PRINT	Particle Replication In Non-wetting Templates
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RSV	respiratory syncytial virus
RTP	Ribavirin triphosphate
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SRM	Study Reference Manual
t1/2	Elimination half-life
Tmax	Time of maximum concentration
ULN	Upper limit of normal
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WBC	White blood cells
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	Red blood cells (RBC) Indices: Mean corpuscular hemoglobin (MCV) Mean corpuscular volume (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Fasting Glucose	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis			

Laboratory Assessments	Parameters
	C virus antibody) • Serum pregnancy test in women • Coagulation parameters in the BAL cohorts The results of each test must be entered into the CRF.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

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

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Agreement to definition of source data.

Study and Site Closure

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

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

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

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

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Guidance for Grading Adverse Events

Taken from the Food and Drug Administration (FDA) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

The purpose of this appendix is to provide guidance and it is to be used in conjunction with the investigator's judgment.

Guidance for Grading Vital Signs Adverse Events

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements
** Oral temperature; no recent hot or cold beverages or smoking
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing

Allergic Reactions

Grade 1 allergic reaction (Pruritis without rash):

Participants with Grade 1 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

- Temperature >38.5°C

- Eosinophilia
- Respiratory involvement including brochospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 1 allergic reaction may continue the study drug at the discretion of the investigator. The participant should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK.

Grade 2 allergic reaction (Localized urticaria):
Participants with Grade 2 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

- Temperature >38.5°C
- Eosinophilia
- Respiratory involvement including brochospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 2 allergic reaction may continue the study drug at the discretion of the investigator. The participant should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK.

Grade 3 allergic reaction (Generalized urticaria or angioedema):
Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Grade 4 allergic reaction (Anaphylaxis):
Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Revised ACTG Toxicity Grade	Definition	Investigator action
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria Angioedema	Discontinue therapy
Grade 4	Anaphylaxis	Discontinue therapy

Definition of SAE

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

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

c. Results in death

d. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

e. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

f. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

g. Is a congenital anomaly/birth defect

h. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events (CV)

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are

requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor and the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Male participants

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

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 3 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner are not eligible to participate.
- In addition male participants must refrain from donating sperm for duration of study and for 7 months after study completion or from last dose.

Table 3 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion

NOTES:

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

Female participants

Female participants of childbearing potential are not eligible to participate.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who can become pregnant are not eligible to participate

12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 h
• Record the liver event data, and complete an SAE data collection tool if the event also meets the criteria for an SAE2
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
• Do not restart or rechallenge participant with study treatment
MONITORING:
<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Blood sample for pharmacokinetic (PK) analysis, obtained within 48 h of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event</td></tr>
</table>

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James,2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Collect Liver Imaging and/or Liver Biopsy data.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally,if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**,indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excludingstudies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

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

12.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.1 for the list of GSK medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

TITLE PAGE

Protocol 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.

Protocol Number: 205822 /02

Short Title: Study of safety and drug levels of CCI15106 inhalation powder in healthy adults and adults with moderate chronic obstructive pulmonary disease. Study of CCI15106 levels in people standing near the person inhaling the drug.

Compound Number: CCI15106

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): EudraCT **2017-001070-42**

Approval Date: 11-OCT-2017

SPONSOR SIGNATORY:

PPD

_____ 11 OCT 2017

D[redacted]tienne Dumont **Date**

Director, Clinical Development

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	11-Oct-2017
Amendment 1	31-May-2017
Original Protocol	20-Apr-2017

Amendment 02 11-Oct-2017

Overall Rationale for the Amendment: ensuring that the COPD population in this study is more reflective of the real-world COPD population.

Section # and Name	Description of Change	Brief Rationale
6.1.2 Inclusion Criteria for Participants with COPD	Changed BMI requirements	Ensuring that the COPD population in this study is more reflective of the real-world COPD population
6.2.2 Exclusion Criteria for Participants with COPD	Removed some of the exclusion criteria for screening ECG	Ensuring that the COPD population in this study is more reflective of the real-world COPD population
6.2.2 Exclusion Criteria for Participants with COPD	Reworded exclusion criterion around pulmonary diseases that participants can have, in addition to COPD	Ensuring that the COPD population in this study is more reflective of the real-world COPD population
7.3 Treatment assignment 9 Study Assessments and Procedures	Several changes made previously via Note to file	Changes and clarifications made previously via Notes to file are now incorporated into the protocol

TABLE OF CONTENTS

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1. SYNOPSIS

Protocol 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). A concomitant study to evaluate environmental and healthy bystander exposure levels during dosing.

Short Title: Study of safety and drug levels of CCI15106 inhalation powder in healthy adults and adults with moderate chronic obstructive pulmonary disease. Study of CCI15106 levels in people standing near the person inhaling the drug.

Rationale:

This study is the first administration of CCI15106 inhalation powder hard capsules (CCI15106:polyvinyl alcohol 99:1 w/w 0.9x1 μm cylinder shape crystalline particles presented in capsules, from here on referred to as CCI15106-IP) to humans. This study will evaluate the safety, tolerability, and lung and systemic pharmacokinetics (PK) of CCI15106-IP delivered using Monodose RS01 device in healthy participants and in participants with moderate COPD.

The intention of this study is to provide sufficient confidence in the safety of the molecule delivered by inhalation to inform progression to further repeat dose and proof of concept studies.

A different formulation of CCI15106 (CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape particles) has been previously administered to humans in the first time in human study (FTiH) 202031.

Marketed CCI15106 is classified as teratogenic and is contra-indicated in women who are pregnant and in male partners of pregnant women and it is important to understand whether bystanders may be exposed to CCI15106 when it is used by patients in a dry powder, inhaled form. This study will evaluate the levels of CCI15106 in room air and in the plasma of bystanders. The study aims to replicate the real-life scenarios of dosing as close as possible. Real-life scenarios may include dosing of multiple patients in a single room in a nursing home or dosing of a single patient at home. A realistic worst-case scenario for bystanders is dosing of multiple patients in a standard size room in a nursing home.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• 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 CCI15106 during self-administered dosing of participants.	• Concentration of CCI15106 in plasma of bystanders 15-20 minutes (min) after dosing (at predicted tmax) and 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	
• 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.
• 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.

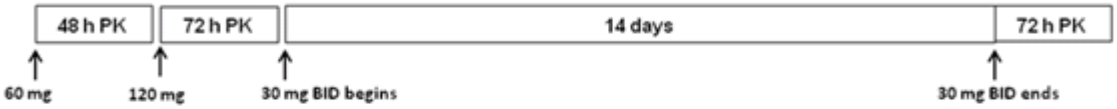
Overall Design:

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.

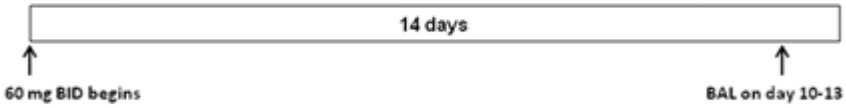
Study schematic is presented below:

Part 1 Healthy Participants

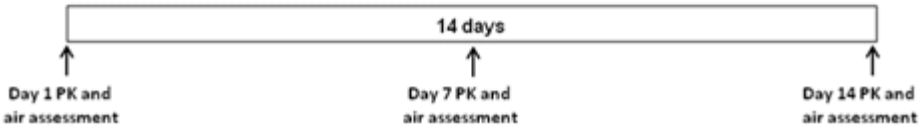
Cohort A: 8 participants (6 active; 2 placebo)



Cohort B: 14 participants (12 active; 2 placebo)

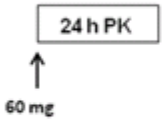


Cohort C: 14 bystanders for environmental exposure, to be run concomitantly with Cohort B

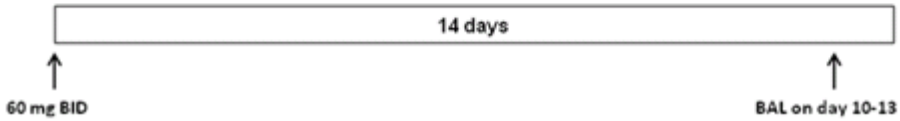


Part 2 Participants with COPD

Cohort A: Single dose; 8 participants (6 active; 2 placebo)



Cohort B: Multiple dose; 14 participants (12 active; 2 placebo)



Number of Participants:

Approximately 36 healthy participants and approximately 22 participants with COPD will be randomized in this study for dosing.

Treatment Groups and Duration:

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. Doses administered and treatment duration for participants in each specific cohort will be as defined in the study schematic above. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

The total study duration will be approximately 82 days for Cohort A Part 1; approximately 75 days for Cohort B Part 1 and Cohort C Part 1; approximately 77 days for Cohort A Part 2; and approximately 90 days for Cohort B Part 2.

2. SCHEDULE OF ACTIVITIES (SOA)

If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order pre-dose:

1. Telemetry start
2. spirometry
3. 12-lead electrocardiogram (ECG)
4. vital signs
5. blood draws

and in the following order post-dose:

1. 12-lead ECG
2. vital signs
3. blood draws
4. spirometry

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Any change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GlaxoSmithKline (GSK) study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

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[2]	Notes
Informed consent	X		1. Screening assessments can be performed over multiple screening visits 2. All male participants will be called approximately 7 months after the follow-up visit to ensure no partner pregnancy 3. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required 4. To be drawn fasting (for at least 8 h) 5. To be administered to participants with COPD only, 15-30 minutes prior to spirometry 6. To be done at screening for participants with COPD only, following salbutamol dosing 7. To be performed in the bronchoalveolar lavage (BAL) cohorts only to confirm participant eligibility 8. 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[3]	X		
Haematology, clinical chemistry and urinalysis (include liver chemistries)[4]	X	X	
Salbutamol administration[5]	X		
Spirometry[6]	X		
12-lead ECG and vital signs	X	X	
Coagulation parameters[7]	X		
Capillary pCO_2[8]	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

3. INTRODUCTION

3.1. Study Rationale

This study is the first administration of CCI15106-IP (CCI15106:polyvinyl alcohol 99:1 w/w 0.9x1 μm cylinder shape crystalline particles produced using Liquidia's Particle Replication In Non-wetting Templates [PRINT] technology) to humans. The study will evaluate the safety, tolerability, and lung and systemic pharmacokinetics (PK) of single and repeat ascending doses of CCI15106-IP delivered by inhalation in healthy participants and in participants with moderate chronic obstructive pulmonary disease (COPD). The study will use a Monodose RS01 device for drug delivery by inhalation.

A different formulation of CCI15106 (CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape particles) has been previously administered to humans in the first time in human study (FTiH) 202031. That formulation was referred to as CCI15106 capsules for inhalation (CCI15106-CFI).

The intention of this study is to provide sufficient information regarding the safety of the molecule to inform progression to further repeat dose and proof of concept studies. The dose range proposed in this study is based on a starting dose previously investigated with the different formulation in the FTiH and escalating to a dose not to exceed the the no observed adverse effect level (NOAEL) in the most sensitive species (Section 5.5).

The other intention of this study is to investigate the level of CCI15106 that will be released into the air and may be found in the blood of the bystanders around participants inhaling CCI15106-IP.

3.2. Background

CCI15106 is ribavirin, which is a generic, broad spectrum nucleoside antiviral, discovered in the early 1970s, with both clinical and nonclinical data available, which is approved and used for oral administration in the treatment of chronic hepatitis C virus. It is also approved for respiratory syncytial virus (RSV) bronchiolitis by pulmonary inhalation in paediatric patients. CCI15106 is active versus RSV, human metapneumovirus, parainfluenza, influenza, adenovirus, and human rhinovirus (HRV), although HRV is 4-15-fold less susceptible than the others (GlaxoSmithKline Document Number 2015N249287_00). Based upon published data coronaviruses could also be susceptible without co-administration of interferon [Kurai, 2013, Morgenstern, 2005]. CCI15106 is not considered to be the active form, rather it is actively transported into target organs/cells and converted to ribavirin triphosphate (RTP) believed to be the active form against the viruses [Thomas, 2012]. The major limitation of the use of CCI15106 is hemolytic anemia due to accumulation of RTP in red blood cells and teratogenicity.

Liquidia's Particle Replication In Non-wetting Templates (PRINT) technology uses lithographic etching processes to produce particles with highly defined size and shape. CCI15106 plus the excipient, polyvinyl alcohol, are combined in a ratio of 99:1 w:w using Liquidia's technology to produce CCI15106-IP, a highly dispersible powder of uniform 0.9x1 μm cylinder shape particles which has afforded a 24-fold increase in lung

concentration at maximum (Cmax) relative to micronised CCI15106:Lactose formulation in a solid dose inhaled rat PK study (GlaxoSmithKline Document Number 2015N242219_00 [N20691-39]). The size and uniformity of the Liquidia particles provides an opportunity to improve the efficiency of CCI15106 administration to the lung while limiting systemic exposure that has the potential to limit hemolytic anemia and teratogenicity.

Acute exacerbations of COPD are a significant cause of morbidity and mortality [Vestbo, 2013; Kurai, 2013]. Multiple studies show that viral and/or bacterial respiratory infections are the most commonly associated triggers of COPD exacerbations. Respiratory viruses are detected in 20-60% of acute exacerbations of COPD [Kurai, 2013].

High efficiency lung delivery of broad spectrum CCI15106-containing engineered particles will establish an antiviral state in the lung. This has the potential to prevent the establishment or spread of the virus in the lower respiratory tract from the upper respiratory tract and/or increase the viral clearance translating to prevention of an exacerbation or a decrease in exacerbation severity and/or duration.

CCI15106 has been previously administered to humans in a different formulation, CCI15106:Trehalose:Trileucine 35/55/10 w/w 1 μm pollen shape PRINT particles (CCI15106 capsules for inhalation, referred to as CCI15106-CFI). Forty eight healthy participants have been administered a single dose of that formulation in one FTiH study 202031 and 12 participants received placebo. This study was planned as a double-blind (sponsor unblind), randomized, placebo-controlled, single and repeat escalating dose study to investigate the safety, tolerability, and pharmacokinetics of CCI15106-CFI in healthy participants and participants with moderate chronic obstructive pulmonary disease (COPD). In the single dose part of the study, CCI15106-CFI was administered by inhalation using Modified Air Inlet Rotahaler device at doses of 7.5 mg, 15 mg, 30 mg, and 60 mg. Overall, no clinically meaningful changes in vital signs or electrocardiograms (ECGs) were observed. There were no serious adverse events (SAEs) reported. Of the 60 subjects in the study, 25 reported adverse events (AEs) and 12 reported possibly drug-related AEs. The most common AEs were headache and cough (11 and 3 subjects, respectively). The comprehensive review conducted after single dose cohorts revealed acceptable safety profile, but lung epithelial lining fluid (ELF) levels of CCI15106 measured with 30 or 60 mg dose were below the levels predicted by pre-clinical evaluations and the increase in dose from 30 to 60 mg did not appear to result in a substantial increase in the lung concentration. Development of the CCI15106-CFI formulation was terminated before dosing repeat dose or COPD cohorts as a new formulation (CCI15106-IP) was developed that has higher ratio of active pharmaceutical ingredient to inactive ingredients per unit of powder and allows achieving the same dose in 1 capsule instead of 4. This is expected to lead to a higher lung ELF Cmax. The decision to terminate was not based on safety data.

Marketed formulations of CCI15106 are classified as teratogenic and is contra-indicated in women who are pregnant and in male partners of pregnant women. Currently approved aerosolised forms of CCI15106 are recommended to be administered in a negative pressure environment [Virazole USPI 2013]. It is important to understand whether bystanders may be exposed to CCI15106 when it is used by patients in a dry

powder, inhaled form. The most likely route of exposure of bystanders will be through inhalation of powder released during dosing. The study aims to replicate the real-life scenarios of dosing as close as possible. Real-life scenarios may include dosing of multiple patients in a single room in a nursing home or dosing of a single patient at home. A realistic worst-case scenario is dosing of multiple patients in a standard size room in a nursing home.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of CCI15106 may be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2015N250735_02]. Information specific to the approved formulations of CCI15106 can be found in the labels for oral CCI15106 approved for the treatment of hepatitis C and CCI15106 nebulizer approved for the treatment of respiratory syncytial infections in children [Rebetol SPC 2009; Virazole USPI 2013].

Based on pre-clinical safety assessment studies summarized in the IB and the clinical experience with CCI15106-CFI, as well as oral and inhaled (nebulised) CCI15106, the following clinical parameters will be monitored throughout the study in order to better characterize the safety and tolerability of CCI15106-IP (Section 3.3.1). Refer to SoA, Section 2, for the timing of all clinical assessments.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product, CCI15106-IP		
Teratogenicity and embryocidal effects	CCI15106 showed embryocidal and teratogenic effects in animals. The no observed adverse effect level (NOAEL) in oral embryofetal development studies in rats and rabbits was 0.3 mg/kg/day, considerably lower than the maximum proposed inhaled clinical dose of 120 mg/day CCI15106 (0.02-fold to 0.05-fold based on mg/m^2). In addition, human seminal fluid contains ~2-fold higher concentrations of CCI15106 compared to serum. There are limited data from the use of CCI15106 in pregnant women (5 cases of measles-pneumonia and 1 case of influenza-pneumonia)) [Virazole SPC, 2014]. Four pregnancies were completed and resulted in the birth of healthy children. A further 7 cases are known in which nurses administered Virazole dry substance during pregnancy (n=6) or just before conception (n=1). In 6 cases, healthy children were born. In one case, a chromosomal translocation was reported with mild developmental delay [Virazole SPC, 2014].	Women of child-bearing potential and male partners of women who are pregnant or breastfeeding will be excluded. Effective contraception for female partners of male participants will be required up to 7 months post study. Any pregnancies that occur during the study or up to 7 months post study will be reported by the investigator to the pregnancy registry. The informed consent form will describe these reproductive risks, as well as the risk to female partners of male participants. Systemic exposure for the target clinical dose of CCI15106 is expected to be lower than exposure for currently available oral and nebulized CCI15106. The maximum inhaled total daily single dose of CCI15106 in Protocol 205822 will be 120 mg and the maximum inhaled multiple daily doses will be 60 mg twice daily (BID). These proposed maximum clinical doses are significantly lower than the currently approved doses of CCI15106 (800-1400 mg for Copegus and Rebetol and 6 g for inhaled Virazole).
Mutagenicity	CCI15106 is clastogenic in vitro and in vivo but is Ames negative. The pattern of genotoxicity is consistent with that reported for other nucleoside analogues. Point of departure modelling (an accepted method of risk assessment for nucleoside analogues) indicates a negligible genotoxic concern. CCI15106 was not tumorigenic in lifetime rodent studies at doses up to 75 mg/kg/day in the mouse and 40 mg/kg/day in the rat (~3-fold the maximum proposed inhaled clinical dose of CCI15106-IP based on mg/m^2),	The data indicate a negligible genotoxic concern, which is mitigated by the lower expected systemic and lung exposure compared with currently available oral and nebulized CCI15106 and shorter duration of clinical treatment (≤ 14 days). The maximum inhaled single total daily dose of 120 mg or multiple total daily doses of 60 mg BID for Protocol 205822 are significantly lower than the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	or in the transgenic p53(±) mouse model at doses of up to 300 mg/kg/day.	currently approved doses of CCI15106 (800-1400mg for Copegus and Rebetol and 6 g for inhaled Virazole).
Increased exposure in participants with severe renal impairment	As CCI15106/ribavirin is substantially excreted by the kidneys, exposure may be increased in those with pre-existing renal impairment CCI15106 is contraindicated in patients with chronic renal failure, patients with creatinine clearance < 50mL/min, and/or on hemodialysis [Rebetol SPC, 2009] However, the Copegus labels allow dose modifications for patients with CrCl <50 mL/min [Copegus USPI, 2015; Copegus SPC, 2015].	The maximum inhaled single total daily dose of 120 mg or multiple total daily doses of 60 mg BID proposed for Protocol 205822 are significantly lower than the currently approved doses of CCI15106 (800-1400mg for Copegus and Rebetol and 6 g for inhaled Virazole). COPD patients with impaired renal function (eGFR <30 cc/min, using CKD-EPI equation) will be excluded and renal function will be monitored.
Pulmonary effects	**GSK's formulations:** In toxicity studies conducted by GSK, no adverse pulmonary toxicity was observed following administration of either CCI15106:trehalose:trileucine particles or CCI15106-IP in GSK studies of 28 day duration at dose levels of ≤32.5 mg/kg in rat or ≤34.2 mg/kg in dog. The deposited lung doses at the NOAELs on the 28 day studies using CCI15106-IP were estimated 6- to 8-fold higher than in human at the maximum proposed clinical administration of CCI15106-IP of 120 mg/day (conservatively assuming 100% human lung deposition). Adverse lung pathology (including neutrophilic inflammatory cell infiltrates) and unscheduled deaths were observed in rats in a 14 day inhaled tolerability study with CCI15106-IP at an estimated dose of 68.7 mg/kg. Rat deaths and lung pathology have been reported during oral and inhalation toxicology programs for approved/marketed formulations of CCI15106 at systemic exposures and inhalation dose levels similar or less than those delivered in this study. As CCI15106-IP is dry powder, it has a reduced risk of acute lung effects compared to low osmolarity nebulised solution. No bronchospasms were observed in the FTIH study 202031; however there were occurrences of non-serious cough and dyspnoea. Maximal amounts of powder administered were higher in the FTIH study than those planned for the	Repeat dosing will be evaluated in healthy participants in this study prior to dosing in participants with COPD. Patients with poorly controlled COPD will be excluded (see Section 6.2.2). Lung function will be monitored with frequent spirometry and physical examinations will be conducted. If they become medically necessary, short-acting bronchodilators may be administered as needed by the clinical staff. Oxygen and resuscitation measures will be available in the unit in the event they would be needed. The trial is to be conducted in a dedicated phase I unit with supplementary (Medicines & Healthcare Products Regulatory Agency) accreditation and experience in the conduct of Phase I studies.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	current study. **Labels of approved formulations:** Virazole SPC (13 November 2014) includes the following: • Sudden deterioration in pulmonary function associated with aerosolized CCI15106/ ribavirin has been observed in children, and significant deterioration in pulmonary function has been observed in patients with asthma and chronic obstructive pulmonary disease (COPD) during CCI15106/ribavirin treatment. • Bronchospasm has been reported following CCI15106/ribavirin use by patients with COPD and asthma. Pulmonary adverse reactions reported in clinical studies or in postmarketing use of aerosolized CCI15106/ribavirin include bacterial pneumonia, pneumothorax, laryngitis, pharyngitis, dyspnoea, cough, hypo- and hyperventilation, apnoea, and bronchospasm.	
Haemolytic anaemia	The primary toxicity of approved formulations of CCI15106 is haemolytic anemia, which was observed in 10% of oral CCI15106 plus interferon alpha2b combination-treated participants and occurs within 1 to 2 weeks of start of therapy [Rebetol USPI, 2015]. Haemolytic anemia associated with CCI15106 may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarction. CCI15106 is known to accumulate in the red blood cells and may cause hemolysis, which may result in increased uric acid [De Franceschi, 2000]. Anemia has been shown to occur frequently with experimental oral and intravenous CCI15106 in humans [Virazole USPI, 2013]. Haemolytic anaemia is monitorable and reversible with reduction / cessation of treatment [Rebetol USPI, 2015]. **GSK formulations:** In toxicity studies conducted by GSK, mild anaemia was seen in 4 week studies following inhalation administration of CCI15106:trehalose:trileucine particles (rat and dog) or CCI15106-IP (rat only).	Participants will be monitored regularly with complete blood counts and hematocrit, as per SoA (Section 2). Participants with hemoglobinopathies will be excluded. Due to the short dose and duration and the red blood cell count monitoring in place, laboratory monitoring for hemolysis is not warranted in this study. Participants will have an ECG assessment prior to and during the study. Cardiac monitoring, including assessment of blood pressure and heart rate, along with 12-lead electrocardiograms (ECGs) will be performed, per protocol. If cardiac status deteriorates on therapy, study medication should be suspended and/or discontinued.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cardiac effects	**GSK formulations:** Heart toxicity was not observed in definitive 4 week toxicity studies in rats and dogs following inhalation administration of CCI15106:trehalose:trileucine particles or CCI15106-IP. Minimal lymphocytic/mononuclear or mixed inflammatory cell infiltrate in the myocardium was observed following inhalation administrations of 68.7 mg/kg/day as CCI15106-IP at higher dose levels during a 14 day tolerability study (AUC_{0-24h} was 5-fold higher than the human AUC_{0-24h} estimated at 120 mg CCI15106-IP). These findings were also observed following oral and inhalation administrations of approved/marketed formulations of CCI15106-IP and do not, therefore, present at a greater risk compared to marketed/approved CCI15106 formulations which are approved for administration at higher inhaled and oral dose levels/ systemic exposures and administered for longer treatment durations than those proposed for CCI15106-IP. There were no cardiac events reported in the FTIH study of CCI15106-CFI. The following cardiovascular adverse reactions have been reported in clinical studies and in the postmarketing setting of CCI15106, which included severely ill infants with life-threatening underlying disease: cardiac arrest, hypotension, bradycardia, and digitalis toxicity [Virazole USPI, 2013]. Bigeminy, bradycardia, and tachycardia, have been described in patients with underlying cardiac disease.	Participants will have ECG prior to dosing and will be assessed prior to and during therapy by 12-lead ECG and telemetry. If cardiac status deteriorates on therapy, study medication should be suspended and/or discontinued. Participants with uncontrolled or unstable cardiac diseases will be excluded.
Photosensitization	Photosensitivity reaction has been reported commonly in clinical trials and in the postmarketing setting for CCI15106 [Rebetol SPC, 2009]. Photoallergic reaction with CCI15106 has been described in the literature [Stryjek-Kaminska, 1999].	Physical examination to include skin exams will be performed and documented as per SoA (Section 2). Any findings suggesting photosensitivity reaction will be promptly addressed according to appropriate standard of care and followed up for resolution.
Oral erosions	Ulcerative stomatitis, stomatitis, mouth ulceration are undesirable effects associated with CCI15106 [Rebetol SPC, 2009]. Nasal erosions were	Physical examination to include oral exam will be performed and documented as per SoA (Section 2). Any

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	observed in the squamous epithelium of the nasal turbinates of a proportion of dogs (but not rats) receiving the high dose (25.1 mg/kg/day) following administration of CCI15106-CFI and ≥16.3 mg/kg following administration CCI15106-IP for 4 weeks. These effects were considered non adverse and unlikely to be clinically relevant since CCI15106 will be administered to humans by oral inhalation, compared with oro-nasal administration (over 60 minutes) in the dog study, thereby minimising the potential for nasal exposure. Histopathological findings in rats included epithelial changes in the larynx (squamous metaplasia) in animals given the control article and CCI15106 formulation over 4 weeks. These changes were low in incidence and severity and showed full recovery following completion of the off-dose period. The findings were consistent with low grade non-specific irritation and, being an adaptive change of low severity, are considered non-adverse [Kaufmann, 2009] and a poor predictor of irritancy in humans given that the rat larynx is known to be particularly sensitive to inhaled irritants [Lewis, 1991].	findings suggesting oral erosion will be promptly addressed according to appropriate standard of care and followed up for resolution.
Testicular toxicity	**Testicular toxicity:** Testicular toxicity was seen in mice treated orally with CCI15106 for 3 to 6 months at doses of 15 mg/kg/day and [Rebetol SPC, 2009]. Recovery occurred within one or two spermatogenic cycles. No stage specific or cell specific abnormalities of spermatogenesis were observed in GSK studies which were conducted on the testes of rats (CCI15106:trehalose:trileucine particles and CCI15106-IP) and dogs (CCI15106-IP only) during definitive 4 week inhalation toxicity studies.	Given the shorter duration of clinical treatment (≤ 14 days) and lower expected exposure compared with currently available oral and nebulized CCI15106, the risk of testicular toxicity is considered to be low.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
BAL procedure	BAL requires bronchoscopy and sedation. Bronchoscopy can be performed safely on an outpatient basis [Du Rand, 2013], however, serious complications occurred in 1.1% of patients, including mortality in 0.02% of patients in a retrospective series (n=20,986 patients). Common adverse events reported with bronchoscopy, included tachycardia/bradycardia, major and minor bleeding, bronchospasm, laryngospasm, cough, dyspnea, sore throat, apnea, seizure, desaturation, pneumothorax, and pulmonary edema.	BAL will be performed by an experienced pulmonologist in dedicated bronchoscopy suite with close monitoring in recovery area post procedure.
Other		
Bystander exposure, including healthcare workers	Detectible levels of CCI15196-IP may be present in the immediate inhalation area during routine care activities. Labels of approved formulations: The Virazole patient information leaflet (last revision August 2014) states the following: • Virazole is to be administered in a hospital setting only, by a doctor or a nurse. • The nebuliser through which Virazole is given should be turned off 5 to 10 minutes before visitors see the patient to minimise unnecessary exposure to Virazole. • Pregnant women, women who are trying to become pregnant, and sexually active men should avoid exposure to Virazole, because the risk of harm to an unborn baby is unknown. Breast-feeding women are also to avoid exposure to Virazole. Postmarketing surveillance of CCI15106 has revealed reports of adverse events in individuals providing direct care to infants receiving aerosolized CCI15106 [Virazole USPI 2013]. The most common signs and symptoms were headache, conjunctivitis, rhinitis, nausea, rash, dizziness, pharyngitis,	Levels in air and in bystanders will be assessed. Whenever study participants are dosed outside the negative pressure room, all hospital personnel will be asked to leave the room and will not re-enter until 15 min after dosing. Pregnant women or women of child-bearing potential will be warned of the potential risks. Training on the potential health hazard will be provided to study personnel, including protective equipment, monitoring, and waste disposal. No women of child-bearing potential will be enrolled as participants or as bystanders.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and lacrimation. Several cases of bronchospasm and/or chest pain have been reported, usually in individuals with reactive airways disease. Seven cases are known in which nurses administered Virazole dry substance during pregnancy (n=6) or just before conception (n=1). In 6 cases, healthy children were born. In one case, a chromosomal translocation was reported with mild developmental delay.	

Exposure risk for additional medications administered in the study (Salbutamol):

See package leaflet (https://www.medicines.org.uk/emc/PIL.22837.latest.pdf).

3.3.2. Benefit Assessment

As this Phase I study is being conducted to assess the safety and PK in healthy participants and participants with COPD, there is no direct clinical benefit to study participants. Participation in this study may contribute to the process of developing new therapies in an area of unmet need.

3.3.3. Overall Benefit:Risk Conclusion

CCI15106 is an approved product as an oral agent in combination with interferon α or β (pegylated and non-pegylated) for chronic hepatitis C in patients 3 years of age and older with compensated liver disease (Copegus, Rebetol), and is approved in the nebulised form for use in infants and young children with severe respiratory syncytial virus infections (Virazole). CCI15106-CFI has been administered to healthy participants in single doses up to 60 mg with acceptable safety and tolerability profile. The risk of adverse effects is minimized for the population being investigated in the proposed study by careful selection of participants for the study, the relatively short duration of exposure, and the extent of safety monitoring incorporated into the study. The highest dose planned in this study (single dose of 120 mg or multiple doses of 60 mg BID) is significantly lower than the currently approved doses of CCI15106 (800-1400 mg for Copegus and Rebetol and 6 g for aerosolized Virazole). The risk to study staff will be managed by occupational precautions.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• 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 CCI15106 during self-administered dosing of participants.	• Concentration of CCI15106 in plasma of bystanders 15-20 minutes (min) after dosing (at predicted tmax) and 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	
• 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.

Objectives	Endpoints
Tertiary/Exploratory	
• 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)

5. STUDY DESIGN

5.1. Overall Design

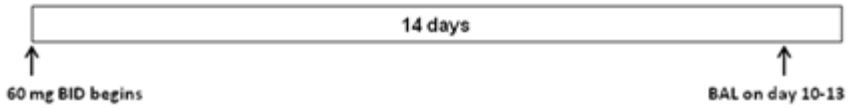
This is a two-part, double-blind (sponsor unblind), randomized, placebo-controlled, single and repeat escalating dose study. Investigator and participants will be blinded to treatment type (active or placebo), but will know what dose of the medication is being administered. Part 1 will investigate single 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.

Study schematic is presented below:

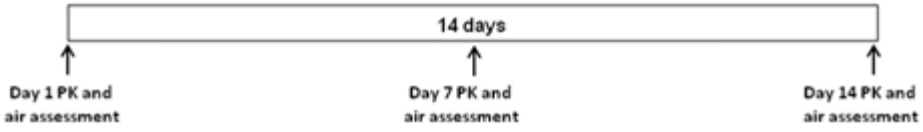
Part 1 Healthy Participants

Cohort A: 8 participants (6 active; 2 placebo)

Cohort B: 14 participants (12 active; 2 placebo)

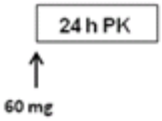


Cohort C: 14 bystanders for environmental exposure, to be run concomitantly with Cohort B

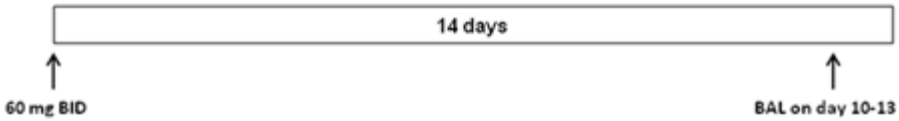


Part 2 Participants with COPD

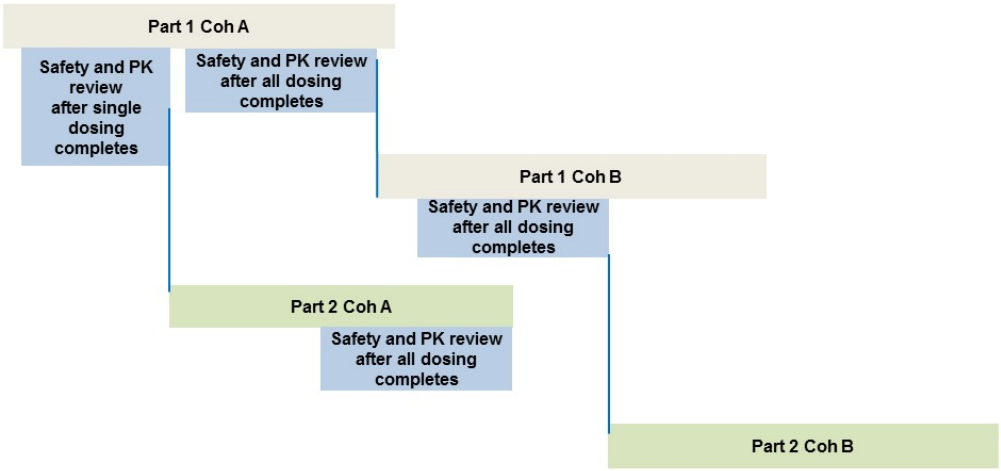
Cohort A: Single dose; 8 participants (6 active; 2 placebo)



Cohort B: Multiple dose; 14 participants (12 active; 2 placebo)



The following reviews will be conducted during the study progression:



- In Part 1, Cohort B dosing can begin only after review of safety/tolerability and PK of all dosing in Part 1 Cohort A (see Section 7.2 for composition of the review team).
- In Part2, Cohort A dosing can begin only after review of safety/tolerability and PK for a single dose administration of 60 and 120 mg in all participants in Part 1 Cohort A (see Section 7.2 for composition of the review team).
- In Part 2, Cohort B dosing can begin only after the comprehensive review of all data obtained in Part 1, including safety and systemic PK, as well as lung PK where available (see Section 7.2 for composition of the review team) and after review of safety/tolerability of Part 2 Cohort A.
- Environmental and bystander exposure review may be conducted at any time after the data are collected. Until this review is completed and exposure found acceptable, all subsequent cohorts will be dosed in the negative pressure environment.
- The planned doses may be modified, repeated or cancelled based upon safety/tolerability/ and/or PK from preceding cohorts (See Section 7.2 for more information). Single doses will not exceed 120 mg and repeat doses 60 mg BID.
- The planned dose frequency or duration may be modified based on emerging safety/tolerability and PK data from previous cohorts. The total daily dose will not exceed 120 mg.
- The number of cohorts may be reduced or expanded if needed.

- All participants in Part 1 Cohort B and in Part 2 Cohort B (60 mg BID dose for both Cohorts) will undergo BAL once during the study on days 10, 11, 12, or 13 after the first (morning) dose. Based on the lung ELF concentrations of CCI15106 observed, additional double-blinded, single-blinded or open-label repeat dose cohort(s) may be added at a dose not to exceed 120 mg daily. The total number of participants will not exceed that specified in Section 5.2.
- BAL may be used in the additional cohorts to obtain a more accurate estimation of the dose to lung exposure ratio and provide data for future dose predictions.

There will be approximately 3 cohorts of healthy participants in this study and approximately 2 cohorts of participants with moderate COPD. Participants in the dosing cohorts will be randomized to receive either CCI15106-IP or matching Liquidia particles without the active ingredient (lactose:polyvinyl alcohol 98:2 w/w 0.9x1 μm cylinder shape amorphous particles, referred to as placebo). Participants in Cohort C will be assigned to participants in Cohort B on a one to one basis for the entire duration of the study.

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.

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. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). Participants will be dosed the following morning on Day 1 followed by post-dose assessments. Blood for PK assessments will be collected for the next 48 hours (h). On Day 3 (after collection of 48 h PK time point), participants will receive a single dose of 120 mg followed by post-dose assessments and PK assessments for the next 72 h. Repeat dosing will begin on the morning of Day 6 (after collection of 72 h PK time point) and will continue for 14 days BID. Participants will remain in the unit for additional 2 days until 72 h PK timepoint is collected. Dosing frequency and duration may be adjusted based on emerging safety and tolerability data. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

For Cohort B Part 1, Repeat Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). 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. BAL procedure will be performed as soon as possible (within 1 h) after the first (morning) dose on one of the following days: 10, 11, 12, or 13. Participants will be discharged on Day 15 following completion of all post-dose assessments after the last dose, or later if additional PK collection or other assessments are required. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

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. Bystanders will report to the unit on Day

-1 and will remain for all 14 days of dosing of Cohort B. They will be positioned in the room with the dosing participants for every dose taken, as described in Section 9.4.8. Air sampling and bystander PK evaluation will be conducted on days 1, 7, and 14 as described in Section 9.4.8. Bystanders will be discharged on Day 15 following completion of all post-dose assessments after the last dose. Bystanders will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

For Cohort A Part 2, Single Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). They will be dosed the following morning on Day 1 followed by post-dose assessments. Participants will be discharged following completion of the post-dose assessments the next day (Day 2). They will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

For Cohort B Part 2, Repeat Dose SoA will be followed for the duration of the study. Participants will report to the unit on Day -1 for assessments and randomization (randomization can also be done on Day 1, prior to dosing). 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. BAL procedure will be performed as soon as possible (within 1 h) after the first (morning) dose on one of the following days: 10, 11, 12, or 13. Participants will be discharged on Day 15 following completion of all post-dose assessments after the last dose, or later if additional PK collection or other assessments are required. Participants will return for the follow-up visit approximately 30 days after discharge. All male participants will also be called approximately 7 months after the follow-up visit to ensure no partner pregnancy.

The total study duration will be approximately 82 days for Cohort A Part 1; approximately 75 days for Cohort B Part 1 and Cohort C Part 1; approximately 77 days for Cohort A Part 2; and approximately 90 days for Cohort B Part 2.

5.2. Number of Participants

Approximately 36 healthy participants and approximately 22 participants with COPD will be randomized in this study for dosing.

Evaluable participants will be defined in the Reporting and Analysis Plan (RAP).

Additional participants or cohorts may be enrolled to allow for evaluation of additional dose levels or to increase numbers on prior doses or to increase the number of bystanders. The total number of participants in this study will not exceed 86 and the total number of cohorts will not exceed 7, including the bystander cohort(s).

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

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

5.4. Scientific Rationale for Study Design

Participants and all site personnel, with the exception of the study pharmacist or designee, will be blinded to participant randomization throughout the study. The GSK study team participating in the dose escalation meetings will review blinded data and will be un-blinded on a need to know basis only if necessary to facilitate review of the safety, tolerability and PK data as appropriate in real time to inform dose escalation decisions. The GSK study team or personnel at any contract research organization that may be involved in data management or in statistics and programming will not reveal the treatment assignments to the site personnel or participants.

In repeat dosing cohorts, CCI15106-IP will be administered for 14 days to mimic the expected duration of treatment in target patient populations.

Inclusion of Bronchoscopy

BAL will be performed on 14 healthy participants (Cohort B Part 1) and 14 participants with COPD (Cohort B Part 2) to evaluate levels of CCI15106 in the ELF. BAL will be performed once, as soon as possible (within 1h) after the first (morning) dose. This will allow assessment of CCI15106 levels at around tmax in the ELF. The timing of BAL in Part 2 Cohort B may be adjusted based on BAL results obtained in Part 1. Available models [Weber, 2017] predict that the level of CCI15106 in the bronchoalveolar fluid following 14 days of 60 mg BID dosing may be achieved above 200 μM around T_{max} which is above the EC50 for all respiratory viruses including HRV and expected to prevent or minimise the migration of an upper respiratory tract viral infection to the lower respiratory tract. These data will enable a more accurate estimation of the dose to lung exposure ratio and provide valuable information for future dose predictions.

Inclusion of Participants with COPD Cohort

Due to potential exposure differences as a function of COPD-induced lung damage, participants with moderate COPD will be included to aid in dose selection for the future proof of concept studies in participants with COPD. This cohort will also help obtain some safety and tolerability data in this patient population prior to a wider administration in the Proof of Concept study.

Inclusion of Bystander Cohort

Due to known teratogenic potential of CCI15106, we need to evaluate how much of it gets into the environment around the dosing participant to ensure that no potentially pregnant bystanders are put at-risk due to secondary exposure. Participants dosed in the

Cohort used to evaluate environmental and bystander exposure will be dosed outside a negative pressure enclosure. All other participants will be dosed inside the enclosure. When participants dose outside the enclosure, all personnel will leave the room and not re-enter until 15 min after dosing. During this time, participants will be observed through a window in the door.

5.5. Dose Justification

The dose proposed for Part 1 Cohort A is based on the data from 202031 where CCI15106-CFI up to 60 mg single dose has been evaluated, and no SAEs or severe AEs were observed, as well as the investigation of the four week toxicity and toxicokinetics in rats and dogs in which the NOAEL was determined [GSK Document Number 2017N312240_00 and GSK Document Number 2017N312247_00].

Table 1 below shows the safety margins in terms of lung and systemic exposure with respect to the NOAEL obtained from the pre-clinical studies, and the folder cover with respect to the systemic exposure following oral administration of the marketed dose (1200 mg/day) in humans for the doses proposed in this study. These data indicated reasonable safety margins for Cohort A in Parts 1 and 2, where single dose of CCI15106-IP will be administered.

The selection of appropriate dose for Part 1 Cohort B will be performed upon consideration of available safety, tolerability and systemic PK data from Part 1 cohort A. The review data set for this selection will, at minimum, consist of: any adverse events, liver function test results, vital signs, ECG, spirometry data, and laboratory findings, and any available systemic PK results.

The selection of appropriate dose for Part 2 Cohort A will be performed upon consideration of available safety and tolerability data following the single doses (60 and 120 mg) in all participants in Cohort A of Part 1.

The selection of appropriate dose for Part 2 Cohort B will be performed upon consideration of available safety, tolerability, systemic PK and lung concentration data from Part 1 Cohort B.

The dose level in any cohort may be titrated up or down based on emerging safety, tolerability, and systemic PK and lung data where available. The maximum dose will not exceed 120 mg per day.

Table 1 Prediction of Human Systemic and Lung Exposure and Safety Margins of CCI15106

Dose Frequency	Proposed human dose per day (mg)	Human Lung Dose (mg/g)	Lung Safety Margin (Rats)	Lung Safety Margin (Dogs)	Human Systemic expoure AUC(0-24) (ng.h/mL) *	Systemic Safety Margin (Rats)	Systemic Safety Margin (Dogs)	Systemic Safety Margin (human Oral Ribavirin)
Assume 100% lung deposition in humans								
SD	60	0.06	12	16				
SD	120	0.12	6	8				
Assume 59% lung deposition in humans								
SD	60	0.04	20	26	552	17	40	92
SD	120	0.07	10	13	1104	8	20	46
BD**	30	0.04	20	26	3080	3	7	16
BD	60	0.07	10	13	6150	2	4	8

Assumptions:

human: body weight 70 kg, lung weight 1000 g; 100% or 59% inhaled dose into lungs are assumed

59% was predicted from the MPPD for lung deposition of the device

rat: mean body weight 0.244kg, mean lung weight 1.145 g, 10% inhaled dose into lungs;

dog: mean body weight 8 kg, mean lung weight 73.1 g, 25% inhaled dose into lungs.

Rat NOAEL dose = 32.5 mg/kg, AUC=9.34 μg.h/mL (whole study means)

Dog NOAEL dose = 34.2 mg/kg, AUC=22.2 μg.h/mL (whole study means)

Human oral AUC(0-24) =2xAUC0-12=50.722 μg.h/mL (Steady state) [Copegus USPI, 2015]

* human systemic AUC(0-24) is predicted from a mechanistic model [Weber, 2017]

** BD - twice daily dosing; AUC(0-24) on Day 14

6. STUDY POPULATION

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

6.1. Inclusion Criteria

6.1.1. Inclusion Criteria for Healthy Participants and Bystanders

Participants are eligible to be included in the study only if all of the following criteria apply. Rescreening is allowed only if approved by the Medical Monitor.

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator (in consultation with the Medical Monitor if required) decide and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

4. Body weight ≥50 kg for males and 45 kg for females and body mass index (BMI) within the range 19 to 31 kg/m^2 (inclusive) for males and 17 to 31 kg/m^2 (inclusive) for females.

Sex

5. Male OR Female

   a. Male participants:

   A male participant with female partner of child bearing potential must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 7 months after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

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

Informed Consent

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

6.1.2. Inclusion Criteria for Participants with COPD

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

Age

1. Participant must be 40 to 75 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosed with moderate COPD (GOLD class II) by a qualified physician as defined by the GOLD guidelines (http://www.goldcopd.org/).
3. The participant has spirometry at screening, conducted 15-30 minutes after administration of 400 microgram (μg) salbutamol via metered dose inhaler showing:
    - post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% and <80% predicted normal [Quanjer, 2012] and
    - post-bronchodilator FEV_1/ forced vital capacity (FVC)<0.7, where FEV_1 is forced expiratory volume in 1 second and FVC is forced vital capacity.
4. Participant is a smoker or an ex-smoker with a smoking history of at least 10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or equivalent).
5. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor if required agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

6. Body weight ≥ 45 kg and BMI within the range 17 – 34 kg/m^2 (inclusive), unless morbidly obese.

Sex

7. Male OR Female

c. Male participants:

A male participant with female partner of child bearing potential must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 7 months after the last dose of study treatment and refrain from donating sperm during this period.

d. Female participants:

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

Informed Consent

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

6.2. Exclusion Criteria

6.2.1. Exclusion Criteria for Healthy Participants and Bystanders

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

Medical Conditions

1. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)

2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
4. QTc > 450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate (HR) according to Fridericia's formula (QTcF), machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
   - For purposes of data analysis, QTcF will be used as specified in the RAP.
5. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<40 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcF interval	>450 msec	

6. Any clinically significant central nervous system (e.g., seizures), cardiac, pulmonary, metabolic, renal, hepatic or gastrointestinal conditions or history of such conditions that, in the opinion of the investigator may place the participant at an unacceptable risk as a participant in this trial or may interfere with the absorption, distribution, metabolism or excretion of drugs.

Prior/Concomitant Therapy

7. Past or intended use of over-the-counter or prescription medication (including herbal medications) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to dosing until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study. Specific medications listed in Section 7.7 may be allowed.

Prior/Concurrent Clinical Study Experience

8. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 month period.
9. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.

10. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Diagnostic assessments

11. Hemoglobin (Hgb) below the lower level of the normal range with one repeat testing allowed, or known hemoglobinopathies.
12. Known severe hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme.
13. Presence of Hepatitis B surface antigen (HBsAg) at screening, Positive Hepatitis C antibody test result at screening.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

14. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

15. Positive pre-study drug/alcohol screen
16. Positive HIV antibody test
17. Regular use of known drugs of abuse

Other Exclusions

18. Male partners of women who are pregnant or lactating
19. Regular alcohol consumption within 3 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
20. Breath test indicative of smoking at day -1.
21. History of sensitivity to any of the study medications, including CCI15106 or components thereof and, for cohorts that will undergo BAL, those that may be used in association with the BAL procedure or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
22. For cohorts that will undergo BAL, contraindications to bronchoalveolar lavage including hypercapnia >50 mm Hg, abnormal blood coagulation parameters, known or suspected intolerance of medications necessary for bronchoscopy, refractory hypoxemia, reactive airway disease or asthma, unstable angina or acute myocardial infarction.
23. Documented lactose allergy/intolerance for dosing cohorts.

6.2.2. Exclusion Criteria for Participants with COPD

1. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. QTc > 450 msec or QTc > 480 msec in participants with Bundle Branch Block

   NOTES:

   - The QTc is the QT interval corrected for HR according to Fridericia's formula (QTcF), machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
   - For purposes of data analysis, QTcF will be used as specified in the RAP.
5. Participant has poorly controlled COPD, defined as the occurrence of **either** of the following:
   - Acute worsening of COPD requiring use of antibiotics or systemic corticosteroids in the 6 weeks prior to screening visit **OR**
   - More than 2 exacerbations of COPD requiring treatment with oral steroids in the preceding year or hospitalization for the treatment of COPD within 3 months of screening or more than twice during the preceding year.
6. History of an upper or lower respiratory tract infection requiring antibiotics in the 4 weeks prior to screening
7. Participant has a diagnosis of active tuberculosis, lung cancer, or any other respiratory condition that might, in the opinion of the Investigator, compromise the safety of the participant or affect the interpretation of the results. Participants with other respiratory disorders (e.g. **clinically significant:** asthma, pulmonary fibrosis, bronchiectasis) are excluded if these conditions are the primary cause of their respiratory symptoms.
8. Unstable or uncontrolled cardiac disease.
9. Participants who have past or current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect participant safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension) ARE permitted to be entered into the study).

Prior/Concomitant Therapy

10. Participants are not allowed to take oral corticosteroids from 4 weeks prior to screening and for the duration of the study.

11. Participants taking medications for any chronic conditions have to be on stable doses for 4 weeks prior to screening and until after completion of the treatment period. This includes COPD maintenance therapies (e.g. inhaled corticosteroids, long-acting beta-agonists, long-acting muscarinic agonists).
12. Didanosine and azathioprine are not allowed.
13. Use of short-acting inhaled bronchodilators is allowed, but participants must be able to discontinue their medications several times during the study as described in Section 7.7.
14. Use of long-acting bronchodilators is allowed, but participants must be able to modify the schedule of their medications twice during the study as defined in Section 7.7.

Prior/Concurrent Clinical Study Experience

15. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months.
16. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
17. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

Diagnostic assessments

18. Impaired renal function (eGFR <30 cc/min, using CKD-EPI equation).
19. Known severe hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme.
20. Hgb below the lower level of the normal range with one repeat testing allowed or known hemoglobinopathies.
21. Presence of Hepatitis B surface antigen (HBsAg) at screening, Positive Hepatitis C antibody test result at screening.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained

22. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

23. Positive pre-study drug/alcohol screen
24. Positive human immunodeficiency virus (HIV) antibody test
25. Regular use of known drugs of abuse

Other Exclusions

26. Male partners of women who are pregnant or lactating
27. Regular alcohol consumption within 3 months prior to the study defined as:
    - an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
28. Unable to refrain from smoking for 2 h prior to dosing and until all assessments are complete for 4 h after dosing and also for 1 h prior to any vital signs and ECG assessments.
29. History of sensitivity to any of the study medications, including CCI15106 or components thereof and, for cohorts that will undergo BAL, those that may be used in association with the BAL procedure or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
30. For cohorts that will undergo BAL, contraindications to bronchoalveolar lavage including hypercapnia >50 mm Hg, abnormal blood coagulation parameters, known or suspected intolerance of medications necessary for bronchoscopy, refractory hypoxemia, reactive airway disease or asthma, unstable angina or acute myocardial infarction.
31. Documented lactose allergy/intolerance.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will be allowed soft drinks without caffeine starting from 2 h after dosing, including both AM and PM doses. Standardized meals will be provided while the participant is confined to the clinical research unit, as outlined below.
- Participants will report to the clinic fasting (for at least 8 h) for screening visit, Day -1 of treatment periods and for follow-up visit.
- At all mealtimes, food will be served only after completion of protocol specified procedures scheduled at or around the same time.
- The morning dose of the CCI15106-IP will be given after fasting (for at least 8 h). The evening dose of the CCI15106-IP will be given at least 2 h after food. The doses will be approximately 12 h apart. For the first dose for any participant in the study, water should not be allowed for 2 h prior to dosing. For all other doses, water will be allowed freely.
- Participants should not eat for 2 h after dose administration for the single dose cohorts and after the first dose of the multiple dose cohorts.
- Breakfast will not be provided on the mornings of the BAL, however a snack is permitted on this day after the end of the procedure, as long as it does not interfere with any study related procedures.

- All other meals and snacks may be provided as per the clinics schedule. Should a mealtime interfere with a study procedure such as BAL, the investigator in consultation with the sponsor, may modify the meal times to ensure safety of the participants. Also, the fasting requirements may be modified or removed at any time during the study at the discretion of the sponsor in consultation with the investigator.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 h prior to the start of dosing until the participants leave the clinical unit.
- During each dosing session, participants will abstain from alcohol for 24 h prior to the start of dosing until the participants leave the clinical unit.
- For healthy participants, use of tobacco products is not allowed from screening until after participants leave the clinical unit.
- Participants with COPD who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the Clinical Unit. Participants with COPD will be escorted by staff for smoking breaks except during the period for 2 h prior to dosing and until all assessments are complete for 4 h after dosing.

6.3.3. Activity

- Participants will abstain from strenuous exercise from screening until follow-up visit. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study may be rescreened only upon approval of Medical Monitor. Rescreened participants should be assigned a different screening number.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	CCI15106-IP	Placebo
Dosage formulation:	1 capsule	1 capsule
Unit dose strength(s)/Dosage level(s):	30 mg of CCI15106 As 30.3 mg of CCI15106: polyvinyl alcohol 99:1 w/w PRINT 0.9x1 μm cylinder shape crystalline particles	30.3 mg of lactose: polyvinyl alcohol 98:2 w/w PRINT 0.9x1 μm cylinder shape amorphous particles
Route of Administration	By inhalation	By inhalation
Dosing instructions:	Each inhalation will follow instructions provided with the device. The number of inhalations will depend on the dose. The morning dose to be taken fasting (at least 8 h). For repeat dose cohorts, the evening dose to be taken at least 2 h after food. For repeat dose cohort(s) with bystander exposure monitoring, a ±1.5 h window is allowed.	Each inhalation will follow instructions provided with the device. The number of inhalations will depend on the dose. The morning dose to be taken fasting (at least 8 h). For repeat dose cohorts, the evening dose to be taken at least 2 h after food. For repeat dose cohorts with bystander exposure monitoring, a ±1.5 h window is allowed.
Packaging and Labeling	Study Treatment will be provided in a HDPE (high density polyethylene) bottle. Each bottle contains 2 capsules and a desiccant canister. Each bottle is overwrapped in a foil pouch containing a desiccant sachet. Each bottle and each pouch will be labelled as required per country requirement.	Study Treatment will be provided in a HDPE bottle. Each bottle contains 2 capsules and a desiccant canister. Each bottle is overwrapped in a foil pouch containing a desiccant sachet. Each bottle and each pouch will be labelled as required per country requirement.
Device	Monodose RS01	Monodose RS01
Manufacturer	Plastiape S.p.A.	Plastiape S.p.A.

7.1.1. Medical Devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are Monodose RS01.
- Instructions for medical device use are provided in the Study Reference Manual (SRM).
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 9.2).

7.2. Dose Modification

- This protocol allows some alteration from the currently outlined dosing schedule. The maximum daily dose administered will not exceed 120 mg per day either as a single dose or as 60 mg BID.
- The decision to proceed to Part 1 Cohort B will be made by the GSK Study Team comprised at a minimum of the team leader, medical monitor, Global Clinical Safety and Pharmacovigilance scientist or physician (Clinical Pharmacokineticist, Statistician and Preclinical Safety Assessment as necessary), and the Investigator or delegate based on safety and tolerability data obtained in all participants at the prior dose levels in Part 1. The actual doses to be administered may be adjusted based on safety, tolerability, and preliminary PK data if appropriate, at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose. The highest dose in the study will not exceed 120 mg per day either as a single dose or as 60 mg BID.
- The decision to proceed to participants with COPD will be made by the GSK Study Team comprised at a minimum of the team leader, medical monitor, Global Clinical Safety and Pharmacovigilance scientist or physician (Clinical Pharmacokineticist, Statistician and Preclinical Safety Assessment as necessary), and the Investigator or delegate based on safety and tolerability data obtained after single dosing completes in healthy participants in Part 1 Cohort A.
- The actual doses to be administered may be adjusted based on safety, tolerability, and preliminary PK data if appropriate, at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.
- The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety and PK findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional participant(s) or cohort(s) will be the same as that described for other study participants.

7.3. Method of Treatment Assignment

No treatment assignment will be performed for bystander cohort(s).

For all other cohorts, participants will be randomized at the clinic using RandAll-generated randomization schedule prepared by GSK.

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.

Study treatment will be dispensed at all times indicated in the SoA (Section 2).

7.4. Blinding

This will be a double-blind (sponsor unblinded) study. The GSK study team participating in the dose escalation meetings will be blinded to the participant's treatment assignment and will be un-blinded only if necessary to facilitate review of the safety, tolerability and PK data as appropriate in real time to inform dose escalation decisions.

However, the study team performing the analyses to support dose escalation decisions will be unblinded to allow accurate assessment of the data, including the study pharmacokineticists, statisticians, programmers and data managers, who will have access to the randomization codes for analysis purposes. If additional contract research organizations are involved in data analysis or in statistical analysis and programming, the same will apply to their staff as well.

Participants will be randomized to receive study treatment. Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study treatment and will ensure that there are no differences in time taken to dispense following randomization.

This 3rd party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study treatment with the investigator or with other participants.

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

Additional double-blinded, single-blinded or open-label repeat dose cohort(s) may be added at a dose not to exceed 120 mg daily.

- The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- Investigators have direct access to the participant's individual study treatment.

- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding.
- The date and reason for the unblinding must be fully documented.

A participant may continue in the study if that participant's treatment assignment is unblinded, upon discussion with the medical monitor.

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

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- Capsules should be kept refrigerated (2-8°C) in their sealed packaging, protected from moisture.
- Monodose RS01 devices will be supplied in bulk. After use, the devices will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date. Devices will be disposed of at site after reconciliation is verified by study monitor.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM or equivalent.
- Precaution will be taken to avoid direct contact with the study treatment. No women of child-bearing potential will administer study treatment. Staff administering the study treatment will wear protective gown and gloves. A Material Safety Data Sheet describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

Dosing Procedure for Cohorts not Used for Environmental Exposure Monitoring

- Participants will inhale the dose from the Monodose RS01 device inside a negative pressure room or enclosure.
- The investigator/designee will remove the capsule from the bottle and load it into the Monodose RS01 device one at a time in a safety cabinet. One device will be used per capsule. The investigator/designee will be trained to load the capsule into the device and pierce the capsule ready for inhalation (empty capsules will be used for training).
- The participant will inhale the dose, and staff will observe participant doing it. Staff will be trained to listen for a rattle that the device makes during successful dosing. After dosing, the Monodose RS01 device will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date.
- The participant will be trained to use a "fast and deep" inspiration technique per inhalation, to achieve rapidly consecutive maximal inhalations (empty capsules will be used for training). This will ensure optimal and consistent treatment delivery. For participants, the training session will be on either Day -1 or on Day 1, prior to administration of the first dose. Subsequent assessment of Monodose RS01 device technique, and repeat device training where deemed necessary by the investigator/designee, will take place immediately before administration of each dose.

Dosing Procedure for Cohorts Used for Environmental Exposure Monitoring

- Participants will inhale the dose from the Monodose RS01 device in a room designated for dosing. All investigators/designees will leave the room and observe dosing participants and bystanders through a glass in the door. Only participants inhaling the dose and designated bystanders are allowed in the room during inhalation of the dose.
- The bystander will remove the capsule from the bottle and load it into the Monodose RS01 device one at a time. One device will be used per dose (2 capsules in this cohort). The bystander will be trained to load the capsule into the device and pierce the capsule ready for inhalation (empty capsules will be used for training).
- The bystander will pass loaded and charged device to the dosing participant.
- The participant will inhale the dose, and staff will observe participant doing it through a glass in the door. The bystander will be trained to listen for a rattle that the device makes during successful dosing. After dosing, the participant will pass the device back to the bystander.
- The bystander will open the device, remove the capsule and place it on the table between the dosing participant and the bystander. The bystander will then load the second capsule into the same device, pierce the capsule and pass the loaded device back to the dosing participant.
- The participant will inhale the second dose, the bystander will listen for a rattle that the device makes during successful dosing and staff will observe participant doing it

through a glass in the door. After dosing, the participant will pass the device back to the bystander.

- The bystander will open the device, remove the second capsule, and place the open device with both capsules on the table between the dosing participant and the bystander.
- The bystander and participant will remain seated around the table for 15 min. After this time, the bystander will place the Monodose RS01 device and both used capsules into the plastic bag labelled with the participant number, day of dosing, and date. After that is done, bystander and participant can leave the room. The bystander will need to wash their hands prior to leaving the room.
- The participant will be trained to use a "fast and deep" inspiration technique per inhalation, to achieve rapidly consecutive maximal inhalations (empty capsules will be used for training). This will ensure optimal and consistent treatment delivery. For participants and bystanders, the training session will be on either Day -1 or on Day 1, prior to administration of the first dose. Subsequent assessment of Monodose RS01 device technique, and repeat device training where deemed necessary by the investigator/designee, will take place immediately before administration of each dose.

7.6. Treatment Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

The participants will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

If failure of the capsule actuation is suspected (i.e. due to failure to pierce the capsule during device priming), the investigator is permitted to rechallenge the individual with a maximum of two further administrations at the same dose. If dosing failure is suspected for any other reason, the participant may have to be excluded after consultation with the Medical Monitor.

The Monodose RS01 devices will be under the supervision of the study organisers at all times during the clinical trial.

7.7. Concomitant Therapy

7.7.1. Permitted Medications and Non-Drug Therapies

Paracetamol or Acetaminophen, at doses of ≤2 grams/day is permitted.

Medications associated with the BAL procedure are permitted, but these medications are to be disclosed to the Sponsor prior to dosing any participants.

Participants with COPD taking medications for any chronic conditions have to be on stable doses for 4 weeks prior to screening and until after completion of the treatment period.

Salbutamol is administered 15 to 30 min prior to spirometry at screening for diagnostic purposes. Short-acting bronchodilators should not be used from 6 h prior to each morning dose administration until 4 h after that dose. If they become medically necessary during that time, short-acting bronchodilators may be administered as needed by the clinical staff only and their use must be documented.

For participants with COPD, use of long-acting bronchodilators is allowed, but their use must be modified twice during the study as follows: at screening and on Day 1, they must not be taken for at least 2 h prior to spirometry.

Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor.

7.7.2. Prohibited Medications and Non-Drug Therapies

Participants are not allowed to take oral corticosteroids from 4 weeks prior to screening and for the duration of the study.

For participants with COPD, self administration of short-acting inhaled bronchodilators is not allowed at screening, from 4 h prior to spirometry until spirometry is completed. Self administration of short-acting inhaled bronchodilators is not allowed during treatment period from 6 h prior to each morning dose administration until 4 h after that dose.

Didanosine and azathioprine are not allowed.

Except as permitted in Section 7.7.1, participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because most of the participants are healthy and the indication being studied is not life threatening.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

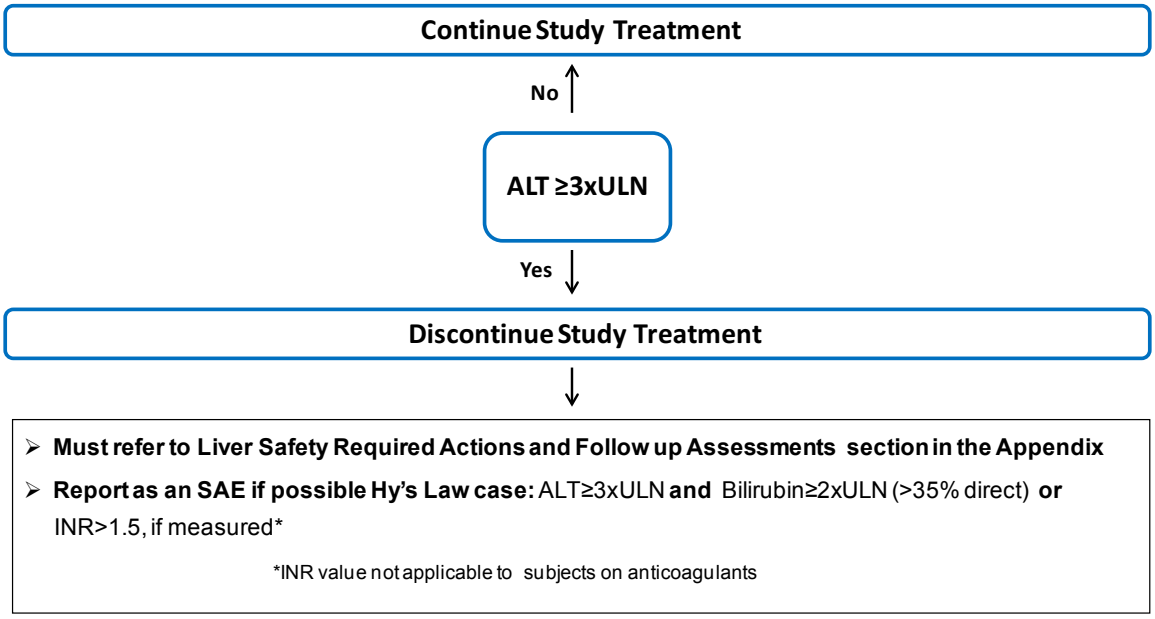
8.1. Discontinuation of Study Treatment

If participant is withdrawn from study treatment, this constitutes withdrawal from study. Participants will have to be followed up for safety reasons as deemed necessary by the Investigator and should be encouraged to return for a follow-up visit as specified in the SoA (Section 2). If this is not possible, procedures specified for the follow-up visit can be performed at the last visit that the participant attends.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined above

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.1.2. QTc Stopping Criteria

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

- QTc, QTcF >500 msec,
- Change from baseline: QTc >60 msec

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

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

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

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Other Stopping Criteria

Dosing will be stopped for any individual participant in case of SAEs and in case of any AEs which in the opinion of the investigator might jeopardise the health of the trial participant.

Additionally, dosing will be stopped and the study will be put on halt if any of the below scenarios occurred. If following an internal safety review the Sponsor deems it appropriate to restart the trial, this can be done following approval of a substantial amendment:

Two (2) or more subjects, within a dose-level, receiving study treatment experience grade 3 respiratory adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience a grade 3 hematologic adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience severe hypersensitivity related adverse event that are deemed possibly or probably related to study drug by the investigator.

Two (2) or more subjects, within a dose-level, receiving study treatment experience a grade 3 vital signs (heart rate and/ or blood pressure) adverse event that are deemed possibly or probably related to study drug by the investigator.

One (1) or more subjects receiving study treatment experience anaphylaxis that is deemed possibly or probably related to study drug by the investigator.

8.1.4. Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (Section 2) for data to be collected at follow-up and for any further evaluations that need to be completed.
- Participants will have to be followed up for safety reasons as deemed necessary by the Investigator and should be encouraged to return for a follow-up visit as specified in the SoA (Section 2). If this is not possible, procedures specified for the follow-up visit can be performed at the last visit that the participant attends.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The following time window tolerances apply to all protocol assessments:

Predose	- 60 to 0 min (- 60 to -15 min for spirometry)
0h - 4h post	- 5 / + 10 min
5h – 24h post	- 20 / + 20 min

9.1. Efficacy Assessments

There are no efficacy assessments in this study.

9.2. Adverse Events

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

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

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and no later than in 24 h, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

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

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The Cardiovascular CRFs are presented as queries in response to reporting of certain Cardiovascular MedDRA terms. The Cardiovascular information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a Cardiovascular Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Pregnancy

- Female participants of child bearing potential are excluded from this study
- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until 7 months after the last dose of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.7. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for inhalation. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2.1, Section 9.2.2, Section 9.2.3, Section 9.2.4 and Appendix 4 of the protocol.

9.2.7.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 7.

9.2.7.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2.1, Section 9.2.2, Section 9.2.3, and Section 9.2.4). This applies to all participants, including those who discontinue study treatment or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.7.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor by facsimile transmission. If facsimile transmission is unavailable, then notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.2.7.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.3. Treatment of Overdose

For this study, any dose of CCI15106-IP greater than the dose specified for the treatment period within a 24 h time period [±4 h] will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until CCI15106 can no longer be detected systemically (at least 30±2 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Screening Assessments

Cardiovascular medical history/risk factors will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

9.4.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems, and skin. Height and weight will also be measured and recorded. Oral exam will be performed.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Oral exam will also be performed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.3. Vital Signs

- Vital signs will be measured in semi-supine position and will include oral or tympanic temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure. The same method of temperature assessment should be used throughout the study.
- For BAL, vital signs will also include oxygen saturation. Oxygen saturation will be evaluated and recorded before, every 5 minutes during the procedure, at the end of, and between 30 and 60 minutes after the bronchoscopy.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Three readings of blood pressure and pulse rate will be taken where indicated as triplicate in SoA (Section 2) and all three readings will be recorded.

9.4.4. Electrocardiograms

- Triplicate OR single 12-lead ECG will be obtained in semi-supine position after 5 minutes rest as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- Continuous cardiac telemetry will be performed where indicated in SoA (Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the participant's source documents.

9.4.5. Spirometry

- Spirometry (FEV1 and FVC) will be performed at time points specified in the SoA (Section 2). Further tests should be performed, at the discretion of the investigator, if the participant has symptoms that could suggest bronchospasm.
- Spirometry manoeuvres will be conducted according to ATS/ERS 2005 spirometry standards [Miller, 2005]. The greatest FEV1 and the greatest FVC from 3 technically acceptable and reproducible manoeuvres will be recorded.
- For participants with COPD, at screening, 400 µg salbutamol will be administered 15-30 minutes prior to performing spirometry. FEV1 and FVC percent predicted values will be derived using the Global Lung Function Initiative reference values [Quanjer, 2012].

9.4.6. Capillary pCO2

The pCO2 levels will be measured at the times indicated in SoA (Section 2). The participant's hand will be heated in warm water (42 degrees) for about 10 minutes and a capillary blood sample will be collected by skin puncture using a lancet or automated incision device.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30±2 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 2).

9.4.8. Environmental and Bystander Exposure Evaluation

Exposure monitoring will be conducted in accordance with the principles outlined in prEN 689:2016, the draft European standard for workplace exposure assessment to airborne contaminants [prEN 689:2016].

9.4.8.1. Air Monitoring

During and after the first daily dose on Days 1, 7 and 14 in Cohort B Part 1, static air samples will be collected on filters within air pumps positioned in two locations in the room. The air disturbance caused by the pumps is negligible and would not be expected to alter the normal air flow patterns in the room. Marks may be placed on the floor to indicate position of the participant and positions of pumps to ensure consistency throughout the study. Samples will be run over 20 and 60 min following dosing in each location. An additional set of samples over 60 min will be taken before the start of dosing on Day 1 to provide a background benchmark for reference.

On days when static air sampling is performed, the dosing sessions will have to be separated by the time necessary to collect the 60 min air sample.

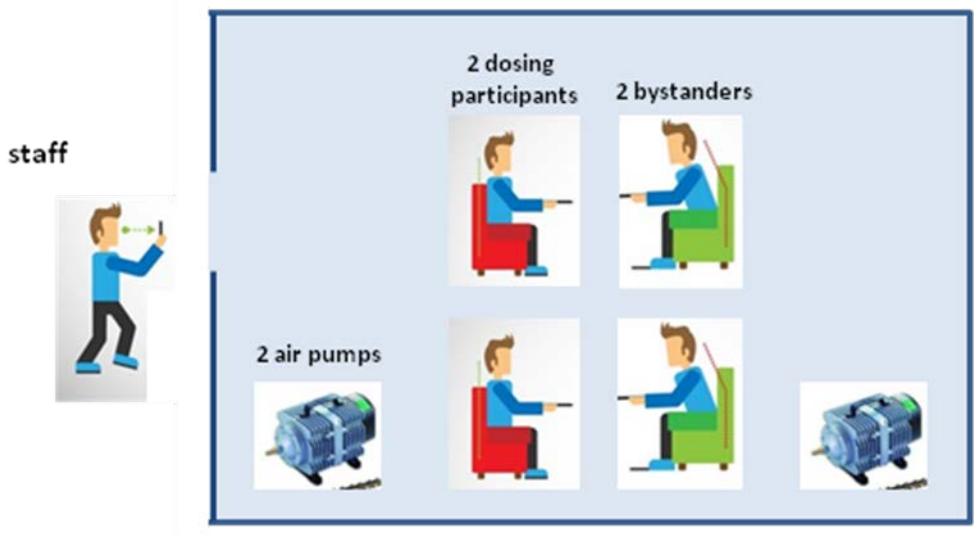
Sampling devices (Institute of Occupational Medicine [IOM] sampling heads connected to sampling pumps) shall be used to measure CCI15106 concentration. The IOM filter cassette assembly will be prepared using an immersion-extraction procedure to avoid any errors through wall deposition. Whenever possible, the Hygienist will observe the room through a glass in the door for the duration of sampling to make observations and note relevant contextual information to assist in the interpretation of the exposure measurements.

Air sample analysis will be performed by the Bureau Veritas laboratory (Bureau Veritas North America Inc, 95 Oakwood Road, Lake Zurich, IL, 60047). For air sampling, field blanks (filters which have been handled during the survey but not had air pulled through them) will be submitted with samples to check for accidental contamination during sample handling and storage. An average of one blank for every ten field samples will be sent for analysis.

9.4.8.2. Bystander Monitoring

Please refer to Figure 1 for the illustration of the design. Each dosing participant will be assigned a designated bystander for the duration of dosing. Two participants will dose at the same time in sitting position. The designated bystander will be seated facing their dosing participant within approximately 1 m of him/her. The first dosing participant will inhale the dose (both capsules), and then the second dosing participant will inhale the dose (both capsules). Please refer to Section 7.5 for detailed instructions on dosing. Each participant and their bystander will stay seated for the next 15 min, after which they will leave the dosing room. The staff will exit the room prior to bystander loading the capsule into the device (see Section 7.5) and remain outside the room for at least 15 min after dosing observing through a glass door.

Figure 1 Bystander and participant design illustration



The next two bystanders will be positioned near the next 2 dosing participants, and so on until all dosing is completed. This procedure will be followed for all doses in Cohort B Part 1, with the same bystanders positioned next to the same inhaling participant. After the first daily dose on days 1, 7 and 14, blood will be collected from bystanders 15 min after dosing (at ~tmax for CCI15106). Additionally, personal exposure air samples will be collected on filters placed on each bystander after the first daily dose on days 1, 7 and 14. The filters will be worn during dosing and for 15-minute period after dosing. Static air monitoring will be performed at the same time during and after the first daily dose on days 1, 7 and 14. During these dosing sessions, each set of two dosing participants will be separated by the time necessary to collect the 60 min air sample.

The filters used for personal exposure (IOM sampling heads connected to sampling pumps) shall be used to measure CCI15106 concentration in the person's breathing zone. The IOM filter cassette assembly will be prepared using an immersion-extraction procedure to avoid any errors through wall deposition. Whenever possible, the Hygienist will observe the room through a glass in the door for the duration of sampling to make

observations and note relevant contextual information to assist in the interpretation of the exposure measurements.

See Section 9.5 for PK assessments of bystanders.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection

Blood samples for PK analysis of CCI15106 in plasma will be collected at the time points indicated in SoA (Section 2). One 3 mL blood sample will be collected at each time point and the actual date and time of each sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the SRM OR equivalent.

9.5.2. BAL Sample Collection

BAL samples for ELF concentration analysis of CCI15106, urea, and cell counts will be collected at the time points indicated in SoA (Section 2). The actual date and time of each BAL sample collection will be recorded.

Details of BAL sample collection, processing, storage, and shipping procedures are provided in the SRM OR equivalent.

Due to the analysis methodology, any cells present in the ELF will be disrupted and their content released and analyzed together with the supernatant.

9.5.3. Urea Blood Sample

A 2 mL blood sample will be collected into Lithium Heparin tubes as soon as practically possible before the BAL samples.

Processing for plasma, storage and shipping procedures will be provided in the SRM or equivalent.

9.5.4. Sample Analysis

BAL and plasma analysis will be performed under the control of Platform Technology and Sciences – in Vitro/in Vivo Translation and Third Party Resourcing, GSK, the details of which will be included in the SRM OR equivalent. Concentrations of CCI15106 will be determined in plasma and BAL samples using the currently approved bioanalytical methodology. Plasma and BAL urea concentrations will be determined by Clinical Pathology, Safety Assessment, GSK. Raw data will be stored in the Good Laboratory Practices archives, GSK.

For bystander exposure, a plasma concentration of less than 0.5 ng/mL (the Limit Of Quantification of the method) represents an acceptable exposure since this is 29-fold

lower than the highest plasma concentration measured at the no effect dose level for teratogenicity in the most sensitive species (rat [Rebetol SPC, 2009]).

Once the plasma and BAL samples have been analyzed for CCI15106, any remaining plasma or BAL may be used for other compound-related metabolites analyses, microbiome analysis, or other exploratory analyses that inform the effect of the drug on the body or the disease, the results of which will be reported under a separate protocol.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

Sample size is based on feasibility and though no formal power calculations are performed, the sample size is deemed adequate to provide a preliminary assessment of safety prior to progression to the next study.

Part 1

In Part 1, the study plans to enrol healthy participants in 3 cohorts. In Cohort A, there will be 6 participants on active and 2 on placebo, in cohort B, there will be 12 on active and 2 on placebo. In cohort C, there will be 14 subjects who will participate as bystanders and they will be associated with the dosing subjects in Cohort B on a one to one basis for the entire duration of dosing. All subjects in Cohort B will also undergo BAL.

Part 2:

In Part 2, 22 participants with COPD are planned to be enrolled. Cohort A will have 6 participants on active dose and 2 on placebo and Cohort B will have 12 participants on active and 2 on placebo. Fourteen participants (12 active and 2 placebo) enrolled in Cohort B Part 2 will also undergo BAL.

Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of seeing adverse events. For example, in Parts 1 and 2, in treatment groups where 6 patients will receive the active drug, if the true adverse outcome rate is 5%, the chance of seeing at least one adverse outcome at a given dose is 26%. Similarly, if the true adverse outcome rate is 20%, the chance of seeing at least one adverse outcome at a given dose is 73%. For the treatment groups with 12 subjects receiving the active treatment, if the true adverse outcome rate is 5%, the chance of seeing at least one adverse outcome at a given dose is 46%. Similarly, if the true adverse outcome rate is 20%, the chance of seeing at least one adverse outcome at a given dose is 93%. This level of predictability is deemed adequate within this Phase 1 setting prior to commencement of the next study.

10.1.1. Sample Size Sensitivity

As sample size is based on feasibility, no sample size sensitivity was performed.

10.1.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Definition / Criteria	Analyses Evaluated
All Participants Screened	• Comprise of all participants who consent to participate in the clinical study. • Defined separately for Part 1 and Part 2.	
Safety	• Comprise of all participants who receive at least one dose of study treatment. • This population will be based on the treatment the participant actually received. • Defined separately for Part 1 (excluding Cohort C) and Part 2.	• Safety • Study Population
Systemic Pharmacokinetic Concentration	• Participants who receive at least one dose of study treatment and who undergo plasma PK sampling and have at least one postdose 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. • Defined separately for Part 1 (excluding Cohort C) and Part 2.	• PK
Lung ELF Concentration	• Participants who receive at least one dose of study treatment and who undergo BAL sampling and have postdose lung ELF CCI15106 and	• BAL

Population	Definition / Criteria	Analyses Evaluated
Population	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. • Defined separately for Part 1 and Part 2	
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

10.3. Statistical Analyses

The analysis and reporting of Part 1 may be conducted prior to the completion of Part 2. For all parts, the analysis and reporting will be performed after the datasets are authorized and released for reporting.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by cohort, participant and time; summaries will be presented by cohort, treatment, and time.

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, n and percent will be used as summary statistics for categorical variables.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings.

Complete details will be documented in the RAP.

10.3.1. Safety Analyses

All safety analyses will be based on the Safety Population.

Endpoint	Statistical Analysis Methods
Adverse events (AEs)	The proportion of participants reporting AEs will be tabulated by treatment and by cohort. AEs will also be tabulated by severity and relationship.
Clinical laboratory	Laboratory results will be included in the reporting of this study for hematology, clinical chemistry, and urinalysis. 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 will also be tabulated.
Electrocardiogram (ECG)	The ECG parameters of PR, QRS, QT, QTc, QTcF and HR (bpm) will be reported. Overall assessment of ECG (Investigator's judgment) will be recorded as Normal, Abnormal - Not Clinically Significant and Abnormal - Clinically Significant. Summary statistics for change from baseline will also be tabulated.
Telemetry	Overall assessment of Telemetry (Investigator's judgment) will be recorded as Normal, Abnormal - Not Clinically Significant and Abnormal - Clinically Significant.
Spirometry	% Predicted forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) values will be tabulated for each timepoint.
Vital signs assessments	The following Vital Signs measurements will be tabulated: supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature. Summary statistics for change from baseline will also be tabulated.
Monodose RS01 Device safety	Safety incidents reported from use of medical device will be tabulated.

10.3.2. Pharmacokinetic Analyses

PK analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation Department (CPMS) within GSK. Plasma CCI15106 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.3 and above. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters may be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-last) and AUC(0-∞) where data

permit for single dose, and AUC(0-τ) for repeat dose], elimination half-life (t1/2), and clearance (CL/F) as data permit.

AUC(0-24), or AUC(0-48), or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality.

Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined from Cohorts B of Part 1 and Part 2.

PK data will be presented in graphical and/or tabular form and will be summarized descriptively. A population PK model (POP PK) may be developed with all available data as appropriate and may be reported separately. Further details of the analysis plan and methods will be detailed within the RAP and data analysis plan OR equivalent.

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.

All pharmacokinetic data will be stored in the Archives, GSK Pharmaceuticals, R&D.

PK exploratory analyses will be described in the reporting and analysis plan. The population PK analysis if conducted, will be presented separately from the main clinical study report.

10.3.3. Bystander and Environmental exposure Analyses

The plasma concentration data from bystanders will be summarised descriptively and listed. The amount of CCI15106 obtained from filters will be tabulated and reported. Additional analyses, where deemed necessary, will be described in the RAP.

If data permit, the plasma concentration measured from bystanders may be plotted against the data collected from the air filters.

10.3.4. Interim Analyses

No formal interim analyses are planned for this study. Safety and tolerability will be evaluated as described in Section 5.1. Systemic and, where available, lung PK may also be evaluated.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

%CV	Coefficient of variation
%CVb	Between-subject coefficient of variation
μg	Microgram
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	AUC from time zero to end of dosing interval
AUC(0-∞)	AUC from time zero to infinity
AUC(0-24)	AUC from time zero to 24 hours
AUC(0-t)	AUC from time zero to the time of last quantifiable concentration
BAL	Bronchoalveolar lavage
BMI	Body mass index
CCI15106-CFI	CCI15106 capsules for inhalation
CI	Confidence interval
CL/F	clearance
Cmax	Concentration at maximum
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case report form
ECG	Electrocardiogram
ELF	Epithelial lining fluid
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FTIH	First time in human
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B surface antigen
Hep B	Hepatitis B
Hep C	Hepatitis C
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
HRV	Human rhinovirus

IB	Investigator brochure
ICH	International conference on harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
Kg	Kilogram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
mg	milligram
min	Minute
mL	Milliliter
mm Hg	Millimeter of mercury
NOAEL	No observed adverse effect level
PK	Pharmacokinetics
POP PK	Population PK
PRINT	Particle Replication In Non-wetting Templates
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RSV	respiratory syncytial virus
RTP	Ribavirin triphosphate
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SRM	Study Reference Manual
t1/2	Elimination half-life
Tmax	Time of maximum concentration
ULN	Upper limit of normal
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WBC	White blood cells
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	Red blood cells (RBC) Indices: Mean corpuscular hemoglobin (MCV) Mean corpuscular volume (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Fasting Glucose	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis			

Laboratory Assessments	Parameters
	C virus antibody) • Serum pregnancy test in women • Coagulation parameters in the BAL cohorts The results of each test must be entered into the CRF.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

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

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Agreement to definition of source data.

Study and Site Closure

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

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

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

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

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Guidance for Grading Adverse Events

Taken from the Food and Drug Administration (FDA) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

The purpose of this appendix is to provide guidance and it is to be used in conjunction with the investigator's judgment.

Guidance for Grading Vital Signs Adverse Events

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements
** Oral temperature; no recent hot or cold beverages or smoking
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing

Allergic Reactions

Grade 1 allergic reaction (Pruritis without rash):

Participants with Grade 1 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

- Temperature >38.5°C

- Eosinophilia
- Respiratory involvement including brochospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 1 allergic reaction may continue the study drug at the discretion of the investigator. The participant should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK.

Grade 2 allergic reaction (Localized urticaria):
Participants with Grade 2 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

- Temperature >38.5°C
- Eosinophilia
- Respiratory involvement including brochospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 2 allergic reaction may continue the study drug at the discretion of the investigator. The participant should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK.

Grade 3 allergic reaction (Generalized urticaria or angioedema):
Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Grade 4 allergic reaction (Anaphylaxis):
Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Revised ACTG Toxicity Grade	Definition	Investigator action
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria Angioedema	Discontinue therapy
Grade 4	Anaphylaxis	Discontinue therapy

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events (CV)

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are

requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor and the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Male participants

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

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 3 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner are not eligible to participate.
- In addition male participants must refrain from donating sperm for duration of study and for 7 months after study completion or from last dose.

Table 3 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion

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

Female participants

Female participants of childbearing potential are not eligible to participate.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who can become pregnant are not eligible to participate

12.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 h
• Record the liver event data, and complete an SAE data collection tool if the event also meets the criteria for an SAE2
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
• Do not restart or rechallenge participant with study treatment
MONITORING:
<u>If</u> ALT≥3xULN AND <u>bilirubin</u> ≥ 2xULN <u>or INR</u> >1.5<u>:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Blood sample for pharmacokinetic (PK) analysis, obtained within 48 h of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event</td></tr>
</table>

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James,2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Collect Liver Imaging and/or Liver Biopsy data.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally,if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**,indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excludingstudies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

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

12.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 7.1 for the list of GSK medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.8. Appendix 8: Protocol Amendment History

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

Amendment 1 (31-May-2017)

Overall Rationale for the Amendment: Changes requested after regulatory reviews

Section # and Name	Description of Change	Brief Rationale
8.1.3 Other Stopping Criteria	Added additional stopping criteria	Enhancing safety parameters in the study
5.1 Overall Design	Added PK review to all reviews required to proceed between study cohorts	Enhancing review requirements between study cohorts
1. Synopsis 2. Schedule of Activities 5.1 Overall Design	Added requirement to call male participants approximately 7 months after study completion to ensure their partner is not pregnant	Enhancing safety monitoring