TITLE PAGE

Protocol Title: A single centre, open label, one sequence, cross-over study to evaluate the effect of itraconazole on the pharmacokinetics of single inhaled doses of nemiralisib in healthy subjects.

Protocol Number: 206874

Short Title: A study to evaluate the effect of itraconazole on the PK of nemiralisib

Compound Number: GSK2269557

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

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12th December 2017.
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1. SYNOPSIS

Protocol Title: A single centre, open label, one sequence, cross-over study to evaluate the effect of itraconazole on the pharmacokinetics of single inhaled doses of nemiralisib in healthy subjects.

Short Title: A study to evaluate the effect of itraconazole on the PK of nemiralisib

Rationale:

The *in vitro* Cytochromes P450 (CYP) phenotyping study and *in vitro* inhibition data indicate CYP3A4 may be the major route of clearance for nemiralisib. Therefore, the co-administration of drug therapies which modulate CYP3A4 (specifically CYP3A4 inhibitors) may alter the exposure of nemiralisib (i.e. increase in exposure). Current recommendations by regulatory agencies Food and Drug Administration (FDA) and European Medicines Agency (EMA) specify that "*when metabolism is a significant pathway (i.e. constitutes 25% or more of the drug's overall elimination) in vivo studies using appropriate inhibitor(s)/inducer(s) are warranted*". In line with recommendations, this clinical drug interaction study with itraconazole (a potent CYP3A4 inhibitor) is required. Ongoing and future clinical studies using nemiralisib will use the data generated from this current study to justify inclusion / exclusion criteria based on concomitant medications which affect CYP3A4 and potentially inform dose modification in case of co-administration with medication affecting CYP3A4 activity.

Objectives and Endpoints:

Objectives	Endpoints
Primary • To characterize the effect of repeat oral dosing of itraconazole on the pharmacokinetics of a single inhaled dose of nemiralisib in healthy subjects	• AUC(0-∞), AUC(0-t), Cmax, tmax , $t_{1/2}$
Secondary • To investigate the safety and tolerability of single inhaled dose of nemiralisib, when dosed alone and concomitantly with itraconazole, in healthy subjects	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) and spirometry
• To investigate the pharmacokinetics of itraconazole and hydroxy-itraconazole when co-administered with nemiralisib	• AUC(0-∞), AUC(0-t), Cmax, tmax, $t_{1/2}$

AUC(0-∞) Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time, AUC(0-t): Area under the plasma concentration versus time curve from time zero to t, Cmax; maximum observed plasma concentration, tmax : time to Cmax, $t_{1/2}$: Terminal phase half-life

Overall Design:

This is a Phase I, single centre, open label, one sequence cross-over study to be conducted in healthy males and females of non-child bearing potential. The study will evaluate the Pharmacokinetic (PK), safety and tolerability of nemiralisib when administered alone and when administered concomitantly with repeat doses of itraconazole, a known strong inhibitor of CYP3A4, to simulate a steady-state exposure of itraconazole.

The pharmacokinetics of itraconazole and hydroxy-itraconazole (its hydroxy-metabolite) will be assessed to provide precise estimates of its pharmacokinetics to validate and support any interaction observed with nemiralisib as well as future usage via *in silico* modelling for nemiralisib and other drugs.

Number of Participants:

Approximately 20 participants will be enrolled such that approximately 16 evaluable participants complete the study.

Treatment Groups and Duration:

Each participant will participate in the study for approximately 7 weeks. They will complete a screening visit, 2 treatment periods (nemiralisib alone followed by nemiralisib co-administered with itraconazole), and a follow up visit.

Screening:

Participants must be screened within 21 days before the first dose (Day 1), and must meet all eligibility criteria.

Period 1:

- Participants will be admitted to the clinical research unit on Day -1 and will remain in-house until collection of the final PK sample on Day 6.
- On Day 1, participants will receive a single dose of 100 mcg nemiralisib.

Period 2:

- There will be a washout of at least 14 days between the administration of nemiralisib in Period 1 and the administration of nemiralisib in Period 2.
- Participants will be admitted to the clinical research unit on Day -1 and will remain in-house until collection of the final PK sample on Day 11.
- From Day 1 to 10 inclusive, participants will receive a single dose of 200 mg itraconazole in the morning.
- On Day 5, participants will receive a single dose of 100 mcg nemiralisib one hour after the dose of 200 mg itraconazole.

Follow-up:

Participants will be instructed to return for a follow-up visit 5-10 days after the last dose of itraconazole.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 Screening and Follow-up

Procedure	Screening (up to 21 days before Day 1)	Follow-up (within 5−10 days of last dose itraconazole)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Past and current medical conditions	X		
Medical history (includes substance usage)	X		Substances: Drugs, Alcohol, tobacco and caffeine
Physical examination	X	X	Full examination (including height and weight) at screening, brief examination at follow-up
Vital signs	X		Triplicate
12-lead ECG	X	X	Triplicate
FEV_1 and FVC	X		Triplicate
Laboratory assessments (hematology and clinical chemistry)	X	X	
Urinalysis	X		
HIV, Hepatitis B and C screening	X		If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Alcohol breath test & drug screen	X		Includes urine cotinine test
SAE review	X	X	
AE review		X	

ECG: Electrocardigram, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, HIV: Human immunodeficiency virus, AE: Adverse event, SAE: Serious adverse event.

Table 2 Period 1

Procedure	Treatment Period Days							Notes
	–1	**1**	**2**	**3**	**4**	**5**	**6**	
Admission	X							
Discharge							X	
Alcohol breath test & drug screen	X							Includes urine cotinine test
Laboratory assessments (hematology, clinical chemistry and urinalysis)	X						X	Day −1 results to be reviewed before dosing on Day 1
Brief physical examination	X						X	
Inhaler (Ellipta™) training	X							Training conducted by reviewing the Patient Information Leaflet with the participant. Additional training may be conducted at the discretion of the investigator.
FEV_1	X							Triplicate.
12-lead ECG		X					X	Single measurement. Pre-dose on Day 1.
Vital signs		X					X	Single measurement. Pre-dose on Day 1.
Study treatment (nemiralisib)		X						
Pharmacokinetic (PK) (nemiralisib)		X	X	X	X	X	X	pre-dose, and 5 min, 30 min, 2 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h and 120 h post-dose
AE review		←==========					→	
SAE review	X	←==========					→	
Concomitant medication review	X	←==========					→	

Table 3 Period 2

Procedure	Treatment Period Days												Notes
	–1	1	2	3	4	5	6	7	8	9	10	11	
Admission	X												
Discharge												X	
Alcohol breath test & drug screen	X												Includes urine cotinine test
Brief physical examination	X											X	
Laboratory assessments (hematology, clinical chemistry and urinalysis)	X										X		Pre-dose at all timepoints. Day −1 results to be reviewed before dosing on Day 1.
Clinical chemistry only			X		X		X		X				Pre-dose at all timepoints. Day 4 results to be reviewed before itraconazole dosing on Day 5.
12-lead ECG		X	X		X		X		X		X		Single measurement. Pre-dose and 3h post-dose (itraconazole) on Day 1. Pre-dose at all other timepoints, Day 4 results to be reviewed before itraconazole dosing on Day 5.
Vital signs		X	X		X		X		X		X		Single measurement. Pre-dose at all timepoints
Study treatment (itraconazole)		X	X	X	X	X	X	X	X	X	X		Approx. 1 h post standard meal.
FEV_1					X								Triplicate
Inhaler (Ellipta) training					X								Training conducted by reviewing the Patient Information Leaflet with the participant. Additional training may be conducted at the discretion of the investigator.
Study treatment (nemiralisib)						X							1 h post itraconazole administration.
PK (nemiralisib)						X	X	X	X	X	X	X	pre-dose, and 5 min, 30 min, 2 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 120 h and 144 h post-dose (nemiralisib)

Procedure	Treatment Period Days												Notes
	–1	1	2	3	4	5	6	7	8	9	10	11	
PK (itraconazole + hydroxy-itraconazole)		X				X	X						Pre-dose, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h post-dose (itraconazole) on Day 1 Pre-dose, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h hours post-dose (itraconazole) on Day 5
AE review		←==========→											
SAE review	X	←==========→											
Concomitant medication review	X	←==========→											

- The timing and number of planned study assessments, including safety and pharmacokinetic 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 changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but 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 (ICF).

3. INTRODUCTION

3.1. Study Rationale

The *in vitro* CYP phenotyping study and *in vitro* inhibition data indicate CYP3A4 may be the major route of clearance for nemiralisib (Investigator's Brochure [GlaxoSmithKline Document Number 2012N141231_08]). Therefore, the co-administration of drug therapies which modulate CYP3A4 (specifically CYP3A4 inhibitors) may alter the exposure of nemiralisib (i.e. increase in exposure). Current recommendations by regulatory agencies Food and Drug Administration (FDA) and European Medicines Agency (EMA) ([EMA, 2012], [FDA, 2017]) specify that "*when metabolism is a significant pathway (i.e. constitutes 25% or more of the drug's overall elimination) in vivo studies using appropriate inhibitor(s)/inducer(s) are warranted*". In line with recommendations, this clinical drug interaction study with itraconazole (a potent CYP3A4 inhibitor) is required. Ongoing and future clinical studies using nemiralisib will use the data generated from this current study to justify inclusion / exclusion criteria based on concomitant medications which affect CYP3A4 and potentially inform dose modification in case of co-administration with medication affecting CYP3A4 activity.

3.2. Background

Nemiralisib (also known as GSK2269557) is a potent and highly selective inhaled phosphoinositide 3-kinase (PI3K)-delta (δ) inhibitor, being developed as an anti-inflammatory agent for the treatment of Chronic obstructive pulmonary disease (COPD) and other inflammatory lung disease such as asthma and bronchiectasis. PI3Kδ is a member of the Class IA family of PI3Ks, that converts the membrane phospholipid phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a second messenger in many cellular processes including cell growth, differentiation and migration.
PI3Kδ has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells. PI3Kδ is thought to play an important part in various epithelial responses relevant for the development of COPD, asthma and bronchiectasis. Chronic treatment with antibiotics such as macrolides is increasingly used in these conditions to prevent exacerbations. Since macrolides, and other drugs used to treat co-morbidities associated with these conditions, are CYP3A4 inhibitors it is important to ensure that co-administration of these drugs does not substantially alter systemic nemiralisib levels. Hence, in this study the systemic pharmacokinetics of nemiralisib will be examined with the co-administration of itraconazole, a strong CYP3A4 inhibitor

Nemiralisib has already been administered as a nebulised solution and dry powder formulation in single and repeated doses to healthy subjects and patients with asthma and COPD, and has been well tolerated across the range of doses used. A detailed description of the chemistry, pharmacology, efficacy, and safety of nemiralisib is provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2012N141231_08].

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of nemiralisib may be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2012N141231_08].

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of itraconazole may be found in the FDA label (Itraconazole Prescribing Information, 2010).

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Bronchospasm	Can potentially occur with any inhaled treatment.	All doses of study treatment will be administered in the clinical pharmacology unit in the presence of trained clinical staff. Treatment with a short-acting inhaled bronchodilator will be available and administered as appropriate and determined by the Investigator. Participants will receive no more nemiralisib treatment and may be withdrawn from the study.
Mucosal irritancy	Detected in 13 week toxicology study in the dog.	Participants will be regularly monitored for AEs. No evidence of mucosal irritancy has been seen so far in clinical studies.
Itraconazole administration	The most common Adverse Drug Reactions associated with the administration of itraconazole are: - Upper respiratory tract infections - Increased hepatic enzymes - Hypoacusis - Headache - Abdominal pain - Diarrhea	Only healthy participants will be allowed to participate in the proposed study. Exclusion criteria, close monitoring of clinical parameters and adverse events will be conducted. Stopping criteria will be utilised to mitigate and assess cardiovascular and liver effects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	- Nausea - Fatigue - Arrhythmia - Cough - Sore throat - Back pain Refer to the FDA label (Itraconazole Prescribing Information, 2010) for itraconazole for the full list of Adverse Drug Reactions.	

3.3.2. Benefit Assessment

Healthy participants in this study will receive no direct medical benefit. They may however benefit from the thorough medical assessments they receive during the course of the study.

3.3.3. Overall Benefit:Risk Conclusion

It is considered acceptable to conduct this study in healthy participants, because whilst they will receive no direct medical benefit, the risks from the study treatment and procedures are minimal. The study will be conducted in a fully equipped clinical pharmacology unit with access to hospital emergency facilities.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To characterize the effect of repeat oral dosing of itraconazole on the pharmacokinetics of a single inhaled dose of nemiralisib in healthy participants	• AUC(0-∞), AUC(0-t), Cmax, tmax , $t_{1/2}$
Secondary • To investigate the safety and tolerability of single inhaled dose of nemiralisib, when dosed alone and concomitantly with itraconazole, in healthy participants	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) and spirometry
• To investigate the pharmacokinetics of itraconazole and hydroxy-itraconazole when co-administered with nemiralisib	• AUC(0-∞), AUC(0-t), Cmax, tmax, $t_{1/2}$

AUC(0-∞) Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time, AUC(0-t): Area under the plasma concentration versus time curve from time zero to t, Cmax; maximum observed plasma concentration, tmax : time to Cmax, $t_{1/2}$: Terminal phase half-life

5. STUDY DESIGN

5.1. Overall Design

This is a Phase I, single centre, open label, one sequence cross-over study to be conducted in healthy males and females of non-child bearing potential. The study will evaluate the PK, safety and tolerability of nemiralisib when administered alone and when

administered concomitantly with repeat doses of itraconazole, a known strong inhibitor of CYP3A4, to simulate a steady-state exposure of itraconazole.

The pharmacokinetics of itraconazole and hydroxy-itraconazole (its hydroxy-metabolite) will be assessed to provide precise estimates of its pharmacokinetics to validate and support any interaction observed with nemiralisib as well as future usage via *in silico* modelling for nemiralisib and other drugs.

Each participant will participate in the study for approximately 7 weeks. They will complete a screening visit, 2 treatment periods (nemiralisib alone followed by nemiralisib co-administered with itraconazole), and a follow up visit (see Figure 1).

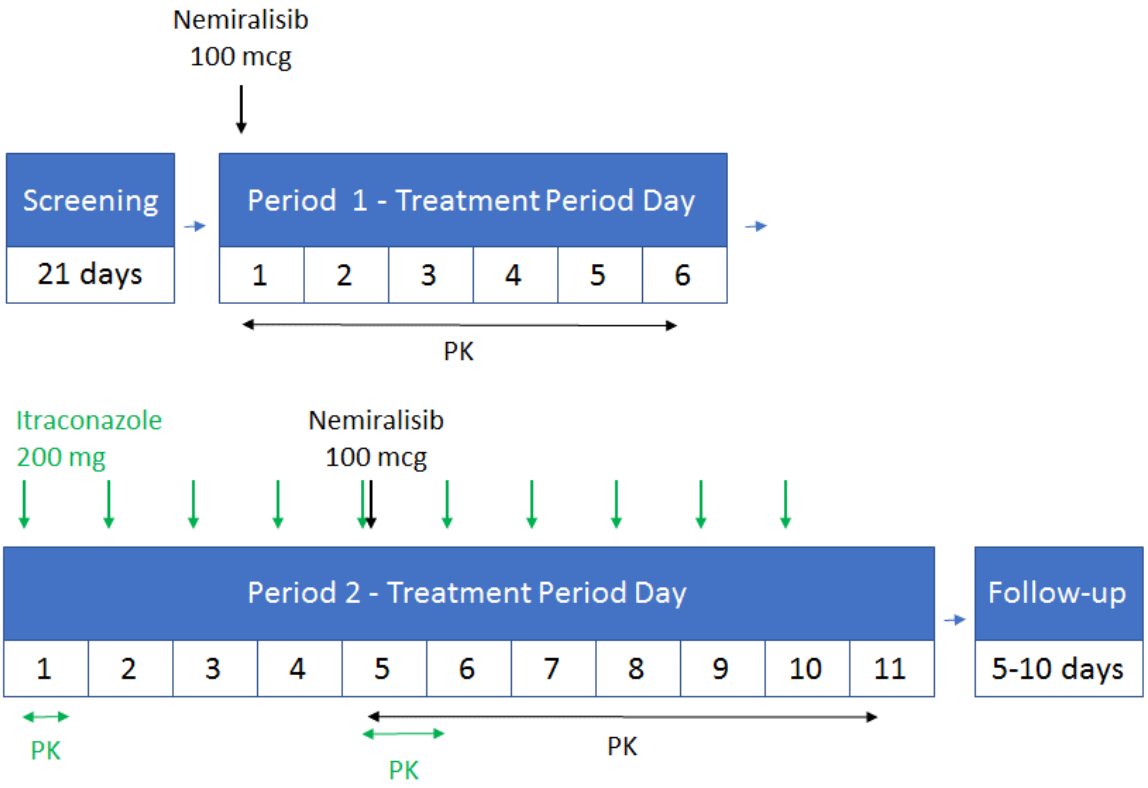


Figure 1 Overall study schematic

Screening:

Participants must be screened within 21 days before the first dose (Day 1), and must meet all eligibility criteria.

Period 1:

- Participants will be admitted to the clinical research unit on Day -1 and will remain in-house until collection of the final PK sample on Day 6.
- On Day 1, participants will receive a single dose of 100 mcg nemiralisib.

Period 2:

- There will be a washout of at least 14 days between the administration of nemiralisib in Period 1 and the administration of nemiralisib in Period 2.
- Participants will be admitted to the clinical research unit on Day -1 and will remain in-house until collection of the final PK sample on Day 11.
- From Day 1 to 10 inclusive, participants will receive a single dose of 200 mg itraconazole in the morning.
- On Day 5, participants will receive a single dose of 100 mcg nemiralisib one hour after the dose of 200 mg itraconazole.
- Participants will receive the administration of nemiralisib on Day 5 and itraconazole doses on Day 5 to Day 10 only if there are no findings that are considered clinically significant by the Investigator (in consultation with the medical monitor if needed) during review of Day 4 clinical chemistry and ECG.
- Itraconazole will be administered at approximately the same time every day and approximately 1 h after a standard breakfast.
- Nemiralisib will be administered at approximately the same time in Period 1 and in Period 2.

Follow-up:

Participants will be instructed to return for a follow-up visit 5-10 days after the last dose of itraconazole.

5.2. Number of Participants

Approximately 20 participants will be enrolled such that approximately 16 evaluable participants complete the study. Evaluable participants are those who have at least one nemiralisib PK sample taken in both periods 1 and 2, and have completed dosing up to the point of any withdrawal.

If participants prematurely discontinue the study, additional replacement participants may be recruited at the discretion of the Sponsor.

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 for the last participant in the study.

5.4. Scientific Rationale for Study Design

This is a drug-drug interaction study in healthy males and females of non-child bearing potential. Participants will be dosed with nemiralisib before and during co-administration of itraconazole and will act as their own control. A sufficient wash-out period is included (at least 14-days between nemiralisib dose administrations in Period 1 and in Period 2) to remove any effect or residual systemic exposure from the first dose of nemiralisib before starting itraconazole dose administration in Period 2.

An open label design was considered appropriate because the primary objective (pharmacokinetic parameters) does not require blinding and no pharmacodynamic markers were included in the study.

Woman of child bearing potential are excluded from participation in this study because itraconazole has shown reproduction toxicity in animal studies. In addition, there is limited information on the use of itraconazole during pregnancy and during post-marketing experience, cases of congenital abnormalities have been reported.

5.5. Dose Justification

The chosen dose level of nemiralisib in this study is 100 mcg delivered via the Ellipta device. This dose level has been chosen as it is within the current dose range chosen for investigation in the ongoing phase 2b study 200879 (50 to 750 mcg) and has previously demonstrated an adequately characterizable PK profile. The optimal efficacious dose is currently unknown but in a previous clinical study in patients (study PII116678 in exacerbating COPD patients) dosed at 1000 mcg/day (equivalent to 500 mcg using the Ellipta device and the formulation proposed in this Drug drug interaction [DDI] study) a positive primary endpoint was achieved (airway volume as measured by functional CT imaging). The 100 mcg dose level will provide an adequate exposure margin over pre-clinical exposure stopping criteria (based on toxicology No observed adverse event level [NOAEL] and toxicokinetics) should the exposure to nemiralisib increase significantly when co-administered with a CYP3A4 inhibitor. Using the predicted exposure of nemiralisib at 100 mcg in humans (extrapolated exposures of 0.41 ng/mL and 1.2 ng.h/mL for Cmax and AUC_{24} respectively) and using the 13 week dog NOAEL exposures (680 ug/kg/day NOAEL on week 13 for male and female combined of 21 ng/mL and 79 ng.h/mL respectively) gave margins of approximately 51-fold and 66-fold for Cmax and AUC_{24} respectively. These margins are considered to provide sufficient cover for any potential increase in nemiralisib exposures that co-administration of itraconazole would be anticipated to cause. The analytical assay for nemiralisib and the known exposure range over the proposed sampling regimen is deemed appropriate to fully characterise the profile out to 120 hours post dose in Period 1 and 144 hours post dose in Period 2, following a 100 mcg single dose. Preliminary data from an ongoing trial (207674 PK bridge study single doses phase 2b material) defined terminal elimination half-life to be approximately 40 hours with a Tmax observed in the sample taken immediately post dose (5 mins) which fell off rapidly in a biexponential manner. The long elimination half-life of nemiralisib is the driver behind the length of the sampling regimen. Nemiralisib is also an *in vitro* inhibitor of CYP3A4 (Ki of 4.2 µM [GSK report reference 2017N345216_00]) however as systemic concentrations are likely to be < 3 nM (1 ng/mL) following a single inhaled dose of only 100 µg the inhibition is predicted to be negligible.

The typical adult dose of itraconazole is 200 mg for up to 12 weeks although intermittent usage can be up to 400 mg/day. Itraconazole dosing of 200 mg once daily for 5 days prior to the concomitant victim (nemiralisib) dose will enable the victim interaction to be observed on a background of steady state exposure and similar to that seen in clinical practise [Ke, 2014]. A more recent publication describing the best practices around the use of itraconazole as a potent CYP3A4 inhibitor in DDI studies recommends at least a 3

day lead-in with co-administration of the victim compound on Day 4 [Liu, 2016]. Maximum inhibition was also seen if the victim drug was given one hour after itraconazole administration [Ke, 2014]. Itraconazole administration will continue after the dose of nemiralisib to ensure that inhibition is maintained throughout the elimination phase of nemiralisib.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 75 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 evaluation.
3. Normal spirometry at Screening (FEV_1 and FVC ≥80% of predicted. Predicted values will be based upon [Quanjer, 2012]. Measurements to be taken in triplicate. The highest value of each individual component must be ≥80% of predicted).
4. A participant with a clinical abnormality or laboratory parameter(s) (except for liver function tests) outside the reference range for the population being studied may be included only if the investigator, in consultation with the medical monitor if needed, agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

5. Body weight >50 kg and body mass index (BMI) within the range 18.0 – 35.0 kg/m2 (inclusive).

Sex

6. Male and/or female

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 10 days 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

7. 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

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

Medical Conditions

1. History or presence of cardiovascular, respiratory (except childhood asthma, which has now remitted), hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data
2. Abnormal blood pressure [as determined by the investigator]
3. Liver function test results above the upper limit of normal (ULN)
4. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
5. QTcF >450 msec

Prior/Concomitant Therapy

6. Past or intended use of over-the-counter or prescription medication including herbal medications within 14 days prior to dosing (Specific medications listed in Section 7.7 may be allowed)

Prior/Concurrent Clinical Study Experience

7. Participation in the study would result in loss of blood or blood products in excess of 500 mL within any 90 day period
8. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day
9. Current enrolment or past participation within the last 30 days before signing of consent in this or any other clinical study involving an investigational study treatment or any other type of medical research

Diagnostic assessments

10. Presence of Hepatitis B surface antigen (HBsAg) at screening or 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 Ribonucleic acid (RNA) test is obtained

11. 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

12. Positive human immunodeficiency virus (HIV) antibody test (according to local policies).
13. Positive drug/alcohol test at screening or on admission (Day -1)
14. Regular use of known drugs of abuse

Other Exclusions

15. Regular alcohol consumption within 6 months prior to the study defined as:
    - an average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.
16. Urinary cotinine levels indicative of smoking or history of regular use of tobacco- or nicotine-containing products within 6 months of screening, or a total pack year history of >5 pack years.
    [number of pack years = (number of cigarettes per day/20) x number of years smoked]
17. Sensitivity to any of the study treatments, or components thereof (including lactose and Magnesium Stearate), or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study
18. Unwillingness to follow the lifestyle restrictions described in Section 6.3.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Participants must be willing to comply with dietary and meal constraints outlined in this section.

- While in the clinic, meals will not contain any of the items listed below:
  - Artificial sweeteners such as mannitol, sorbitol, xylitol, Splenda or other non-absorbable dietary sugars
  - Grapefruit or grapefruit juice and pomelos
  - Apple or orange juice. Apples and oranges are permitted but not the juice of either.

- Anything from the mustard green family (i.e., no mustard greens, kale, kohlrabi, broccoli, collard greens, brussel sprouts, or watercress).
- Charbroiled meats.

- Participants must also abstain from eating any of the items listed above for at least 7 days before checking into the clinic, except there is no restriction on artificial sweeteners while the participants are outside the clinic.
- Participants will fast for at least 6 hours before a fasting glucose sample is taken (fasted at screening only).
- On Period 1, Day 1, participants will receive a standard breakfast 2 hours before drug administration (nemiralisib). Participants will remain fasted until 2 hours post-dose (nemiralisib).
- In Period 2, on all dosing days, participants will receive a standard breakfast 1 hour before drug administration (itraconazole). On Day 5, participants will remain fasted until 2 hours post-dose (nemiralisib).
- At all other times, snacks and meals will be provided by the clinical unit.
- Water will be allowed as desired except for one hour before and one hour after all drug administration occasions.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each study period, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final pharmacokinetic sample.
- During each study period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final pharmacokinetic sample.
- Use of tobacco products is not allowed from 6 months prior to screening and until after the final follow-up visit.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities only during studies.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant 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:	**Nemiralisib ELLIPTA**	**Itraconazole**
Dosage formulation:	Nemiralisib succinate blended with lactose and magnesium stearate[1]	US sourced, commercially available itraconazole capsules
Unit dose strength(s)/Dosage level(s):	100 mcg Dry Powder Inhaler (single-strip presentation) with 30 doses per inhaler / 100 mcg total dose	100 mg per capsule / 200 mg (2 capsules) per day
Route of Administration	Oral Inhalation	Oral
Dosing instructions:	Inhale ONCE from this Inhaler, as directed	To be administered with 240 mL of water and approx. 1 h after a standard meal.
Packaging and Labeling	Study Treatment will be provided in a foil overwrap. Each foil overwrap will be labelled as required per country requirement.	Itraconazole will be sourced by the clinical site
Manufacturer	GSK	Itraconazole will be sourced by the clinical site

1. Magnesium stearate 0.4% w/w of total drug product

7.2. Dose Modification

Not applicable

7.3. Method of Treatment Assignment

All participants will receive the same treatments in the periods/days specified in Section 5.1.

7.4. Blinding

This is an open-label study.

7.5. Preparation/Handling/Storage/Accountability

1. 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.
2. 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.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

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. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested (itraconazole only).

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 14 days before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen, at doses of ≤2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy participants are eligible for study participation.

8. DISCONTINUATION CRITERIA

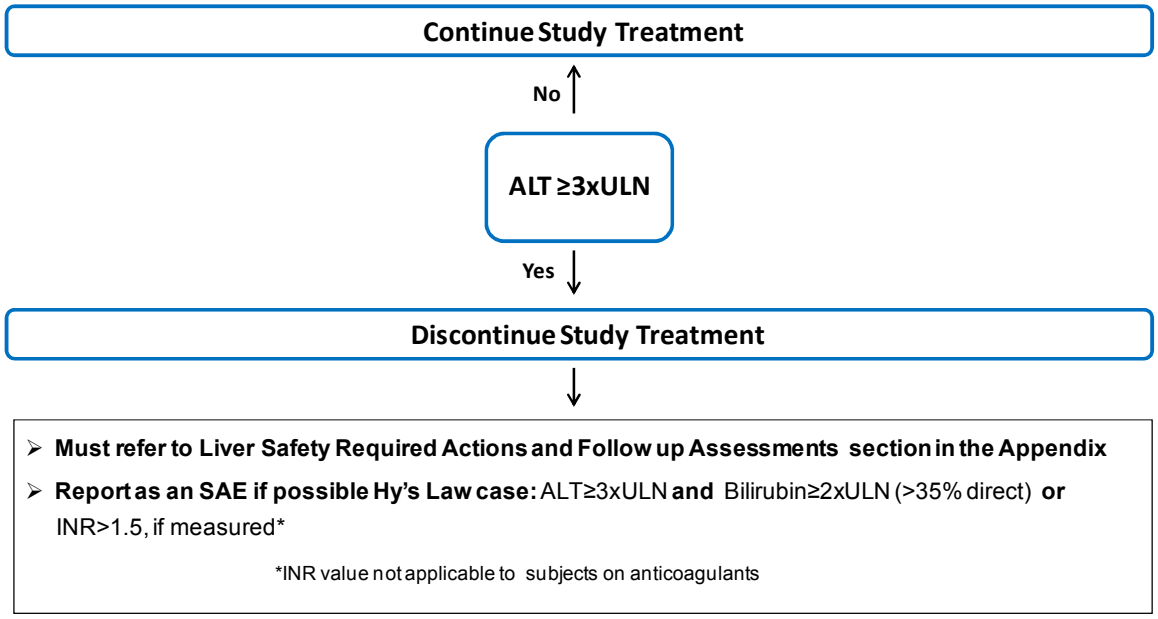
8.1. Discontinuation of Study Treatment

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.

Study treatment will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

8.1.2. QTc Stopping Criteria

A participant that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.

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

The decision to withdraw a participant will be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QTcF, obtain 2 more ECGs over a brief period (5−10 minutes), and then use the averaged QTcF values of the 3 ECGs to determine whether the participant should be discontinued from the study.

8.1.3. FEV_1 stopping criteria

A participant who experiences a fall in FEV_1 of ≥25% from baseline (screening) will be withdrawn from the study. Triplicate FEV_1 measurements will be taken. The decision to withdraw a participant will be based on the highest of the 3 measurements.

Participants who are withdrawn and are found to have respiratory symptoms should undergo appropriate diagnostic tests, to be agreed by the investigator and sponsor medical monitor.

8.1.4. Other study stopping criteria

A participant will be discontinued from the study if they experience a serious adverse event and/or unacceptable adverse events, as determined by the investigator and/or medical monitor. Every effort should be made to complete safety follow-up procedures after a participant is discontinued from study drug.

The study will be halted for an internal safety review if there is a SAE or 2 severe AEs, considered to be at least possibly related to the study treatment (nemiralisib or itraconazole).

8.1.5. Temporary Discontinuation

A participant withdrawn from the study treatment will no longer continue in the trial.

8.1.6. Rechallenge

8.1.6.1. Study Treatment Restart or Re-challenge

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.
- Participants who are withdrawn should complete any safety assessments that the investigator considers necessary for the well being of the participant, and the assessments planned for the follow-up visit.

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.
- 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, 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.
- 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.
- If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

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

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

9.1. Efficacy Assessments

There will be no efficacy assessments for this study.

9.2. Adverse Events

Planned time points for all safety assessments are listed in the SoA (Section 2). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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 treatment (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).
- 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 under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours 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 (as defined in Section 9.2), 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

- Immediate 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 (SUSAR) 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. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until follow-up.
- 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.

9.3. Treatment of Overdose

For this study, any dose of nemiralisib greater than 100 mcg within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose of nemiralisib. The Investigator (or physician in charge of the participant at the time) will use clinical judgment to treat any overdose.

For this study, any dose of itraconazole greater than 200 mg within a 22-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose of itraconazole. The Investigator (or physician in charge of the participant at the time) will use clinical judgment and the information available in the FDA label to treat any overdose.

In the event of an overdose, the Investigator (or treating physician) should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 14 days).
3. Obtain a plasma sample for PK analysis within 7 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.

9.4.1. Physical Examinations

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

9.4.2. Vital Signs

- Vital signs will be measured in a supine or semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- For time points where vital signs are collected in triplicate, only systolic and diastolic blood pressure, and pulse rate should be repeated. There should be at least a 2 minute interval between readings.
- Baseline will be defined as the mean of the 3 pre-dose measurements taken on Day 1 for each Period.

9.4.3. Electrocardiograms

- 12-lead ECGs will be measured in a supine or semi-supine position after 5 minutes rest.
- 12-lead ECGs will be obtained at each time point during the study, as outlined in the SoA (see Section 2). This will be performed using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS duration, QT and QTcF intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At time points at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession (no more than 2 minutes apart). The full set of triplicates should be completed in less than 4 minutes.

9.4.4. Spirometry

- Spirometry assessments will be performed whilst the participant is in a seated position (if the assessment is done on a bed, the participant's legs should be over the edge).
- Spirometry assessments will be repeated until 3 technically acceptable measurements have been made. The highest of the 3 values will be recorded in the CRF.
- Refer to Section 8.1.3. for the FEV_1 withdrawal criterion.

9.4.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or at the follow-up visit 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.

9.5. Pharmacokinetics

A 2 mL blood sample for PK analysis of nemiralisib will be collected at each time-point listed in the SoA. A 2 mL blood sample for PK analysis of itraconazole and hydroxy-itraconazole will be collected at each time-point listed in the SoA.

At timepoints where nemiralisib, itraconazole and hydroxy-itraconazole are measured, a single 3 mL blood sample will be collected.

The actual date and time of each blood sample collection will be recorded. Sample storage and shipping instructions will be included in the Study reference manual (SRM) or equivalent.

Analysis of plasma samples for nemiralisib will be performed within PTS-IVIVT-BIB, GlaxoSmithKline. Concentrations of nemiralisib will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at GSK.

Analysis of plasma samples for itraconazole and hydroxy-itraconazole will be performed under the control of PTS-IVIVT-BIB/TPR GlaxoSmithKline. Concentrations of itraconazole and hydroxy-itraconazole will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site for a specified portion of the retention period.

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

The primary objective of the study is to characterize the effect of repeat oral dosing of itraconazole on the pharmacokinetics of a single inhaled dose of nemiralisib in healthy participants. No formal hypotheses will be tested.

10.1. Sample Size Determination

The sample size has primarily been based on feasibility; however it has also been chosen such that the estimated level of precision achieved for AUC(0-∞) and Cmax is considered to be acceptable.

Variability estimates have been taken from preliminary PK data (with nominal sampling times) for the 207674 study, since it used the same formulation as in this study. The 500mcg dose is the closest to 100mcg, so this has been chosen; indeed variability has been observed to increase with dose, so this is considered a conservative estimate.

Study 207674 observed total between subject standard deviations (SD) on the loge scale of 0.382 for AUC(0-∞) and 0.411 for Cmax. Based on correlation observed in the 201544 study (rho=0.253 and 0.302 for AUC(0-∞) and Cmax respectively) the within subject SD on the loge scale has been assumed to be 0.330 for AUC(0-∞) and 0.343 for Cmax for this study.

It is consequently estimated that with 16 subjects providing the relevant PK parameter data, the upper bound of the 90% confidence interval (CI) will be within approximately 22% of the point estimate and the lower bound within 18% for AUC(0-∞). For Cmax the upper bound of the 90% CI is estimated to be within approximately 23% of the point estimate and the lower bound within 19%. The following gives the expected CIs under the assumption of various ratios between the two groups:

Ratio (nemiralisib co-administered with itraconazole / nemiralisib administered alone)	CI	
	AUC(0-∞)	Cmax
1	(0.82, 1.22)	(0.81, 1.23)
2	(1.64, 2.44)	(1.63, 2.46)
5	(4.10, 6.09)	(4.07, 6.14)

10.1.1. Sample Size Sensitivity

If the within subject standard deviation observed in AUC(0-∞) and Cmax is 10% or 20% higher than estimated, the upper and lower bounds of the 90% CI would be as follows:

	% increase in SD	SD	Percentage Within which the 90% CI lies	
			Upper bound	Lower bound
AUC(0-∞)	10%	0.3634	24%	20%
	20%	0.3965	25%	20%
Cmax	10%	0.3773	27%	21%
	20%	0.4116	28%	22%

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants screened and for whom a record exists on the study database.
Enrolled	All participants who passed screening and entered the study. Included are: run-in failures and participants who took treatment.
Safety	All participants enrolled in the study, who took at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
Pharmacokinetic	All participants enrolled in the study who took at least 1 dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed. Participants will be analysed according to the treatment they received.

10.3. Statistical Analyses

Statistical analysis will be performed by, or under the direct auspices of Clinical Statistics, GlaxoSmithKline. Complete details of the planned statistical analyses will be provided in the Reporting and Analysis Plan (RAP).

10.3.1. Pharmacokinetic Analyses

All PK analyses will be performed on the Pharmacokinetic Population.

Endpoint	Statistical Analysis Methods
Primary	Plasma nemiralisib concentration-time data will be analysed by non-compartmental methods using WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined for both Day 1 in period1 and Day 5 in period 2, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], terminal half life ($t_{1/2}$) and the percentage of extrapolation for AUC(0-∞). Pharmacokinetic concentration data will be presented in graphical and/or tabular form. Derived pharmacokinetic parameters will be listed [subjects with greater than 20% extrapolated AUC (0-∞) will be highlighted] and descriptive statistics (n, arithmetic mean, SD, 95% CI, minimum, median and maximum) will be calculated for all pharmacokinetic parameters by treatment. In addition, for loge-transformed variables the geometric mean with associated 95% CI, SD on $\log_e$-scale and between subject coefficient [%CVb (100 * √ (exp(SD2) -1)] will be provided, where the SD is the standard deviation of $\log_e$ transformed data. To estimate the ratio of exposure of nemiralisib administered alone and co-administered following repeat doses of itraconazole, mixed effects analyses will be performed for both $\log_e$ transformed Cmax and $\log_e$ transformed AUC(0-∞). The geometric mean ratios will be provided along with 90% confidence intervals and the mean squared error (MSE).
Secondary	Plasma itraconazole concentration-time data and PK parameters [Cmax, Tmax, AUC(0-t), AUC(0-∞) and $t_{1/2}$] for both Day 1 (first dose of itraconazole) and Day 5 (5^{th} Day of dosing Itraconazole or steady state) in period 2, will be analysed, listed and summarised as described for nemiralisib. No formal statistical analysis will occur.

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) and spirometry, will be listed and summarized by treatment.

10.3.3. Interim Analyses

A preliminary analysis of PK may be performed following the availability of the PK data, for internal decision making.

11. REFERENCES

European Medicines Agency (EMA), *Guideline on the investigation of drug interactions*, Committee for Human Medicinal Products (CHMP), 2012, CPMP/EWP/560/95/Rev. 1 Corr. 2

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Ke AB, Zamek-Gliszczynski MJ, Higgins JW, Hall SD. Itraconazole and Clarithromycinas Ketoconazole Alternatives for Clinical CYP3A Inhibition Studies. *Clinical Pharmacology & Therapeutics*. 2014; 95:473-6.

Liu L, Bello A, Dresser MJ, Heald D, Komjathy SF, O'Mara E et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. *J Clin Pharmacol*. 2016; 56(2):143-51

Quanjer PH, Stanojevic S; Cole T et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. European Respiratory Journal. 2012; 40: 1324–1343

U.S. Department of Health and Human Services Food and Drug Administration (FDA), *Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications, Guidance for Industry, Draft Guidance,* Center for Drug Evaluation and Research (CDER), 2017.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate Aminotransferase
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
Cmax	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CT	computerised tomography
CYP	Cytochromes P450
DDI	Drug drug interaction
ECG	Electrocardigram
EMA	European Medicines Agency
FDA	Food and drug administration
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
kg	Killogram
mcg/ ug	Microgram
mg	Milligram
mL	Milliliter
MSDS	Material Safety Data Sheet
MSE	Mean squared error
ng	Nanogram
NOAEL	No observed adverse event level
PI3K	Phosphoinositide 3-kinase
PIP2	phospholipid phosphatidylinositol 4,5-biphosphate
PIP3	phosphatidylinositol 3,4,5-trisphosphate
PK	Pharmacokinetic
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's

	formula
RAP	Reporting and analysis plan
RNA	Ribonucleic Ac
SAE	Serious adverse event
SD	Standard deviation
SOA	Schedule of activities
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Half life
tmax	Time to Cmax
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 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 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume Mean Corpuscular Hemoglobin %Reticulocytes	White Blood Cell count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (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
	Glucose (fasted at screening only)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase 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) • Alcohol breath test and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine cotinine • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and			

Laboratory Assessments	Parameters
	hepatitis C virus antibody) 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 6. 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 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.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

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 participants, as appropriate.
- 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.

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 from the issue of the final Clinical Study Report (CSR)/ equivalent summary 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 Data Entry Tracking Guidelines or equivalent document.

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.

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.

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 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 **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 enrolment.

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 5 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- In addition, male participants must refrain from donating sperm for duration of study and for at least 10 days after the last dose.

Table 5 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 / ligation
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

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.

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.

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

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</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</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 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin <2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 7 days 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 alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥2xULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects 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; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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 (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; 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 subjects 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 PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject'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.