TITLE PAGE

Protocol Title: A randomised, double-blind, parallel group study to evaluate the safety, tolerability and pharmacokinetics of a single dose of GSK2269557 administered via the ELLIPTA™ dry powder inhaler to healthy participants.

Protocol Number: 207674

Short Title: Double-blind study to evaluate the safety, tolerability and pharmacokinetics of a single dose of GSK2269557 in healthy participants.

Compound Number: GSK2269557

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

4.4.2017.

Anthony Cahn
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Date

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1. SYNOPSIS

Protocol Title: A randomised, double-blind, parallel group study to evaluate the safety, tolerability and pharmacokinetics of a single dose of GSK2269557 administered via the ELLIPTA™ dry powder inhaler to healthy participants.

Short Title: Double-blind study to evaluate the safety, tolerability and pharmacokinetics of a single dose of GSK2269557 in healthy participants.

Rationale: This is the first study using a new formulation of GSK2269557 in healthy participants. GSK2269557 will be administered via the ELLIPTA™ dry powder inhaler (DPI) formulated in a blend containing 0.4% MgSt (magnesium stearate). The previous formulation contained 0.6% MgSt. Healthy participants are considered appropriate to assess the new formulation since previous studies assessing device and formulation have been conducted in healthy participants. Furthermore no significant differences in the pharmacokinetic (PK) profiles have been observed between healthy participants and chronic obstructive pulmonary disease (COPD) patients. Therefore data derived from this study will inform on the PK profile and systemic exposure expected in patients during Ph2b.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the pharmacokinetic profile of a single dose of GSK2269557 administered via the ELLIPTA™ DPI to healthy participants.	GSK2269557 plasma concentration data and derived pharmacokinetic parameters including area under the plasma drug concentration versus time curve area under the plasma drug concentration versus time curve from zero to time t, area under the plasma drug concentration versus time curve from zero to 24 hours, area under the plasma drug concentration versus time curve from zero to infinity ($AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), Concentration at trough (Ctrough), terminal half-life ($T_{1/2}$), where data allow.
Secondary	
To assess the safety and tolerability of a single dose of GSK2269557 administered via the ELLIPTA™ DPI to healthy participants.	Safety and tolerability of GSK2269557 as assessed by clinical monitoring of: • Vital Signs • Electrocardiogram (ECG)

Objectives	Endpoints
	• Spirometry • Laboratory safety data • Adverse events (AEs)

Overall Design: The study is a randomised, double blind, parallel group, single dose study in healthy participants. The study will be conducted at a single centre. Approximately twelve participants will be randomised to receive a single dose of GSK2269557 750 µg or a single dose of GSK2269557 500 µg. Participants will be randomised to GSK2269557 750 µg or GSK2269557 500 µg in a 1:1 ratio.

Number of Participants: A sufficient number of participants will be screened in order to randomise approximately twelve participants such that six participants complete on the GSK2269557 750 µg treatment group and six participants complete on the GSK2269557 500 µg treatment group. Participants will be replaced if necessary.

Treatment Groups and Duration: Participants will be randomised to receive 750 µg of GSK2269557 or 500 µg of GSK2269557 in a 1:1 ratio.

The study consists of the following visits:

- *Screening:* within 28 days of first dose
- *Treatment Period:*
    - Participants will be admitted on Day -1
    - Study treatment will be administrated on Day 1. Participants will be discharged after completion of all 24h post dose assessments on Day 2 and if there are no safety concerns.
    - On Day 3 and Day 6, participants will return to the study clinic on an outpatient basis, in order to complete the assessments described in the SOA (Section 2).
- *Follow-up:*
    - Participants will receive a telephone call at 10-12 days post dose to ensure there are no AEs to report or safety concerns.

The duration of the study for each participant (including screening and follow-up) will last up to 6 weeks.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
Informed consent	X							
Inclusion and exclusion criteria	X							Recheck clinical status before randomization
Demography	X							
Full physical examination including height and weight	X							
Medical history (includes substance usage and current medical conditions)	X							Substances: Drugs, Alcohol, tobacco and caffeine
Urine pregnancy test (WOCBP only)	X	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

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
Admission to unit		X						
Outpatient visit	X				X	X		
Discharge				X				
Laboratory assessments (include liver chemistries)	X	X		X				
Urine Drug, Alcohol and Smoking breath test	X	X						
12-lead ECG	X		X	X				Screening only: ECG in triplicate Day 1: pre-dose, 5 mins & 6 hrs post-dose Day 2: before discharge
Vital signs	X		X	X				Screening only: blood pressure and pulse in triplicate Day1: pre-dose, 1h and 6h post-dose

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
Spirometry [FEV1 and FVC] (triplicate)	X		X					Day 1: pre-dose, 30 min post-dose
Brief physical examination		X						
Inhaler training		X						Training conducted by reviewing the Patient Information Leaflet with the participant. Additional training may be conducted at the discretion of the investigator.
Dosing study treatment			X					
AE review			←==========→					
SAE review	←==========→							
Concomitant medication review			X	X	X	X	X	

Procedure	Screening (up to 28 days before Day 1)	Treatment Period [Days]					Follow-up (10-12 days post dose)	Notes
		–1	1	2	3	6		
Pharmacokinetic blood sample			X	X	X	X		Day 1: pre-dose, 5 min and 0.5, 2, 6 and 12 hours post-dose. Day 2: 24 hours post-dose. Day 3: 48 hours post-dose Day 6: 120 hours post dose.

- 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., for safety purposes or 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 ICF.

3. INTRODUCTION

GSK2269557 is a potent and highly selective inhaled Phosphoinositide 3 Kinase delta (PI3Kδ) inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airways diseases.

3.1. Study Rationale

This is the first study using a new formulation of GSK2269557 in healthy participants. GSK2269557 will be administered via the ELLIPTA™ dry powder inhaler (DPI) formulated in a blend containing 0.4% MgSt (magnesium stearate). The previous formulation contained 0.6% MgSt. Healthy participants are considered appropriate to assess the new formulation since previous studies assessing device and formulation have been conducted in healthy participants. Furthermore no significant differences in the pharmacokinetic (PK) profiles have been observed between healthy participants and chronic obstructive pulmonary disease (COPD) patients. Therefore data derived from this study will inform on the PK profile and systemic exposure expected in patients during Ph2b.

3.2. Background

Phosphoinositide 3-kinase δ (PI3Kδ), a lipid kinase expressed predominantly in leukocytes, is a potential therapeutic target for inflammatory conditions such as COPD and asthma. Neutrophils and T cells are the two major inflammatory cell types involved in COPD, and both are targeted by inhibition of PI3Kδ [Hatcher, 2011]; [Okkenhaug, 2007]; [Sadhu, 2003].

GSK2269557 has been administered to healthy participants and healthy smokers in previous studies, as follows:

- *Study PII115117 (healthy participants):* single and repeat doses of a nebulised solution of GSK2269557 – daily doses up to 6400 μg for 7 days.
- *Study PII116617 (healthy smokers):* single and repeat doses of a dry powder formulation (DISKUS DPI) of GSK2269557 – single doses up to 3000 μg, and daily doses up to 2000 μg for 14 days.
- *Study 201544 (healthy participants):* single centre, three part, randomised, study to evaluate the safety, tolerability and pharmacokinetics of GSK2269557 administered via the ELLIPTA™ dry powder inhaler (0.6% MgSt formulation) – single doses up to 200 μg, and daily doses of 200 μg for 10 days (study completed but not yet reported).
- *Study 205759 (healthy Japanese participants):* single and repeat doses of GSK2269557 administered via the ELLIPTA™ dry powder inhaler (0.6% MgSt formulation) – single doses up to 700 μg, and daily doses up to 700 μg for 10 days (study completed but not yet reported).

GSK2269557 was well tolerated across the range of doses tested in all studies.

GSK2269557 has been administered to stable COPD patients, patients experiencing a COPD exacerbation and patients with persistent, uncontrolled asthma:

- *Study PII115119 (stable COPD patients):* daily doses of up to 2000 µg GSK2269557 are being administered via the DISKUS DPI for 14 days.
- *Study PII116678 (patients experiencing a COPD exacerbation):* daily doses of 1000 µg GSK2269557 are being administered via the DISKUS DPI for 12 weeks.
- *Study 201543 (patients with persistent, uncontrolled asthma)*: daily doses of 1000 µg GSK2269557 are being administered via the DISKUS DPI for 28 days (study completed but not yet reported).

There are also two ongoing studies in the clinical phase, one in patients experiencing a COPD exacerbation and one in patients with activated PI3K delta syndrome (APDS)/ p110 delta-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI):

- *Study 201928 (patients experiencing a COPD exacerbation):* daily doses of 1000 µg GSK2269557 are being administered via the DISKUS DPI for 12 weeks.
- *Study 204745 (patients with APDS/PASLI)*: daily doses of 700µg GSK2269557 are being administered via the ELLIPTA dry powder inhaler.

More information about the non-clinical and clinical studies is available in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2012N141231_06].

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2269557 may be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2012N141231_06].

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2269557]		
Bronchospasm	A general risk with all Inhaled treatments	Study treatment will be administered in the clinical pharmacology unit in the presence of trained clinical staff. Treat immediately with a short-acting inhaled bronchodilator. Participants will be withdrawn from the study.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Participants will be monitored for AEs. Thus far this has not been seen in clinical studies.
Unknown risks to an embryo, foetus or nursing infant	There are no studies with GSK2269557 in pregnant or lactating women.	As specified in the protocol: • Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. • If a female participant becomes pregnant during the study, she must let the study doctor know immediately. • For women of reproductive potential, a pregnancy test will be performed at Screening and Day-1. • Male participants with female partners of reproductive potential must use highly effective contraception methods to avoid pregnancy while in this study.

3.3.2. Benefit Assessment

Healthy participants participating in this study will receive no direct medical benefit. They might benefit from the thorough medical examination and assessments they receive during the course of the study.

3.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK2269557 are considered justified.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To assess the pharmacokinetic profile of a single dose of GSK2269557 administered via the ELLIPTA™ DPI to healthy participants.	• GSK2269557 plasma concentration data and derived pharmacokinetic parameters including area under the plasma drug concentration versus time curve area under the plasma drug concentration versus time curve from zero to time t, area under the plasma drug concentration versus time curve from zero to 24 hours, area under the plasma drug concentration versus time curve from zero to infinity ($AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), Concentration at trough (Ctrough), terminal half-life ($T_{1/2}$), where data allow.
Secondary • To assess the safety and tolerability of a single dose of GSK2269557 administered via the ELLIPTA™ DPI to healthy participants.	• Safety and tolerability of GSK2269557 as assessed by clinical monitoring of: • Vital Signs • Electrocardiogram (ECG) • Spirometry • Laboratory safety data • Adverse events (AEs)

5. STUDY DESIGN

5.1. Overall Design

This is a randomised, double-blind, parallel group, single centre study to evaluate the safety, tolerability and pharmacokinetics of a single dose of GSK2269557 administered via the ELLIPTA™ dry powder inhaler to healthy participants.

Eligible participants will be admitted on Day -1 and receive GSK2269557 on Day 1. Participants will be discharged after completion of all 24 h post dose assessments on Day 2 and if there are no safety concerns.

On Day 3 and Day 6, participants will return to the study clinic on an outpatient basis.

Participants will receive a telephone call at 10-12 days post dose to ensure there have been no safety issues since discharge.

The duration of the study for each participant (including screening and follow-up) will last up to 6 weeks.

5.2. Number of Participants

A sufficient number of healthy participants will be screened in order to randomise approximately twelve participants such that six participants on the GSK2269557 750 µg treatment group and six participants on the GSK2269557 500 µg treatment group complete the final sampling timepoint (120 hours post-dose).

An evaluable participant is a participant who takes at least one dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed.

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

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the Follow Up Phone Call.

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

5.4. Scientific Rationale for Study Design

This is the first study that GSK2269557 will be administered via the ELLIPTA DPI formulated in a blend containing 0.4% MgSt. Magnesium stearate has been reduced in this final formulation from that studied in previous trials and has resulted in a change in the respirable mass of the drug product. It is anticipated that this will impact the PK profile in man and resulting in an increase in systemic exposure. Cmax may increase, by an average of approximately 50%-70% compared to the previously studied MgSt containing formulation. The final sampling timepoint (120 hours post-dose) has been

selected to confirm the terminal half-life based on preliminary data from study 205759 in healthy Japanese participants which has shown a half-life of approximately 46 hours.

This study will inform on the exposure of GSK2269557 administered via the ELLIPTA DPI formulated in the new blend containing 0.4% MgSt. Previous studies conducted across healthy participants and patients have shown no major differences in exposure.

5.5. Dose Justification

This study is planned to test two separate dose strengths, 750 and 500 µg via a single dose of GSK2269557. Higher doses of other formulations of GSK2269557 as well as longer treatment duration have been tested in previous healthy participant studies: twice daily doses of 3200 µg were tested as a nebulised solution in healthy participants for 7 days; and daily doses of 2000 µg were tested using the DISKUS DPI in healthy smokers for 14 days and in healthy non-smokers for 10 days at a once daily dose of 200 µg using the ELLIPTA DPI containing 0.6% magnesium stearate (preliminary data, not reported yet). For more detailed information, see the GSK2269557 IB [GlaxoSmithKline Document Number 2012N141231_06].

This is the first study that GSK2269557 will be administered via the ELLIPTA DPI formulated in a blend containing 0.4% MgSt. The change in formulation is expected to increase systemic exposure by up to 50% based on an observed increase in respirable mass as measured by *in vitro* drug product performance (Aerodynamic Particle Size Distribution).

Table 1 below shows the expected multiples of the predicted clinical exposure following a single inhalation of 750 µg or 500 µg compared to both pre-clinical margins and in relation to previously observed clinical exposure. The number presented is the most conservative estimate of cover using the highest exposed individual within study 201544 and compared to the expected geometric mean value derived from pre-clinical data (rat 3 month no observed adverse effect level [NOAEL] exposures) as well as the data from the highest exposed clinical data to date (PII115117; 7 days dosing bid of 3200 µg nebulised GSK2269557 to steady-state).

Table 1 GSK2269557 Systemic Exposure Margins to Pre-Clinical Safety and Clinical Data Following Administration via ELLIPTA DPI Containing Either 0.4% Magnesium Stearate

Dose	Parameter[1]	Exposure Margin	
		Pre-clinical[2]	Clinical[3]
500 µg	C_{max} (ng/mL)	17	2.0
500 µg	AUC_{0-24h} (ng.h/mL)	23	6.9
750 µg	C_{max} (ng/mL)	11	1.4
750 µg	AUC_{0-24h} (ng.h/mL)	15	4.6

1. Using the highest measured exposed individual based on study 201544 (200 µg top dose) to generate (linear extrapolation including an increase of 1.71 fold for Cmax and 1.54-fold on AUC) the most conservative multiple for either a 500 µg or a 750 µg single dose based on Day 1 data. Cmax and AUC0-24h of 2.6 ng/mL and 12.4 ng.h/mL for 500 µg and a Cmax and AUC0-24h of 3.9 ng/mL and 18.6 ng.h/mL for 750 µg respectively.
2. Based on the NOAEL derived from the rat 3 month toxicology study R29876 with a Cmax and AUC of 43.7 ng/mL and 286 ng.h/mL respectively.
3. Based on the highest achieved geometric mean value derived from reported trials to date of 5.3 ng/mL and 85 ng.h/mL based on exposure on Day 7 following repeat daily single doses.

Based on the above calculations the exposure following a single 750 µg inhaled dose is expected to be well within pre-clinical safety margins and in addition is expected to be lower than the maximum exposure seen to date in reported studies with no adverse events of note associated with that clinical systemic exposure.

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

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and ECG tests. Re-screening will be allowed once, at the discretion of the Principal Investigator in consultation with GSK medical monitor (see Section 6.4).
3. Normal spirometry at Screening forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) ≥80% of predicted – measurements to be taken in triplicate and the highest value for each component must be ≥80% of predicted).

Weight

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

Sex

5. Male or female

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 2 of this protocol during the treatment period for at least 5 half-lives + 90 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 2), not breastfeeding, and at least one of the following conditions applies:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 2

   OR

   (ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period for at least 5 half-lives + 90 days after the last dose of study treatment .

Informed Consent

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

6.2. Exclusion Criteria

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

Medical Conditions

1. Asthma or a history of asthma (except in childhood, which has now remitted)
2. Significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, 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
3. Abnormal blood pressure [as determined by the investigator]
4. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
5. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
7. Corrected QT interval (QTc) >450 msec

NOTES:

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

Prior/Concomitant Therapy

8. Past or intended use of over-the-counter or prescription medication including herbal medications within 7 days prior to dosing. Specific medications listed in Section 7.7 may be allowed.
9. Live vaccine(s) within 1 month prior to screening, or plans to receive such vaccines during the study

Prior/Concurrent Clinical Study Experience

10. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days
11. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day

Consider adding the following criteria if participants can only be enrolled once per study.

12. Current enrollment or past participation within the last 90 days before signing of consent in any other clinical study involving an investigational study treatment or any other type of medical research

Diagnostic assessments

13. Presence of Hepatitis B surface antigen (HBsAg) at screening Positive Hepatitis C antibody test result at screening.

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

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

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

15. Positive pre-study drug/alcohol screen

16. Positive human immunodeficiency virus (HIV) antibody test
17. Regular use of known drugs of abuse

Other Exclusions

18. Regular alcohol consumption within 3 months prior to the study defined as:

    An average weekly intake of >14 units for males and females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
19. Current smoker or a history of smoking 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]
20. Sensitivity to any of the study treatments, or components thereof (including lactose and MgSt), or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of Seville oranges, grapefruit or grapefruit juice from 7 days before the start of study treatment until collection of the final pharmacokinetic (PK) sample.

6.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee and cola drinks) for 6 hours before the start of dosing until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
- Participants will abstain from alcohol for 12 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Smoking is not permitted during the study.

6.3.3. Activity

- Participants will abstain from strenuous exercise for a minimum of 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

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

demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. 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:	GSK2269557 ELLIPTA™ DPI (500 µg)	GSK2269557 ELLIPTA™ DPI (750 µg)
Dosage formulation:	DPI	DPI
Unit dose strength(s)/Dosage level(s):	500 µg	750 µg
Route of Administration	Inhalation	Inhalation
Dosing instructions:	Inhale as directed	Inhale as directed
Packaging and Labelling	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.
Manufacturer	GSK	GSK
Device:	ELLIPTA™	ELLIPTA™

7.2. Dose Modification

This protocol does not allow alteration from the currently outlined dosing schedule.

7.3. Method of Treatment Assignment

Study using Pre-Coded Randomization	On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order by the Interactive Voice Recognition System/ Web Response Centre (IVRS/IWRS). The randomization number encodes the participant's assignment to one of the treatment arms of the study, according to the randomization schedule generated prior to the study by the Clinical Statistics Department at GSK. Each participant will be dispensed blinded study treatment, labelled with a unique container number.

7.4. Blinding

Blind Break (IVRS/IWRS)	The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken by the investigator or treating physician in the case of an emergency, or if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The investigator is encouraged to discuss with the GSK Medical Monitor or appropriate GSK study personnel before the blind is broken If GSK is not notified before the blind is broken, they must be notified as soon as possible after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

A participant may continue in the study if that participant's treatment assignment is unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the case report form (CRF).

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

7.5. Preparation/Handling/Storage/Accountability

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.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- 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

- When participants are dosed at the site, they 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.

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 dietary or herbal supplements but excluding simple analgesics and vitamins) within 7 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 if required.

7.8. Treatment after the End of the Study

There is no treatment following the end of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

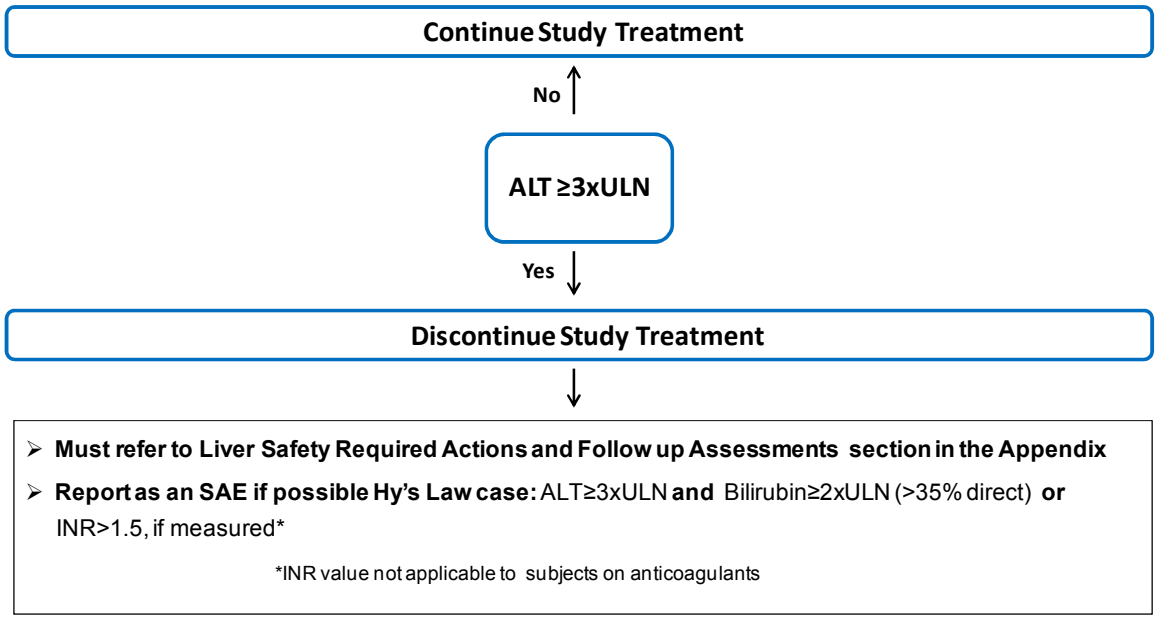
8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

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 4.

8.1.2. QTc Stopping Criteria

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

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

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

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

8.2. 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 will receive a follow-up telephone call at 10 – 12 days post dose. Refer to the SoA for data to be collected at the follow-up telephone call.

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.

9.1. Adverse Events

The definitions of an AE or SAE can be found in Appendix 5.

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

9.1.1. 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) and not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 5. 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 5.

9.1.2. 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.

9.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 5.

9.1.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment

under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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.

9.1.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until 7 days post dose.
- 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 2.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

For this study, any dose of GSK2269557 greater than 750 µg within a 24-hour time period ± 2 hour will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose and may be used in case of overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis within 3 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.

9.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.3.1. 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.
- 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.

9.3.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed semi supine with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature (single reading), systolic and diastolic blood pressure and pulse. Three readings of blood pressure and pulse will be taken at screening only. They will be recorded at intervals of no more than 2-5 minutes apart. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF. Single readings will be recorded at all other timepoints.

9.3.3. Electrocardiograms

- Triplicate OR Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2. for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2-5 minutes apart. The full set of triplicates should be completed in less than 5-10 minutes.

9.3.4. Spirometry

- The maximal amount of air forcefully exhaled in 1 second (FEV1) and forced vital capacity (FVC) will be measured using a spirometer at the time indicated in the SoA.
- FEV1 and FVC measurements will be repeated until three technically acceptable measurements (within 150 mL of each other) have been made. Only the best 3 measurements of each component will be recorded in the electronic case report form (eCRF).
- A full description of the timing and conduct of spirometry procedures will be provided in the study reference manual (SRM).

9.3.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 6 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 6, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.4. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK2269557 as specified in the SoA.. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Processing, storage and shipping procedures are provided in the SRM.

- Samples will be used to evaluate the PK of GSK2269557. Samples collected for analyses of GSK2269557 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Plasma analysis for GSK2269557 will be performed under the control Bioanalysis, Immunogenicity, Biomarkers, BIB /Third Party Resourcing, TPR, GlaxoSmithKline.
- Genetic analyses will not be performed on these whole blood samples. Participant confidentiality will be maintained. At visits during which whole blood samples for the determination of plasma concentrations of GSK2269557 will be taken, one sample of sufficient volume can be used.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.5. Genetics

Genetics are not evaluated in this study.

9.6. Biomarkers

Biomarkers are not evaluated in this study.

9.7. 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 objective is to assess the pharmacokinetic profile of a single dose of GSK2269557 administered via the ELLIPTA™ DPI to healthy participants.

An evaluable participant is a participant who takes at least one dose of study treatment and for whom a pharmacokinetic sample was obtained and analysed.

10.1. Sample Size Determination

The total number of participants for this study is 12 ; 6 on the GSK2269557 750 μg arm and 6 on the GSK2269557 500 μg arm. The objective of the trial is to obtain a preliminary assessment of safety, tolerability and PK of GSK2269557 administered via the ELLIPTA DPI with the addition of 0.4% MgSt.

The sample size has been chosen based on feasibility. However, consideration has been given to the level of precision we would expect to achieve for the main PK parameters assuming the variability is the same as seen previously using the ELLIPTA DPI with the addition of 0.6% MgSt in Japanese participants.

Assuming estimates of the between participant standard deviation, obtained from the most variable estimate between the 500 µg and 700 µg single doses from GSK study (Study 205759), of 0.346 (log scale) for Cmax and 0.382 (log scale) for AUC(0-24), the precision estimate for the half width of a 90% confidence interval is 0.285 for Cmax and 0.314 for AUC(0-24).

10.1.1. Sample Size Sensitivity

If the between participant standard deviation observed in the PK parameters is 10% or 20% higher than standard deviation in Study 205759, the precision estimate for the half width of the 90% confidence interval will be 0.313 and 0.342, respectively for Cmax, and 0.346 and 0.377, respectively for AUC(0-24).

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.
Safety	All participants randomised to treatment and who received at least one dose of study medication. Participants will be analysed according to the treatment they received.
Pharmacokinetic	All randomised participants who take 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 (PK) Analyses

All PK analyses will be performed on the Pharmacokinetic Population.

Endpoint	Statistical Analysis Methods
Primary	Plasma GSK2269557 concentration-time data will be analysed by non-compartmental methods with 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, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration-time curve [AUC(0-t), AUC(0-24) and AUC(0-∞)], concentration at trough (Ctrough) and apparent terminal phase half-life (t½). Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarised descriptively. Listings will be generated and summary statistics (n, arithmetic mean with associated 95% CI, standard deviation, minimum, median, maximum, geometric mean with associated 95% CI, single dose (SD) on loge-scale and between subject coefficient [%CVb]) will be calculated for each derived plasma PK parameter for each treatment group.

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), Spirometry, will be summarized by treatment

11. REFERENCES

GlaxoSmithKline Document Number 2012N141231_06: GSK2269557 Investigator's Brochure. 31-AUG-2015

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Okkenhaug K, Ali K and Vanhaesebroeck B. Antigen receptor signalling: A distinctive role for the p110δ isoform of PI3K. Trends in Immunology, 2007; 28: 80-7.

Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI3K delta in neutrophil inflammatory responses. Biochem Biophys Res Commun. 2003; 308(4): 764-769.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine Aminotransferase/ Alanine Transaminase
APDS	Activated PI3K Delta Syndrome
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Drug Concentration versus Time Curve
AUC(0-t)	Area Under the Plasma Drug Concentration versus Time Curve from zero to time t
AUC(0-24)	Area Under the Plasma Drug Concentration versus Time Curve from zero to 24 hours
AUC(0-inf∞)	Area Under the Plasma Drug Concentration versus Time Curve from zero to infinity
BMI	Body Mass Index
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
C_{max}	Maximum Observed Plasma Drug Concentration
%CVb	Between subject coefficient
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CRF	Case Report Form
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
Hrs/h	hours
hCG	Human chorionic gonadotropin
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HRT	Hormonal Replacement Therapy
IB	Investigator Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	International normalized ratio

IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVRS/ IWRS	Interactive Voice Recognition System/ Web Response Centre
Kg	Kilogram
Kg/m^2	Kilogram/square meter
LDH	Lactate dehydrogenase
µg	Microgram
MgSt	Magnesium Stearate
mins	Minutes
mL	Milliliter
msec	Milliseconds
MSDS	Material Safety Data Sheet
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
PASLI	p110 delta-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency
PI3Kδ	Phosphoinositide 3 Kinase delta
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RNA	Ribonucleic Acid
SAEs	Serious Adverse Events
SD	Single dose
SDA	Source Document Agreement
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	Terminal Half-life
ULN	Upper Limit of Normal
WOCBP	Woman Of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS
ELLIPTA™

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 2 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
- Refrain from donating sperm for duration of study and for at least 5 half-lives + 90 days from last dose

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 2

Table 2 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[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
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.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 5 half-lives + 90 days after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test
- Additional pregnancy testing is not required during the treatment period and at FU.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the test kit approved by the sponsor and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will be withdrawn from the study

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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years 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 Source Document Agreement (SDA).

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: 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>• 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 participant 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 participants 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 liver event follow up assessments within 24-72 hrs</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• 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 antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • 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 participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis 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

References

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

12.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the

participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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.

12.6. Appendix 6: Clinical Laboratory Tests

- The tests detailed in Table 3 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 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) 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 (fasting for screening)	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) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as			

Laboratory Assessments	Parameters
	needed for women of childbearing potential)[2] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • additional local laboratory assessments are needed, include the following: and list the exceptions.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 4 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).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.