TITLE PAGE

Protocol Title A Randomised, Double-blind, Placebo-controlled Study of the Safety, Tolerability, Pharmacokinetics, Target Engagement and Immunogenicity of a single subcutaneous dose of GSK3858279 administered to Healthy Caucasian, Chinese and Japanese Participants.

Protocol Number: 212979/ Amendment 02

Compound Number GSK3858279

Brief Title: Safety, tolerability, pharmacokinetics and target engagement of GSK3858279 after a single subcutaneous dose in healthy Caucasian, Chinese and Japanese participants

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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Approval Date: 29 Apr 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 02	29 Apr 2022	*TMF-14597981*
Amendment 01	*11-JAN-2022*	*TMF-14393139*
Original Protocol	*16-Nov-2021*	*TMF-13921276*

Amendment 2 29 Apr 2022

Overall Rationale for the Amendment:

This is a protocol amendment with changes to the inclusion criteria, extension of time window for PK and TE samples taken post Day 113, changes to the extended follow up to make visits after Day 113 optional for Chinese and Japanese participants, updates to the Schedule of Activities table, removal of Covid stopping criteria and a minor update of the Risk Assessment table with respect to Covid Contingency Planning. These amendments were made following feedback from the study site and changes to internal guidance at GSK.

Section and Name	Description of Change	Brief Rationale
Global change	Update through out to specify visits after Day 113 are mandatory for Caucasian participants.	To aid with participant recruitment and compliance to the study schedule
Objectives and Endpoints	Secondary endpoint (evaluation of TE) updated to include fold increase compared to baseline in total CCL17 at Days 7, 14, 28 and 56 post-dose.	To ensure that TE measures (% reduction in free CCL17, fold increase in total CCL17) are calculated at the same timepoints
Objectives and Endpoints	CCI [redacted]	
1.3 SOA	Removal of COVID-19 SARS-CoV-2 testing at Day 57, 113 and CCI [redacted] and early withdrawal testing.	IP is only administered once at the beginning of the study, and the remainder of the visits are data collection. Therefore, there is no reason to retest for COVID as withdrawal from the study will not occur based on a positive COVID test alone.
1.3 SOA	Addition of collection of smoking status information	To aid understand impact of smoking on CCL17 levels
1.3 SOA	Update to footnotes	Administration update
1.3 SOA	Extending visit window to ± 4 days for visits on Day 141, 155 and CCI [redacted]	To aid with compliance to the study schedule
2.3.1 Risk Assessment	Deletion of 'COVID-19 Contingency Plan Any subject that presents with COVID-19-related symptoms and/or has a positive SARS-CoV-2 PCR will be excluded from (further) participation in the trial and will receive follow-up medical attention as per local procedure'	Contradicts text in 7.2.3 – Covid stopping criteria

4.2 Scientific Rationale for Study Design	Updated protocol reference	Administration change
5.1 Inclusion Criteria #7	Geographical Ancestry criteria for Chinese participants update to include participants from Chinese Hong Kong or Taiwan	To aid with participant recruitment
5.1 Inclusion Criteria Requirements for Male Participants schematic	Removal of 'Requirement for Male Participants' schematic	Included in error. Decision tree is required for internal use only.
6.3 Measures to Minimize Bias: Randomization and Blinding	Removal of '(sponsor-open)' in text of section	This study is double blind and not sponsor-open. This was initially added in error so needed to be removed in this amendment.
7.2.3 SARS-CoV-2 related stopping criteria	Removal of COVID stopping criteria	This criterion is no longer necessary as a positive COVID test alone will not be reason for withdrawal from the study. COVID testing has been removed from the study, except testing prior to Day 1.

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Randomised, Double-blind, Placebo-controlled Study of the Safety, Tolerability, Pharmacokinetics, Target Engagement and Immunogenicity of a single subcutaneous dose of GSK3858279 administered to Healthy Caucasian, Chinese and Japanese Participants

Brief Title:

Safety, tolerability, pharmacokinetics and target engagement of GSK3858279 after a single subcutaneous dose in healthy Caucasian, Chinese and Japanese participants**.**

Rationale:

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), target engagement (TE) and immunogenicity of a single subcutaneous (SC) dose of GSK3858279 when administered to healthy Caucasian, Chinese and Japanese participants.

This study will facilitate inter-ethnic comparisons while minimising variations rendered by cross-study assessments.

The outcomes of this study are intended to support the inclusion of Chinese and Japanese participants in global Ph2/3 studies.

Objectives and Endpoints

Objectives	Endpoints
• **Primary**	
• To evaluate the safety and tolerability of a single SC dose of GSK3858279 compared with placebo administered to healthy participants including cohorts of Japanese, Chinese and Caucasians	• Incidence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs • Occurrence of clinically important changes from baseline in clinical laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs (blood pressure, heart rate, body temperature), and cardiac parameters (electrocardiogram)
• To assess the pharmacokinetic (serum PK) profile up to 56 days following a single SC dose of GSK3858279 in	• PK parameters: area under the concentration-time curve (AUC(0-56), AUC(0-t) post-dose), time of

Objectives	Endpoints
healthy participants including cohorts of Japanese, Chinese and Caucasians	occurrence of last quantifiable concentration (tlast), maximum observed concentration (Cmax), and time of occurrence of Cmax (tmax) per cohort as data permits
• **Secondary**	
• To evaluate target engagement (TE) up to 56 days following a single SC dose of GSK3858279 in healthy participants including cohorts of Japanese, Chinese and Caucasians.	• Reduction (%) from baseline in free CCL17: maximum, minimum and at Days 7, 14, 28 and 56, post-dose • Total CCL17 (free and when bound to GSK3858279): maximum observed concentration (Cmax), time of Cmax (tmax), maximum fold increase compared to baseline, fold increase compared to baseline at Days 7, 14, 28 and 56, post-dose.
• To assess the potential for anti-drug antibody (ADA) formation	• Incidence of pre-existing ADAs • Incidence of treatment-emergent ADAs over time (and whether neutralising)
• **Exploratory**	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Overall Design:

This is a randomised, double-blind, placebo-controlled, study with a single SC dose of GSK3858279 administered to healthy Caucasian, Chinese and Japanese participants.

To try to eliminate any time dependant variability among ethnic groups, we will aim to treat Caucasian and Asian groups concurrently.

Participants will attend a screening visit at the clinical units within 28 days of Study Day 1. If eligible for the study, participants will return on Day -1 and maybe admitted to the unit overnight for final screening checks in preparation for randomization and dosing (Day 1). Participants will remain at the clinical units until Day 3.

- All participants will remain in the study until at least CCI [redacted] It will be mandatory for the Caucasian cohort to continue CCI [redacted]. The extended follow-up period CCI [redacted]) is to better understand the apparent non complete return of free CCL17 to baseline values as observed in Part A of Study 207804 across all dose groups. CCI [redacted] (primary endpoints defined from data up to and including Day 57). Safety information will be collected throughout the study.

- Study intervention will be administered as four separate SC injections of either GSK3858279 CCI [redacted]) or placebo in a 7:3 ratio, respectively for each cohort.

Study Population

Although reproductive toxicity studies have not yet been conducted, both males and females (of non-reproductive potential) are permitted under the conditions specified (see Inclusion Criteria).

Healthy participants have been chosen because:

- Comorbidities and concomitant medications of patient participants may confound analysis.

- Patient participants (e.g. osteoarthritis) will derive little or no benefit from a single dose of GSK3858279, and their participation in this study would preclude treatment with accessible efficacious therapies.

Number of Participants:

Approximately 10 participants are to be randomized (7 active: 3 placebo) per cohort aiming to achieve at least 6 evaluable participants on active and 2 on placebo per cohort. An evaluable participant is one that has been dosed and has safety and all PK data up to Day 57.

Replacements (assigned to the same treatment) are permitted at the discretion of the sponsor in consultation with the investigator. For example, in the event of a participant withdrawing before Day 57 the participant will be replaced.

Note: Enrolled means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Intervention Groups and Duration:

Three cohorts of approximately 10 participants in each cohort (Caucasian, Chinese and Japanese) will be randomized to a single dose of CCI SC GSK3858279 or placebo (7:3 ratio) (Appendix 1).

- Approximately 10 eligible participants per cohort will be admitted to the clinical unit on the day prior to dosing (Day-1). On Day 1, each participant will receive a SC dose of GSK3858279 or placebo, administered as four separate SC injections, in a 7:3 ratio, respectively.
- Participants will then remain as an in-patient until discharged on Day 3 after assessments have been performed.
- Participants will then return to the clinical unit for outpatient visits as described in the SoA.

- The final required follow up visit will be at the clinical unit on CCI for Chinese and Japanese participants. NB: Japanese and Chinese participants have an option to remain in the study CCI.
- The final follow up visit will be at the clinical unit on CCI for Caucasian participants.
- The maximum dose will not exceed CCI SC.

The study duration is not expected to exceed a maximum of CCI: (Screening [up to 28 days] and a follow-up period of up to CCI. Follow-up may be extended if a serious or clinically significant AE has not resolved by CCI.

Data Monitoring/ Other Committee:

No blinded Safety Review Team (uSRT)

CCI

1.3. Schedule of Activities (SoA)

Screening period

Procedure	**Screening (Day -28 to Day -1)**
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full Physical examination including height and weight	X
Medical/medication/drug/alcohol history[1]	X
Alcohol & Tobacco screens[2]	X
Urine drug screen	X
FSH (in WONCBP)	X
HIV, Hepatitis B and C screening	X
Haematology, clinical chemistry, urinalysis	X
COVID-19 (SARS-CoV-2) PCR or rapid antigen test	X
TB screening (QuantiFERON)	X
12-lead ECG[3]	X
Vital signs[4]	X
Echocardiogram	X
AE assessment	X
SAE assessment	X
Target Engagement Sample Collection	X

1. To include substance usage, family history of premature cardiovascular disease, medication, drug/alcohol history
2. As per local standard practice
3. Performed in triplicate
4. Vital signs are to be taken before blood collection for laboratory tests

Treatment and Follow-up

Procedure			**Treatment and Follow-up (FU)**															
Week							*1*	*2*	*3*	*4*	CCI							**EW[1]**
Day	**-2**	**-1**	**1[a]**	**2 [a]**	**3[a]**	**5[b]**	**8[b]**	**15[b]**	**22[b]**	**29[b]**								
Outpatient visit	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient Stay		X	X	X														
Discharge from clinical unit					X													
Inclusion and exclusion criteria			X[2]															
Brief Physical examination			X[3]	X				X				X					X	X
Alcohol & Tobacco screens		X																
Urine drug screen		X																
12-lead ECG (triplicate)		X	X[4]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X[5]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Smoking Status		X				X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure			**Treatment and Follow-up (FU)**															
Week							*1*	*2*	*3*	*4*	CCI							**EW[1]**
Day	**-2**	**-1**	**1[a]**	**2 [a]**	**3[a]**	**5[b]**	**8[b]**	**15[b]**	**22[b]**	**29[b]**								
Haematology, clinical chemistry, urinalysis		X	X	X	X		X	X	X	X	X	X[6]	X	X	X	X	X	X
COVID-19 SARS-CoV-2 PCR or rapid antigen test	X[7]																	
Randomization			X															
Dosing (SC) injections			X[8]															
PK & TE	X[9]		X[10]	X[10]	X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity			X[11]					X		X		X		X	X		X	X
PD serum/plasma samples (For protein biomarkers)			X		X		X	X	X	X								X
PD WB PAXgene samples (For transcriptomic analyses)			X		X		X			X								X

Procedure			**Treatment and Follow-up (FU)**																
Week							*1*	*2*	*3*	*4*	CCI								**EW[1]**
Day	**-2**	**-1**	**1[a]**	**2 [a]**	**3[a]**	**5[b]**	**8[b]**	**15[b]**	**22[b]**	**29[b]**									
PGx			X[12]																
SAE and AE (SAEs recorded throughout. AEs recorded from first SC injection)	<---------->																	X	
Concomitant meds	<---------->																	X	

AE= adverse event; ECG= Electrocardiogram, SC = subcutaneous; PD = pharmacodynamics, PK= pharmacokinetics; SAE= serious adverse event, TE = Target engagement
* Visits optional for Chinese and Japanese participants
a ± 2hrs
b ± 1 day
c ± 4 day

1 Early withdrawal
2 Re-check clinical status before dose of study medication
3 Prior to dosing
4 pre-dose and 60 mins post start of SC injections
5 pre-dose, 30 mins, 1h, 2h, 3h & 4 h post start of SC injections
6 NT-pro BNP. NB: Troponin I at all time points
7 Result to be available prior to dose of study drug. Day -2 for PCR or rapid antigen test
8 Study intervention administered as 4 separate injections
9 Only TE sample
10 PK and TE blood samples taken pre-dose, 6h, 12h, 24h, 36h and 48h post start of SC injections, respectively
11 Blood sample to be taken pre-dose
12 Taken pre-dose

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study 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 Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study Rationale

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), target engagement (TE) and immunogenicity of a single subcutaneous (SC) dose of GSK3858279 when administered to healthy Caucasian, Chinese and Japanese participants.

The outcomes of this study are intended to support the inclusion of Chinese and Japanese participants in global Ph2/3 studies.

2.2. Background

CCL17, previously known as thymus and activation regulated chemokine (TARC), is a member of the CC-family of chemokines that binds and signals through the G-protein coupled CC-chemokine receptor, CCR4 [Imai, 1996; Imai, 1997]. CCL17 is produced by numerous immune and non-immune cell types. CCR4 is predominantly expressed on Th2 cells but is also present on other immune and non-immune cell types.

CCI [redacted], monoclonal antibody (mAb), binding specifically to the chemokine CCL17. It functionally inhibits CCL17 activating the chemokine receptor CCR4, to prevent downstream consequences of CCR4 signalling.

At the time of this protocol, GSK3858279 is being developed for treatment of osteoarthritis pain. Alleviating chronic pain is a major unmet need, as current therapies (e.g. NSAIDs, opioids) have significant side effects and addiction liabilities that prevent their effective use in treating the patient's pain.

Rationale for CCL17 neutralisation in OA pain has been generated in vivo pre-clinically and inflammatory and arthritis models. CCL17 has been recently identified as a peripheral mediator of inflammatory pain and can itself induce arthritis.

In light of the global COVID-19 pandemic, all participants will be screened for COVID-19 at the beginning of the study and will be required to have a negative SARS-Cov-2 test prior to commencing the study. All participants will also be required to show evidence of complete COVID vaccination to be eligible to participate in the study. Please see further details for risk assessment and mitigation strategy below.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK3858279 may be found in the see Investigator's Brochure CCI [redacted] Effective 02 JUL 2021.

Details of these risks, as well as the risks associated with the procedures, and the proposed strategy to mitigate/monitor these risks are detailed in Section 2.3.1.

In this study, safety will be monitored closely both by subjective reporting and by objective means, i.e. serial assessments of vital signs, clinical laboratory information and cardiac monitoring. The study will be run in a clinical unit with access to hospital facilities for the treatment of medical emergencies. Participants will remain monitored in the clinic for a minimum of 2 hours after completion of dosing but will remain in the clinic until Day 3 and will only be discharged from the unit if the investigator deems it safe to do so.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Hypersensitivity, including injection site and infusion reactions	The administration of any (human) mAb has the potential to induce local or systemic immunologic reactions, for example acute allergic reactions (type I) and immune complex disease (ICD) associated with the formation of anti-drug antibodies (ADA) (type III). CCI [redacted]	**Participant Selection**: Participants with a history of sensitivity to the study medication, or a history of any drug or other allergy that, in the opinion of the investigator, contraindicates their participation, will not be permitted to enter the study. Participants with renal disorders will also be excluded. **Participant monitoring:** In Part A of FiH study (207804), participants remained in the inpatient facility for 48 hours post dosing to allow adequate monitoring by trained site personnel. In Part B of FiH (207804) and in this study (212979), participants will be monitored for a minimum of two hours post dosing. Emergency resuscitation facilities will also be available.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	Participants will be instructed in the Informed Consent Form (ICF) as to the signs and symptoms of hypersensitivity reactions and be instructed to seek immediate clinical care should they develop.
Immunogenicity		Samples will be drawn at baseline and at regular intervals to test for immunogenicity, and participants will be monitored for any evidence of adverse reaction as detailed in the hypersensitivity section of this table. Clinical laboratory safety assessments are included in the study. Urine microscopy and laboratory quantification of proteinuria will be investigated following unexplained dipstick proteinuria or haematuria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	
Risk of Infection	The intended pharmacologic effect of GSK3858279 may result in an CCI [redacted]. CCI [redacted]	**Participant Selection** Participants with active or chronic infections or a history of recent or recurrent infections will not be included in the study – see Section 5.1. **Participant Monitoring** Participants will be monitored for infection. Participants will be instructed in the ICF as to the signs and symptoms of infection, and to contact the site personnel should they develop.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI	
Vaccination Reactions		**Participant selection and non-permitted medications:** Attenuated live vaccines should not be administered to participants within 30 days prior to dosing and for five half-lives after dosing. If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered whilst receiving GSK3858279 based on an assessment of the benefit:risk (e.g. risk of decreased responsiveness).
Cardiac Risks		**Participant Exclusion:** Participants with a history of cardiac disease or cardiac abnormalities (including abnormal Troponin I and NT-proBNP) that, in the opinion of the investigator, would compromise cardiac safety will be excluded from the study. **Participant monitoring:** Investigations during screening include ECG,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	echocardiogram and troponin I and NT-proBNP. Troponin I and NT-proBNP will be monitored after dosing.
Bleeding Risk	CCI [redacted]	**Participant exclusion and non-permitted medication** Participants with a previous or current history of bleeding diathesis will be excluded.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	Use of anti-coagulants or anti-platelet agents will be prohibited.
Skin Reactions		**Participant Exclusion** Participants with a history of drug-induced skin reactions and Stevens-Johnson Syndrome will be excluded. **Participant Monitoring** Clinically significant skin reactions will be reviewed by a dermatologist and, if appropriate, a skin biopsy will be requested for histological analysis.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical There were no reports of any clinically significant skin reactions during Part A of the FiH study (207804) in healthy participants.	
Study Procedures		
Risk associated with blood draws	Fainting, mild pain, bruising, irritation or redness at phlebotomy site, may be associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws
Other		
SARS-CoV-2	The current SARS-CoV-2 pandemic can pose a challenge to integrity of the trials, protection of participants' rights, safety and wellbeing and the safety of clinical trial staff. Therefore, risk mitigation strategies will be put in place for this trial and will be evaluated on an ongoing basis for the duration of this trial, or until there is a consensus that the period of the SARS-CoV-2 outbreak in the Australia has passed. If the dynamics of the SARS-CoV-2 outbreak change in such a way that the safety of the trial participants and clinical trial staff or integrity of the data collected during this clinical trial cannot be guaranteed, the trial will be halted. CCI [redacted]	**Participant selection and monitoring** Healthy subjects in the current study fall in a low risk category for complications of COVID-19, the disease caused by the SARS-CoV-2 virus. To reduce the risk of SARS-CoV-2 infections among trial participants, measures and procedures based on the advice issued by GSK Global COVID Guidance should be followed. These would include but are not limited to counselling participants regarding the importance of infection control measures such as hand washing, reducing inter-personal contacts as much as possible and participant awareness of potential COVID-19 symptoms.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	Participants must also show evidence of complete COVID-19 vaccination to be eligible to participate in the study Site trial staff in direct contact may receive additional protection via the use of Personal Protective Equipment (PPE) and disinfectants as per local guidance. All trial subjects will be screened for SARS-CoV-2 with a PCR or lateral flow test: 1) at initial screening 2) prior to admission to the clinical unit and 3) in case of symptoms possibly related to COVID-19 **Protection of Trial Integrity** Adherence to the protocol protects the integrity of the data collected during this clinical trial, as well as participants' data protection rights.

2.3.2. Benefit Assessment

There will be no direct benefit to the healthy participants in this study. However, participants will undergo a medical evaluation during screening (including physical examination, electrocardiogram (ECG), vital signs and laboratory assessments), which may provide important health information The information obtained in this study will inform the conduct of future clinical studies to contribute to the process of developing new therapies for diseases such as Osteoarthritis where there is high unmet medical need.

2.3.3. Overall Benefit: Risk Conclusion

The safety of each individual participant has been prioritised and the eligibility, monitoring, enhanced monitoring and study level stopping criteria described in Section 7 have been designed to minimise risks to participants associated with exposure to GSK3858279. However, participants will undergo a medical evaluation during screening (including physical examination, electrocardiogram (ECG), vital signs and laboratory assessments), which may provide important health information. Taking into account these measures designed to minimise risks, the potential risks identified in association with GSK3858279 are justified.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single SC dose of GSK3858279 compared with placebo administered to healthy participants including cohorts of Japanese, Chinese and Caucasians	• Incidence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs • Occurrence of clinically important changes from baseline in clinical laboratory parameters (haematology, clinical chemistry, urinalysis), vital signs (blood pressure, heart rate, body temperature), and cardiac parameters (electrocardiogram)
• To assess the pharmacokinetic (serum PK) profile up to 56 days following a single SC dose of GSK3858279 in healthy participants including cohorts of Japanese, Chinese and Caucasians	• PK parameters: area under the concentration-time curve (AUC(0-56), AUC(0-t) post-dose), time of occurrence of last quantifiable concentration (tlast), maximum observed concentration (Cmax), and time of occurrence of Cmax (tmax) per cohort as data permits
Secondary	
• To evaluate target engagement (TE) up to 56 days following a single SC dose of GSK3858279 in healthy participants including cohorts of Japanese, Chinese and Caucasians.	• Reduction (%) from baseline in free CCL17: maximum, minimum and at Days 7, 14, 28 and 56, post-dose • Total CCL17 (free and when bound to GSK3858279): maximum observed concentration (Cmax), time of Cmax (tmax), maximum fold increase compared to baseline, fold increase compared to baseline at Days 7, 14, 28 and 56, post-dose.
• To assess the potential for anti-drug antibody (ADA) formation	• Incidence of pre-existing ADAs • Incidence of treatment-emergent ADAs over time (and whether neutralising)
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI	

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind, placebo-controlled, multi-centre study with a single SC dose of GSK3858279 administered to healthy Caucasian, Chinese and Japanese participants.

- Participants will attend a screening visit at the clinical units within 28 days of Study Day 1. If eligible for the study, participants will return on Day -1 and will be admitted to the unit overnight for final screening checks in preparation for randomization and dosing (Day 1).
- Participants will be randomized to either GSK3858279 or placebo in a ratio of 7:3 per cohort.
- Each participant will receive a CCI SC dose of GSK3858279 or placebo, administered as four separate SC injections.
- Participants will then remain as an inpatient until discharged on Day 3 after assessments have been performed.
- Participants will then return to the clinical unit for outpatient visits as described in the SoA.
    - It will be mandatory for the Caucasian cohort to continue CCI, where they will have their final follow up visit at the clinical unit. The final required follow up visit will be at the clinical unit on CCI for Chinese and Japanese participants. NB: Japanese and Chinese participants have an option to remain in the study until CCI
    - The maximum dose will not exceed CCI SC

4.2. Scientific Rationale for Study Design

CCI

CCI

[redacted]

CCI

[redacted]

4.4. End of Study Definition

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

A participant is considered to have completed the primary endpoint if he or she has completed the treatment and day 57.

A participant is considered to have completed the study if he or she has completed the treatment and follow-up phases of the study including the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
1. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring [12-lead ECGs]. A participant with a clinical abnormality or laboratory parameter(s) outside of the reference range for the population being studied that is not specifically listed in the inclusion or exclusion criteria may be included if the Investigator (in consultation with the GSK Medical Monitor if required) agrees and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or interpretation.
AGE
2. Between 20 and 65 years of age inclusive, at the time of signing the informed consent.
INFORMED CONSENT
3. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
COVID-19 (SARS CoV-2) Vaccination
4. Participants who have evidence of completed vaccination for SARS-CoV-2 with an approved vaccine
WEIGHT
5. Body weight within the range 45 – 100 kg and body mass index (BMI) within the range 18-29.9 kg/m^2 (inclusive) for Chinese and Japanese participants. Caucasian participants must exhibit BMI range of 18 – 32.0 kg/m^2 .
GEOGRAPHICAL ANCESTRY
6. Japanese Participants are eligible based on meeting all of the following: • Participants born in Japan • Descendants of four ethnic Japanese grandparents and two ethnic Japanese parents • Have lived outside Japan for less than 10 years at the time of screening 7. Chinese Participants are eligible based on meeting all of the following:

- Participant born in mainland China, Hong Kong or Taiwan
- Descendants of four ethnic Chinese grandparents and two ethnic Chinese parents
- Have lived outside mainland China, Hong Kong or Taiwan for less than 10 years at the time of screening

8. Caucasian Participants are eligible based on meeting the following:

- Declaration of familial Caucasian/European ancestry (having 2 parents of Caucasian/European ancestry and 4 grandparents of Caucasian/European ancestry)

SEX

9. Male or female participant:

a. Male participants:

Male participants are eligible to participate if they agree to the following for at least 28 weeks after the dose of study intervention:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
    - Agree to use a male condom
    - and should also be advised of the benefit for a female partner to use a highly effective method of contraception (see Section 10.4) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant

b. Female participants:

A female participant is eligible to participate if she is of non-reproductive potential as defined in Section 10.4.

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5.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data. 2. Personal or family history of cardiomyopathy. 3. Abnormal blood pressure at screening as determined by the investigator. 4. History of symptomatic herpes zoster 5. Evidence of active or latent tuberculosis (TB) as documented by medical history, examination, and TB testing with a positive (not indeterminate) QuantiFERON test. NOTE: In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once, but they will not be eligible for the study unless the second test is negative. In cases where the QuantiFERON test is positive, the participant should be followed up as per standard of care. If a locally-read follow up chest x-ray shows no evidence of current or previous pulmonary tuberculosis, the participant may be eligible for the study at the discretion of the Investigator and GSK Medical Monitor. 6. Significant allergies to humanized monoclonal antibodies as per principal investigator's and GSK medical monitor's judgements. 7. History or evidence of clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis) 8. History of lymphoma, leukaemia, or any malignancy within the last 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years. 9. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN) 10. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 11. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 12. Corrected QT (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, 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).

13. History of Stevens Johnson Syndrome
14. Known immunodeficiency
15. Participants with a chronic infection (e.g., osteomyelitis), who have been receiving treatment within three months prior to dosing or individuals with an active infection.
16. Previous or current history of bleeding diathesis, excessive bleeding or coagulation disorders
17. History of significant medical illness in the opinion of the investigator would interfere with the study procedures and / or assessments

PRIOR/CONCOMITANT THERAPY

18. Intended use of over-the-counter or prescription medication including herbal medications within 7 days prior to dosing (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.
19. Live vaccine(s) or plans to receive such vaccines within 1 month of screening until final follow-up visit.
20. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing
21. Treatment with antiplatelet or anticoagulant agents within 7 days of dosing
22. Major surgery (as per investigator's judgement) within 3 months prior to dosing

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

23. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 3 months.

24. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
25. Current enrolment or past participation in any other clinical study involving an investigational drug intervention within the last 3 months or 5 half-lives (whichever is longer) of signing the ICF

DIAGNOSTIC ASSESSMENTS

26. Presence of Hepatitis B surface antigen (HBsAg) at screening.
27. Presence of the Hepatitis B core antibody (HBcAb) at screening.
28. Positive Hepatitis C antibody test result at screening.

    NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained
29. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention

    NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.
30. Abnormal clinically significant echocardiogram at screening, as assessed by the investigator.
31. Cardiac troponin or NT-proBNP levels out of normal range at screening.
32. Positive pre-study drug/alcohol screen
33. Positive human immunodeficiency virus (HIV) antibody test
34. Positive coronavirus (COVID-19): SARS-CoV2 PCR or lateral flow test of a combined throat and nasopharyngeal swab or nasal swab only

OTHER EXCLUSIONS

35. Regular alcohol consumption within 6 months prior to the study defined as:
    - an average weekly intake of >11 standard drinks for males and females. One standard drink contains 10g of alcohol.
36. Regular use of known drugs of abuse.
37. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

5.3.1. COVID-19 related restrictions

Participants will be required to adhere to the measures and procedures outlined in the hospital policy, based on the advice issued by the State health minister and COVID-19 measures declared by the Australian government, to reduce risk of SARS-CoV-2 infections among trial participants and clinical site staff.

5.3.2. Meals and Dietary Restrictions

Not Applicable.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will not be allowed to have excessive caffeine consumption, defined as >800 mg per day from 7 days prior to the first dose of the study drug until 24 hours prior to dosing. Participants will abstain from caffeine-containing products for 24 hours prior to each visit to the study unit. Caffeine quantities defined as: one cup of coffee contains 100 mg of caffeine; one cup of tea, or one glass of cola, or portion of chocolate (dark: 100 g, milk: 200 g) contains approximately 40 mg of caffeine; one 250 ml can of Red Bull contains approximately 80 mg of caffeine.
- Alcohol will not be allowed from at least 24 hours before each scheduled visit, and whilst in the study unit until discharge from the study unit. At other times throughout the study, participants should not consume more 1.5 standard drinks of alcohol daily on average (10g alcohol in 1 Australian standard drink). Participants may undergo an alcohol breath test at the discretion of the investigator.
- Non-smokers or light smokers (<= 5 cigarettes / nicotine-forms per week) may be enrolled in the trial. Light smokers must abstain from nicotine-containing products for at least 3 days prior to Day 1 dosing and for the duration of the inpatient stay.

5.3.4. 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 during studies (e.g., watching television, reading).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized/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, any protocol deviations and any serious adverse events (SAEs).

Repeat assessments during the screening period: Assessments, including laboratory assessments, may be repeated once if determined necessary by the investigator, for example: (a) in cases of technical malfunction (e.g. loss of laboratory specimen), (b) in the event of a value close enough to the exclusionary threshold that it may reasonably lie within the degree of variability of the assay or an indeterminate result; (c) if there is reason to believe the result may be false (i.e. contradicts recent result for the same parameter). These are repeat assessments and not rescreening events. If the original result was exclusionary and is confirmed by repeat testing, the participant will be excluded

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, unless a positive SARS-Cov-2 test results is obtained where re-screening is not permitted. Rescreened participants should be assigned a new participant number.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

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

Table 1 Study Interventions Administered

ARM Name	Active	Placebo
Intervention Name	GSK3858279	Placebo
Type	CCI [redacted]	Placebo
Dose Formulation	CCI [redacted]	Solution for injection. CCI [redacted]
Unit Dose Strength	CCI [redacted]	CCI [redacted]
Dosage Levels	CCI [redacted]	Single dose
Route of Administration	SC injection	SC injection
Dosing Instructions	CCI [redacted]	
Use	Experimental	Placebo-control
IMP and NIMP	IMP	Placebo
Sourcing	Study medication is supplied by GSK.	Provided locally by the trial site, subsidiary, or designee.

Packaging and Labelling	Bulk supplies will be provided in a vial contained within a carton. Each vial and carton will be labelled as required per country requirement. Dispensed medication will be labelled as required per country requirement.	Commercial presentation. Dispensed placebo will be labelled as required per country requirement.

CCI [redacted].

6.2. Preparation, Handling, Storage and Accountability

- CCI [redacted]
- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- 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.

Precaution will be taken to avoid direct contact with the study intervention. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants who meet the screening eligibility criteria will be randomised to a treatment group through the Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to the site.

Once assigned, a randomisation number must not be reassigned to another participant in the study. This will be a double blind study with both the investigator and participant blinded to study treatment. Site personnel will remain blinded. There will, however, be an unblinded site pharmacy personnel to prepare the study intervention; but they will not have contact with study participants

The following will apply:

- The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.
- If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind.
- The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.
- GSK's Safety and Medical Governance (SMG) staff may unblind the intervention 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 intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- Sites will be required to make every effort to ensure that the results of study laboratory tests are not proactively communicated to participants during the study unless essential for clinical care.

GSK3858279 PK and Free and Total CCL17 results that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

A participant will be withdrawn if the participant's intervention code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF. The participant will be followed up for safety monitoring if treatment was received

GSK's Safety Evaluation and Risk Management (SERM) staff may unblind the intervention 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 intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention 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 intervention 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 intervention.

6.5. Continued Access to Study Intervention after the End of the Study

This is a single dose study in healthy participants. No study intervention will be provided following the end of the study.

6.6. Treatment of Overdose

For this study, any dose of GSK3858279 greater than the scheduled dose will be considered an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until the study intervention can no longer be detected systemically (at least 5 half-lives but not less than 90 days). 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.

GSK does not recommend specific treatment for an overdose.

6.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest 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, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention 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 ≤ 3 grams/day, is permitted for use any time during the study. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

This is a single dose study. In rare instances a participant may not be able to receive the 4 injections and it may be necessary for the participant to permanently discontinue study intervention. If study intervention is discontinued, the participant will remain in the study for the planned duration.

7.2. Study Stopping Criteria

If any of the following occur, the study will be temporarily halted:

- Any participant experiences a SAE that can be reasonably attributed to GSK3858279.
- Two or more participants experience the same significant clinical or significant laboratory abnormality that may plausibly relate to GSK3858279 (according to the clinical judgement of the investigator)
- Two participants present with unexplained and clinically significant muco-cutaneous bleeding (according to the clinical judgement of the investigator and medical monitor) that is considered causally related to GSK 3858279

Recruitment may be resumed after appropriate review of safety findings by the Principal Investigators, Medical Monitor and SRT, and following approval to restart the study from the regulatory agencies and ethics committees

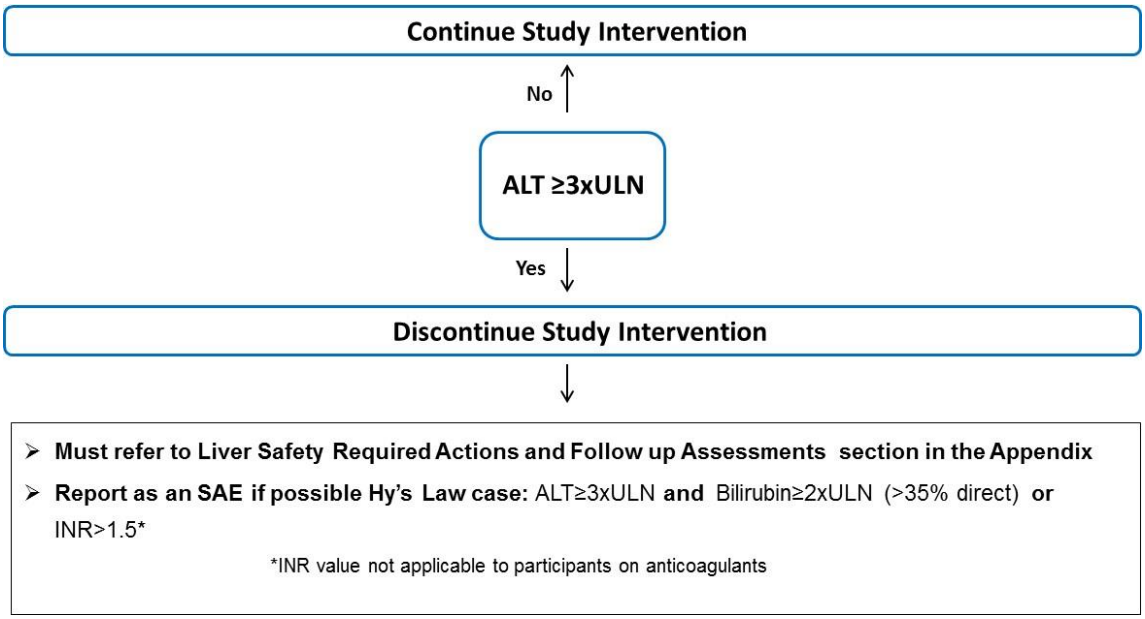
7.2.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology See Section 10.6.

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

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



7.2.2. QTc Stopping Criteria

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

- QTcF > 500 msec,
- Increase from baseline: QTcF > 60 msec
- In this study as QTcF is used for study eligibility, thus QTcF must be used for discontinuation decisions.
- QTcF 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.
- If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (see Section), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study
- If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]]) after enrolment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2.3. SARS-CoV-2 related stopping criteria

N/A

7.3. Participant Discontinuation/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, behavioural, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study at that time.
- 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.

7.4. Lost to Follow Up

A participant will be considered lost to follow-up if he/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, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA, see Section 1.3
- 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 intervention.
- 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 (e.g., 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 timeframe defined in the SoA.
- Safety/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.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy assessments are not applicable to this study.

Planned timepoints for all immunogenicity assessments are provided in the SoA.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height (at screening only) 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.

8.2.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed following the site local procedures.
- Blood pressure and pulse measurements will be assessed in semi supine position 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 (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be used to determine eligibility and be recorded on the CRF

8.2.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.2.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.2.4. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3). If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5. Echocardiogram

A transthoracic echocardiogram will be performed at screening and repeated if clinically significant changes are observed at any time during the study treatment. Images will be obtained in standard views, the time to acquire images should not exceed approximately 45 minutes.

8.2.6. Skin Reactions

Skin reactions will be recorded as AEs. The investigator will assess any skin reactions for their clinical significance and clinically significant skin reactions (as per investigator's judgement) will be reviewed by a dermatologist and if appropriate a skin biopsy will be requested for histological analysis. Further technical details will be provided in the SRM.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) or serious adverse events (SAEs) can be found in Section 10.3 and Section 10.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 / Section 10.6.

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

- All SAEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.
- 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 3 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 information on AEs or SAEs after conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. 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 10.3), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Section 10.3 / Section 10.6.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements

8.3.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for post-intervention contraception determined in Section 10.4.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hoursof learning of the female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

8.4. Pharmacokinetics

Blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of GSK3858279 at the timepoints specified in the SoA. Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the participant on Day 1. The actual date and time of each dose and blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring, if warranted and agreed upon between the investigator and the sponsor.

Details on PK blood sample collection including processing, storage and shipping procures will be provided in the SRM.

Serum analysis will be performed under the control of GSK Invitro/In vivo Translation (IVIVT). Serum concentrations of GSK3858279 will be determined using approved bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g. SRM) and raw data will be archived in the GSK R&D GLP archives. Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. The timing of sample collections may be adjusted based on emerging data or other new information for this study to ensure optimal evaluation of PK.

8.5. Target Engagement

Blood samples (approximately 3.5mL) will be collected from participants in this study to investigate target engagement at the times specified in the SoA. Each TE sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the participant on Day 1. The actual date and time of each blood sample collection will be recorded. The timing of TE samples may be altered and/or TE samples may be obtained at additional time points to ensure thorough TE monitoring, if warranted and agreed upon between the investigator and the sponsor. The timing of sample collections may be adjusted based on emerging data or other new information for this study to ensure optimal evaluation of target engagement. Details of the processing, storage and shipping procedures for all samples are provided in the SRM.

Serum samples will be collected for the evaluation of the free and total CCL17. CCL17 can be detected in circulation and is the biological target for GSK3858279. The intention is to examine the relationship between free and total CCL17 and the effect of administration of GSK3858279 on the free and total levels of CCL17 in the circulation. Details of the sample collection including processing, storage and shipping procures will be presented in the SRM

All samples will be retained for a maximum of 15 years after the last participant completes the study

8.6. Genetics

Information regarding genetic research is included in Appendix 5. Genetic sampling is optional. Participants can refuse genetic sampling but will still be allowed to participate in the study.

CCI

8.8. Immunogenicity Assessments

Serum samples (approximately 5 mL) will be collected from all treated participants at pre-dose and various time points post-dosing, see SoA. Testing will be performed using the typical tiered approach involving screening, confirmation and titration assays [EMEA 2017, FDA 2014], performed by Clinical Immunology, GlaxoSmithKline. If sera contain potential anti-GSK3858279 antibodies, they will be confirmed by immune-competition using excess drug, followed by a titration assay. Results will include the incidence of immunogenicity, antibody specificity and titres.

For each participant, immunogenicity results, including the incidence and titres, will be reported.

9. STATISTICAL CONSIDERATIONS

Complete details of the planned statistical analyses, including PK and TE parameter estimation, will be provided in the Statistical Analysis Plan (SAP). Any deviations from the planned analyses will be described in a SAP addendum or justified in the final clinical study report.

9.1. Statistical Hypotheses

The co- primary objectives of this study are:

- To evaluate the safety and tolerability of a single SC dose of GSK3858279 compared with placebo administered to healthy participants
- To assess the pharmacokinetic (PK) profile of a single SC dose of GSK3858279 in healthy participants

No formal statistical hypotheses will be tested.

9.2. Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	All participants who entered the study, signed the ICF and were eligible for randomisation (regardless of whether the participant went on to be randomised). Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomised	All participants who were randomly assigned to study intervention in the study. Data will be reported according to the randomised study intervention.	Study Population
Safety	All participants who received at least one injection of study intervention. Data will be reported according to the actual study intervention received.	Safety
Pharmacokinetic (PK)	All participants in the safety population who received an active dose of study treatment and had at least one reportable PK assessment (Non-quantifiable [NQ] values will be considered as reportable values). Participants will be analysed according to the study intervention they actually received.	PK
Target Engagement (TE)	All participants in the safety population who had at least one reportable TE assessment (Non-quantifiable [NQ] values will be considered as reportable values). Participants will be analysed according to the study intervention they actually received.	TE

9.2.1. Statistical Analyses

N/A

9.2.2. General Considerations

N/A

9.2.3. Primary Endpoint(s)

The following primary safety endpoints will be summarised descriptively by treatment group and cohort: the incidence of adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs, change from baseline in clinical laboratory parameters, vital signs, and cardiac parameters.

Categorical data will be summarised with the number and percentage of participants in each category. Continuous data will be summarised with n, mean, standard deviation (SD), median, minimum and maximum.

Primary analysis will be performed on the PK parameters AUC (0-56) post-dose and Cmax. The parameters will be $\log_e$ transformed and then analysed using a mixed model, with ethnicity and body weight included as covariates. Geometric mean and 90% confidence intervals will be calculated for each of the ethnic cohorts, along with the comparisons for Japanese/Caucasians and Chinese/Caucasians.

All other PK parameters will be summarised descriptively, with further details to be provided in the SAP.

9.2.4. Secondary Endpoint

TE parameters will be summarised descriptively, with further details to be provided in the SAP.

9.2.5. Exploratory Endpoint(s)

Further details of the exploratory analyses will be provided in the SAP.

9.2.6. Interim Analyses

Interim analyses may be performed, on data assessed in an unblinded manner, to support regulatory submissions. No changes to the conduct of the study will be implemented as a result of the analyses. If deemed necessary to conduct an interim, details will be documented in an interim charter prior to the unblinding, including what data will be reviewed, the level of unblinding (individual vs group summaries) and who will have access to the data.

9.3. Sample Size Determination

Approximately 10 participants are to be randomized (7 active: 3 placebo) per cohort to ensure that a minimum of 6 participants on active and 2 on placebo per cohort are evaluable. An evaluable participant is one that has been dosed and has safety and all PK data up to Day 57. Replacements (assigned to the same treatment) are permitted at the discretion of the sponsor in consultation with the investigator.

The sample size justification is based on simulations with the assumptions given below. Based on these assumptions, for a sample size of 6 evaluable participants receiving a

CCI [redacted]

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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, IB, and other relevant documents (e.g., 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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),), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. 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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant or their 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, privacy and data protect requirements, where applicable, and the IRB/IEC or study centre.
- 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 their legally authorized representative
- Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study intervention or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the the study intervention approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. 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 consent will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease by ticking of a corresponding "Yes" box. Participants who decline further research will tick the corresponding "No" box.

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.1.5. Committees Structure

N/A

10.1.6. Early Safety Data Review AND/OR Committee

- Case unblinding may be performed for above reviews if necessary.

10.1.7. 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 all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- 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 protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the SRM
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- 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 30 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.
- A retention period of 30 years instead of 25 years is used, as the long-term effects of GSK3858279 are still unknown and the to be included healthy volunteers could be of relatively young age; thus, still with a long life-expectancy

10.1.9. 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 and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first healthy participant to be screened is considered the first act of recruitment and will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.10. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-required Clinical Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Urea	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 non-fasting	Calcium	Alkaline phosphatase[2]	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Breath Alcohol test • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines • HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HbcAb] and hepatitis C virus antibody. • QuantiFERON test • Urine albumin-creatinine ratio (UACR) • Complement C3 and C4 • [3]SARS-CoV2 PCR or rapid antigen test The results of each test must be entered into the medical notes
Other Screening and Follow-Up Tests	• Troponin-I (high sensitivity) • NT-proBNP

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 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total 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 to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Combined throat and nasopharyngeal swab or nasal swab only; qPCR or rapid antigen test as per unit coronavirus test vendor protocol

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10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention.

Events <u>Meeting</u> the AE Definition
For efficacy studies, include the penultimate bullet, and for non-efficacy studies involving marketed products in established indications, include the final bullet. • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., 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 condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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 (e.g., 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.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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 admitted (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 or significant 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 (e.g. sprained ankle) that 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:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required form.
- 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 one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention 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 submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in SRM

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical** • 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 data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions of Women of child bearing potential and Women of non-child bearing potential:

WOCBP (NB: WOCBP are not permitted to participate in the study)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are considered WONCBP

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

2. 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, confirmation with more than one FSH measurement is required.
- In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance

Males must use the male condom and should be advised of the benefit for a partner to use a highly effective method of contraception as outlined below.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: 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 intervention. 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*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. *Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)*

10.4.3. 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 who becomes pregnant while participating in this study. This applies only to male participants who receive study intervention.
- 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.
- The female 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

10.5. Appendix 5: Genetics

- **USE/ANALYSIS OF DNA** Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to study intervention They may also be used to develop tests/assays including diagnostic tests) related to study intervention]. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome (as appropriate)
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention (or study interventions of this class) continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

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

Phase 1 Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology.

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• 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, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis as soon as possible, and at least within 7 days, post 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</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. Serum acetaminophen adduct 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 intervention 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, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

10.7. Appendix 7: Abbreviations and Definitions and Trademarks

Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
AUC	Area Under the concentration-time Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA	Competent Authority
CCL17	Chemokine C-C motif ligand 17
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum Observed Concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatine Phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FiH	First in Human
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
HPLC	High-Performance Liquid Chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgM	Immunoglobulin G
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Recognition System
kg	Kilogram
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MCH	Mean Corpuscular Haemoglobin

MRCT	Multiregion Randomised Clinical Trial
MCV	Mean Corpuscular Volume
mg	Milligram
mL	Milliliter
MSDS	Material Safety Data Sheet
NIMP	Non-Investigational Medicinal Product
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PBO	Placebo
PGx	Genetics Sample
PD	Pharmacodynamics
PK	Pharmacokinetics
PPE	Personal Protective Equipment
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RAMOS NG	Randomization and Medication Ordering System Next Generation
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SARS-Cov-2	Severe acute respiratory syndrome– Coronavirus-2
SC	Subcutaneous
sec	Seconds
SGOT	Serum Glutamic-Pyruvic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMG	Safety and Medical Governance
SRM	Study Reference Manual
SoA	Schedule of Activities
TARC	Thymus and Activation Regulated Chemokine
TB	Tuberculosis
TDAR	T-cell Dependent Antibody Response
TE	Target Engagement
tmax	Time of Occurrence of Maximum Observed Drug Concentration
UACR	Urine albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
WBC	White Blood Cells
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Non-childbearing Potential

10.8. Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 11-JAN-2022

Overall Rationale for the Amendment:

This is a protocol amendment with changes to the inclusion/exclusion criteria, assessment time points, clarification regarding consent to further research, clarification regarding alcohol consumption and tobacco use, changes to the protocol title to align with eTrack and correction of typographical errors. These amendments were made following feedback from the study site and HREC.

Section # and Name	Description of Change	Brief Rationale
Global Change	Troponin-T updated to Troponin I" throughout protocol	Troponin T and Troponin I have similar diagnostic accuracy.
1.1 Overall Design	Updated text – 'To try to eliminate any time dependant variability among ethnic groups, we will aim to treat Caucasian and Asian groups concurrently.	This amendment was made for clarification
1.3 Schedule of Activities	Estradiol removed from screening period table	FSH is sufficient to confirm menopause as specified in Section 10.4
1.3 Schedule of Activities	CCI [redacted]	Aid with participant compliance to the study schedule.
1.3 Schedule of Activities	Outpatient visit removed from Day -1.	Error in original protocol. Participants will be admitted on Day -1 for an overnight stay.
1.3 Schedule of Activities	Footnotes 4 and 5 removed from Day -1 12 Lead ECG and Vital signs tests	These were present in error in the original protocol.
1.3 Schedule of Activities	COVID PCR, footnote 7 removed from Day 57, CCI [redacted] and Early Withdrawal visits.	Error in original protocol, footnote applies to Day -2 visit only
1.3 Schedule of Activities - PD	Footnote 10 removed from Day 1 for Serum/Plasma for protein and PD for transcriptomic analysis.	Error in original protocol, footnote 10 applies to PK and TE samples only.
5.1 Inclusion Criteria	Inclusion Criteria #5 Updated to widen the BMI range for Caucasian participants	This amendment was made to maximise the Caucasian participant pool.
5.2 Exclusion Criteria	Exclusion Criterion #12. Typographical error Bazett's" formula is shown as QTcF in protocol, this has been corrected to QTcB	This amendment was made to correct typographical errors.
5.2 Exclusion Criteria	Exclusion Criterion #18 - Added details about enzyme inducers and allowed medications directly into the exclusion criteria	This will ensure that participants are not included in the study when they are not allowed or excluded when they could potentially be eligible.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion Criterion #35 – Amended the definition of an average weekly intake of alcohol to: >11 standard drinks for males and females. One standard drink contains 10g of alcohol	This amendment was made as requested by HREC
5.3.3 Caffeine Alcohol and Tobacco	Text updated 'participants should not consume more 1.5 standard drinks of alcohol daily on average (10g alcohol in 1 Australian standard drink)'	This amendment was made as requested by HREC
5.3.3 Caffeine Alcohol and Tobacco	Protocol text update adding 'Non-smokers or light smokers <= 5 cigarettes / nicotine-forms per week) may be enrolled in the trial. Light smokers must abstain from nicotine containing products for at least 3 days prior to Day 1 dosing and for the duration of the inpatient stay'	Updated text to allow light smokers to participate in the study
8.2.2. Vital Signs	Text added to state the average of triplicate blood pressure measurements confirms participant eligibility.	This amendment was made for clarification
10.1.3 Informed Consent Process	Updated the protocol text replacing the requirement for a separate signature in the ICF to allow use of participant data and/or remaining leftover samples to be used for further research not related to the study/disease with a tick corresponding 'Yes' box	This amendment clarified the inconsistency in wording regarding consent between the ICF and the protocol for further use of participant data and or remaining leftover sample.
Appendix 2: Clinical Laboratory Tests	Table 2: Test for estradiol levels removed.	FSH is sufficient to confirm menopause as specified in Section 10.4

Section # and Name	Description of Change	Brief Rationale
Trademark Information	Additional table added for Trademarks not owned by the GlaxoSmithKline group of companies	Amendment made as requirement of protocol template

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
RAMOS NG

Trademarks not owned by the GlaxoSmithKline group of companies
None

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