Protocol Amendment 07

Study ID: 207804

Official Title of Study: A two-part phase I randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee.

NCT Number: NCT03485365

Date of Document: 09-FEB-2022

TITLE PAGE

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Protocol Number: 207804 /Amendment 7

Compound Number:	GSK3858279

Study Phase: Phase I/Ib

Short Title: GSK3858279 vs PBO, Ph1/1b, two-part, SD, safety, tolerability, pharmacokinetics, and target engagement study in HV and RD in participants with OA

Sponsor Name and Legal Registered Address:

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

Regulatory Agency Identifying Number(s): EUDRACT 2017-004809-41

Approval Date: 09-FEB-2022

SPONSOR SIGNATORY

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PPD

Vice President, Head of Discovery Medicine, Clinical Pharmacology and Experimental Medicine, Immunoinflammation Therapy Area

Date

The signed page is a separate document.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 7	*09-FEB 2022*	*TMF-14447953*
Amendment 6	*12-NOV-2021*	*TMF-11834237*
Amendment 5	*07-SEP-2020*	*2017N342035_05*
Amendment 4	*14-NOV-2019*	*2017N342035_04*
Amendment 3	*18-JUL-2019*	*2017N342035_03*
Amendment 2	*21-NOV-2018*	*2017N342035_02*
Amendment 1	*10-APR-2018*	*2017N342035_01*
Original Protocol	*02-FEB-2018*	*2017N342035_00*

Amendment 7: 09-FEB-2022

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for Amendment 7

To clarify that 1) PK and TE samples will be taken at pre-dose Day 36, 20-36 hrs post-dose on Day 36 and pre-dose on Day 43; 2) Additional Interim analyses may be conducted 3) Clarification of re-screening procedure 4) Minor edits throughout to provide clarification.

Section # and Name	Description of Change	Brief Rationale
CCI [redacted]		
Section 5.4.1 Re-screening	Clarification of re-screening procedure for participants who screen fail because of a non-medical reason	To clarify that participants may be re-screened more than once for non-medical reasons following discussions with medical monitor e.g. receiving a covid booster at short notice

Section # and Name	**Description of Change**	**Brief Rationale**
Section 9.4.5. Interim Analyses and Section 1.1 Synopsis	Potential additional interim analyses may occur during the study	Additional interim analyses may occur to allow interactions with regulatory agencies and/or help inform internal decision making
Throughout	Minor edits throughout the document for consistency	For consistency and clarity

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A two-part phase I randomized, double blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3858279 in healthy participants and to evaluate the efficacy of repeat subcutaneous doses in participants with osteoarthritis of the knee.

Short Title: GSK3858279 vs PBO, Phase 1/1b, two-part, SD, safety, tolerability, pharmacokinetics and target engagement study in HV and RD in participants with OA

Rationale:

This study is the first administration of GSK3858279 to humans. The purpose of this study is two-fold:

Part A, to evaluate the safety, tolerability, pharmacokinetics (PK) and target engagement (TE) of either a single intravenous (IV) or a single subcutaneous (SC) dose of GSK3858279 in healthy males and females of non-reproductive potential. Target engagement in the skin, which is a surrogate for tight tissue compartment, will be assessed via suction blister procedure in certain cohorts. The intention is to provide sufficient confidence in the safety and tolerability of the molecule as well as target engagement to inform progression to the following part of the study.

Part B, to evaluate the safety, tolerability, efficacy, PK, TE and immunogenicity of repeat SC dosing of GSK3858279 in participants with osteoarthritis (OA) of the knee.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Parts A and B To evaluate the safety and tolerability of escalating doses of GSK3858279 following single IV, single SC dosing in healthy participants and repeat SC dosing in OA participants.	• Adverse Events (AE) and Serious Adverse Events (SAE). • Clinical laboratory measurements, 12-lead electrocardiograms (ECG) and vital signs.
Part B To assess changes in pain in participants with OA of the knee following repeat SC dosing.	Change from baseline in average knee pain intensity, at Week 8. Change from baseline in worst knee pain intensity at Week 8.

Objectives	Endpoints
Secondary	
To describe the pharmacokinetics (PK) of GSK3858279 following single IV, single SC in healthy participants and repeat SC dosing in OA participants.	CCI [redacted]
To evaluate the target engagement of CCL17 by GSK3858279 following single IV, single SC dosing in healthy participants and repeat SC dosing in OA participants.	

Overall Design:

This study will be a randomized, double-blind, placebo-controlled, two-part trial. After completing screening procedures successfully, participants will be randomised to either GSK3858279 or placebo on Day 1 just prior to dosing.

Part A will be a single ascending dose escalation study to evaluate the safety, tolerability, PK, and target engagement of GSK3858279 in healthy participants. Single IV doses and a single SC dose will be investigated in separate cohorts of participants.

Part B will investigate the safety, tolerability, efficacy (pain), PK, and TE and immunogenicity in blood of participants with OA of the knee after repeat SC dosing of GSK3858279 or placebo. COVID-19 screening, monitoring and the mitigation strategies are incorporated.

Disclosure Statement: This is a sequential group (Part A) and parallel group (Part B) treatment study with up to 7 arms that is participant and investigator blinded.

Number of Participants:

In Part A, a maximum of 8 participants will be randomly assigned to study intervention or placebo within each cohort such that approximately 5 evaluable participants complete the cohort.

In Part B approximately 50 (a minimum of 20 up to a maximum of 80) participants will be randomly assigned to study intervention or placebo in a 1:1 ratio.

An interim analysis will occur once approximately 20 participants have completed the Week 4 assessment. A second interim analysis and an unblinded sample size re-estimation may occur prior to enrolling the 50th participant, where the sample size could be decreased to a minimum of 20 or increased to a maximum of 80 participants. g

Additional interim analyses may occur in order to inform internal decision making

Intervention Groups and Duration:

In Part A, the total duration of the study (from signing of the informed consent until final follow-up) for each participant will vary between 113 and 168 days depending on the cohort, including a screening period of a maximum of 28 days for all cohorts.

Following successful screening, each participant will receive a single dose of study intervention (GSK3858279 or placebo), either IV or SC. The planned dosing schedule is described in the body of the protocol, although dose levels are subject to change depending on emerging study data. The maximum dose that may be administered in the study will be 10 mg/kg, both for IV and SC cohorts.

In Part A, the decision to proceed to the next dose level of GSK3858279 will be made by the Dose Escalation Committee (DEC). The dose escalation decision will be based on safety, tolerability and preliminary PK and TE data obtained in all participants at that dose level (through 15 days post dose). The actual dose level to be administered may be adjusted based on safety, tolerability and preliminary PK and TE data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose, but will not exceed PK criteria, and the maximum dose administered in this study will not exceed 10 mg/kg. Planned dose levels may also be repeated.

Although the decision to progress one or two IV single dose levels in Part B was to be based on total CCL17 data, following the review of Part A blinded data, it was decided to amend the protocol for subcutaneous administration of repeated doses based on PK and TE data.

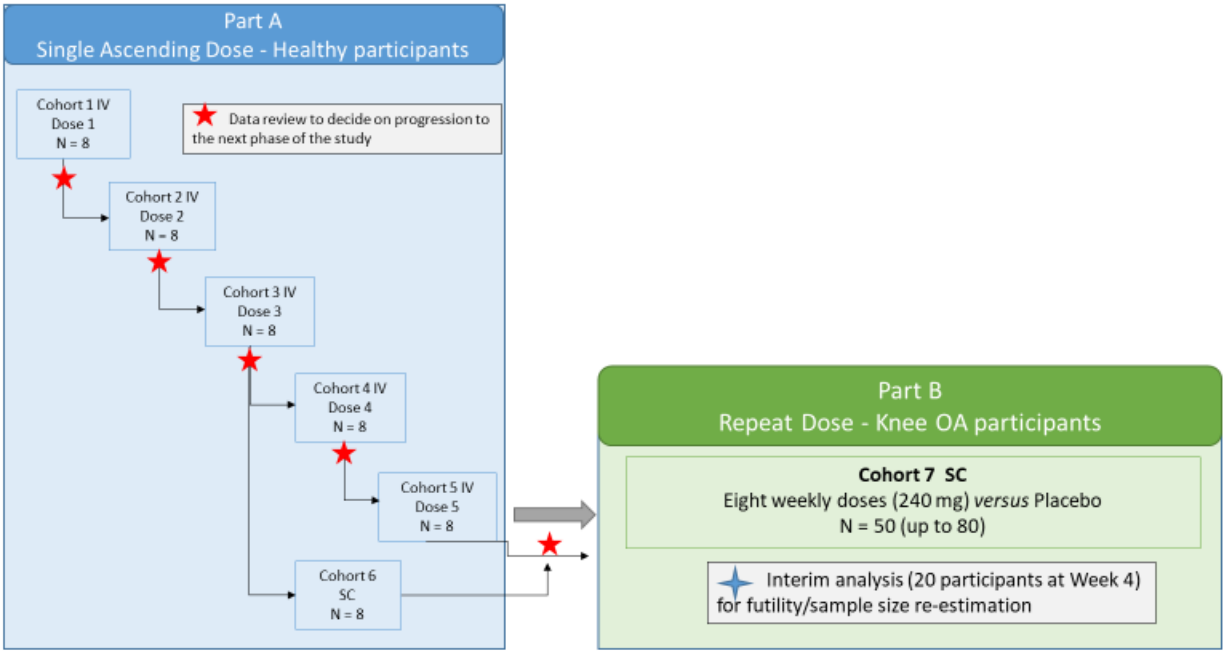
In Part B, the total duration of the study (from signing of the informed consent until final follow-up) for each participant will be up to 182/183 days (inclusive of a screening period of a maximum of 42 days).

Following successful screening, each participant will receive weekly SC doses of either GSK3858279 or placebo in a 1:1 ratio for 8 weeks.

Dose escalation committee: Yes (Part A). A Safety Review Committee is employed in Part B.

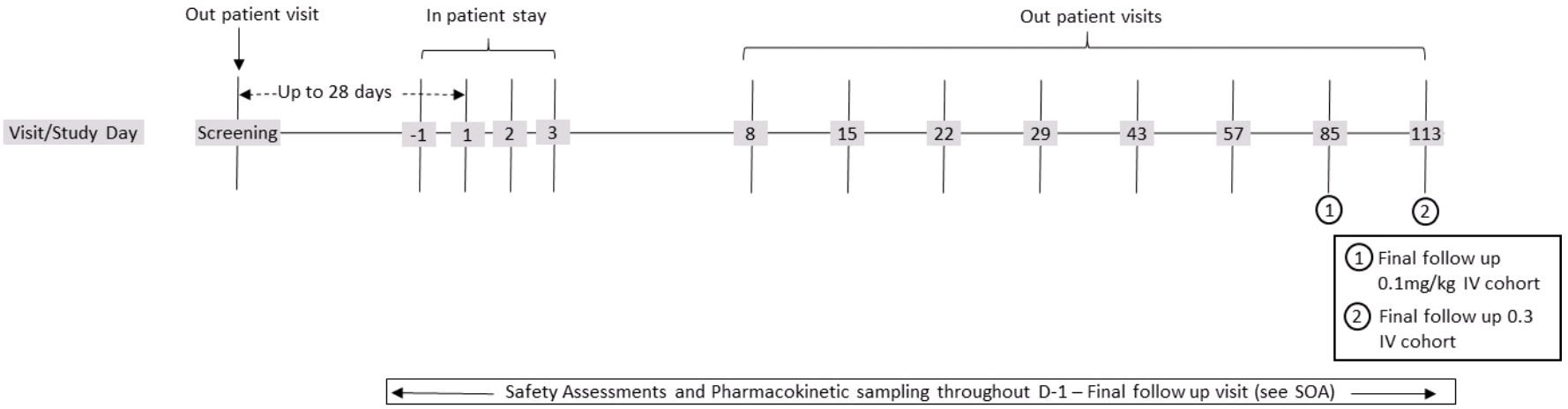
1.2. Schema

Figure 1 Study Design Schematic



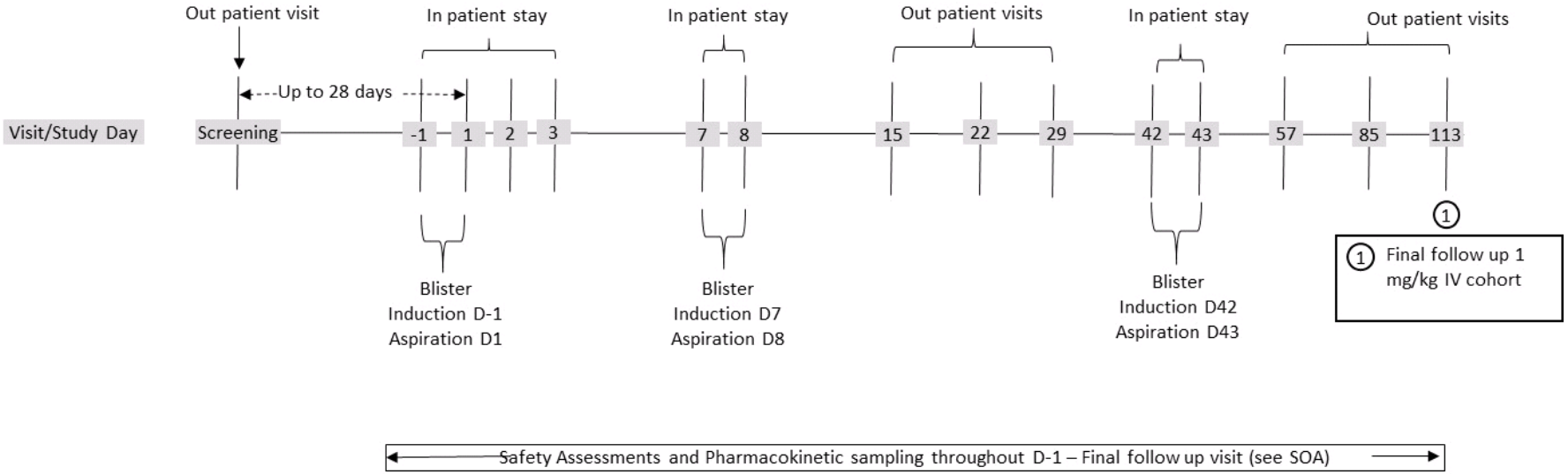
IV: intravenous; N: number of participants; OA: osteoarthritis; PK: pharmacokinetics; SC: subcutaneous

Figure 2 Part A Cohorts Without Blister: 0.1 and 0.3 mg/kg IV



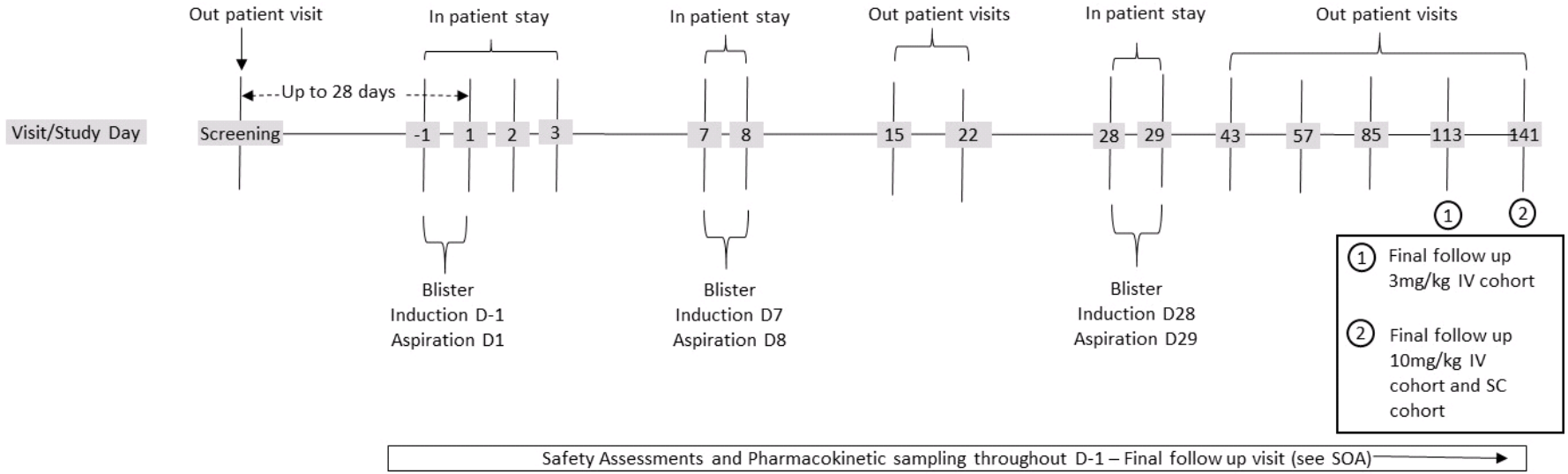
D: day; IV: intravenous; SOA: schedule of assessments.

Figure 3 Part A Cohorts With Blister: 1 mg/kg IV



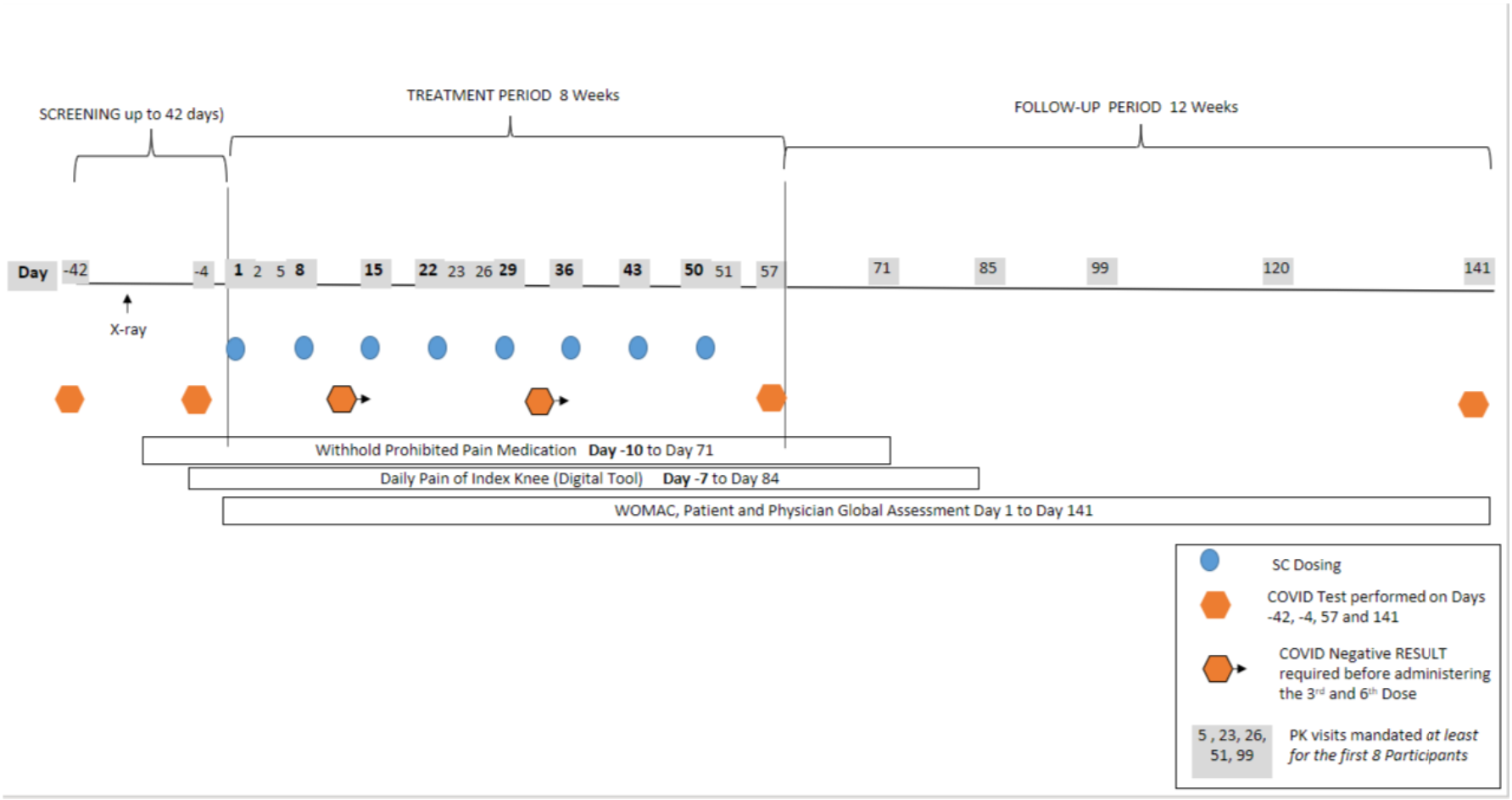
D: day; IV: intravenous; SOA: schedule of assessments.

Figure 4 Part A Cohorts With Blister: 3 and 10 mg/kg IV and SC



D: day; IV: intravenous; SC: subcutaneous; SOA: schedule of assessments

Figure 5 Part B Visit Schematic



1.3. Schedule of Activities (SoA)

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or efficacy assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).
- The visit windows permitted are also specified in the Study Reference Manual (SRM).

1.3.1. Screening

SCREENING

PROCEDURE	**SCREENING PERIOD** Screening may be performed across one or more visits. **Part A:** up to 28 days before Day 1. **Part B:** from Day -42 to Day -5 (up to 42 days before Day 1)	NOTES
Informed consent	X	
Inclusion and exclusion criteria	X	
Demography	X	
Full physical examination	X	
Medical/medication/drug/alcohol history	X	
Alcohol and tobacco screens	X	As per standard local practice. Smoking permitted only in Part B.
Urine drug screen	X	
HIV, Hepatitis B (HBsAg and HBcAb) and Hepatitis C (HepC antibody) screening	X	
Holter monitoring	X	24 hour for Part B only
12-lead ECG	Triplicate	
Vital signs	X	See SRM for details
Echocardiogram	X	
Haematology, clinical chemistry, urinalysis	X	Refer to Appendix 2. C3, C4 and BNP are included.
COVID-19 (SARS-CoV-2)	X	Documented negative COVID test within two days of initial screening OR test performed at the time of initial screening
TB Screening (QuantiFERON)	X	
FSH and estradiol (in WNCBP)	X	
Height and weight	X	
X-ray (K&L of index knee joint)	Part B	Inclusion Criterium. X ray performed *only* if ALL other inclusion and exclusion criteria were already met at initial screening (except NRS). Allow at least 7 calendar days for the X-ray result to be returned from central reading.
Daily pain scores (Digital Tool)	Part B (Day -7 to Day -1)	Scores will be recorded over the 7 consecutive evenings preceding dosing. Average result (Baseline value) will be evaluated for inclusion.
SAE assessment	X	From signing consent

1.3.2. Part A Cohorts Without Blister: 0.1 and 0.3 mg/kg IV

	Day												Early	Notes
Procedure	**–1**	**1**	**2**	**3**	**8**	**15**	**22**	**29**	**43**	**57**	**85**	**113**	**withdrawal**	Allowed visit windows are detailed in the SRM
Out-patient visit					X	X	X	X	X	X	X[1]	X[2]	X	[1] Final follow-up visit for 0.1 mg/kg cohort [2] Final follow-up visit for 0.3 mg/kg cohort
Admission in clinical unit	X													
Discharge from clinical unit				X										
Inclusion and exclusion criteria	X													
Brief physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	
Alcohol and tobacco screens	X													As per standard local practice
Urine drug screen	X													
Cardiac telemetry	X													Telemetry from at least 12 hrs before dosing until 12hrs post dose. Output to be reviewed for abnormalities prior to dosing on Day 1.
12-lead ECG	Triplicate	X[1]	X	X	X	X	X	X	X	X	X	X	X	On day -1 and day 1 ECGs may be generated from telemetry [1] On Day 1, pre dose then every 30 mins during infusion (i.e. 30 mins and 60mins after start of infusion) and then 1 hr post end of infusion.
Vital signs	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	[1] On Day 1, pre dose then every 15 mins during infusion (i.e. 15, 30, 45 and 60mins post the start of infusion) and then 30 mins, 1, 2 and 4 hr post end of infusion.
Haematology, clinical chemistry, urinalysis	X		24hr post dose	48hr post dose	X	X	X	X	X	X	X	X	X	
Weight	X													Weight to be used to calculate the study treatment dose.
Randomization		Pre-dose												
PK blood sample		X	24hr post dose	48hr post dose	X	X	X	X	X	X	X	X	X	D1 samples to be taken at pre-dose, 2 hr, 4 hr, 8 hr, and 12 hr post dose
CCI [redacted]														
Study treatment dosing		X												
AE assessment		<----------										---------->	X	
SAE assessment	<----------											---------->	X	
Concomitant medication review	<----------											---------->	X	

1.3.3. Part A Cohorts With Blister: 1 mg/kg IV

	Day													Early	Notes
Procedure	–1	1	2	3	7	8	15	22	29	42	43	57	85	113	**withdrawal**	Allowed visit windows are detailed in the SRM
Out-patient visit							X	X	X			X	X	X	X	
Admission in clinical unit	X				X					X						
Discharge from clinical unit				X		X					X					
Inclusion and exclusion criteria	X															
Brief physical examination	X	X	X	X	X		X	X	X	X		X	X	X	X	
Alcohol and tobacco screens	X															As per standard local practice
Urine drug screen	X															
Cardiac telemetry	X															Telemetry from at least 12 hrs before dosing until 12hrs post dose. Review for abnormalities prior to dosing on Day 1.
12-lead ECG	Triplicate	X[1]	X	X	X		X	X	X	X		X	X	X	X	On Day -1 and Day 1 ECGs may be generated from telemetry [1] On Day 1, pre dose then every 30 mins during infusion (i.e. 30 mins and 60mins after start of infusion) and then 1 hr post end of infusion.
Vital signs	X	X[1]	X	X	X		X	X	X	X		X	X	X	X	[1] On Day 1, pre dose then every 15 mins during infusion (i.e. 15, 30, 45 and 60mins post the start of infusion) and then 30 mins, 1, 2 and 4 hr post end of infusion.
Haematology, clinical chemistry, urinalysis	X		24hr	48hr	X		X	X	X	X		X	X	X	X	
Weight	X															Weight to be used to calculate the study treatment dose.
Randomization		Pre-dose														
CCI [redacted]																
Study treatment dosing		X														
AE assessment	<----------													>	X	
SAE assessment	<----------													>	X	
Concomitant medication review	<----------													>	X	

1.3.4. Part A Cohorts With Blister: 3 and 10 mg/kg IV and SC

	Day														Early	Notes
Procedure	–1	1	2	3	7	8	15	22	28	29	43	57	85	113	141	**withdrawal**	Allowed visit windows are detailed in the SRM
Out-patient visit							X	X		X		X	X	X[1]	X[2]	X	[1] Final follow-up visit for 3 mg/kg IV cohort [2] Final follow-up visit for 10 mg/kg IV and SC cohorts
Admission in clinical unit	X				X				X								
Discharge from clinical unit				X		X				X							
Inclusion and exclusion criteria	X																
Brief physical examination	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	
Alcohol and tobacco screens	X																As per standard local practice
Urine drug screen	X																
Cardiac telemetry	X																Telemetry from at least 12 hrs before dosing until 12hrs post dose. Review for abnormalities prior to dosing on Day 1.
12-lead ECG	Triplicate	X[1,2]	X	X	X		X	X	X	X	X	X	X	X	X	X	On Day -1 and Day 1 ECGs may be generated from telemetry [1] On Day 1, pre dose then every 30 mins during infusion (i.e. 30 mins and 60mins after start of infusion) and then 1 hr post end of infusion. [2] On Day 1, pre dose then 1 hr post injection.
Vital signs	X	X[1,2]	X	X	X		X	X	X	X	X	X	X	X	X	X	[1] On Day 1, pre dose then every 15 mins during infusion (i.e. 15, 30, 45 and 60mins post the start of infusion) and then 30 mins, 1, 2 and 4 hr post end of infusion. [2] On Day 1, pre dose then 1 hr post injection.
Haematology, clinical chemistry, urinalysis	X		24hr p.d.	24hr p.d.	X		X	X	X	X	X	X	X	X	X	X	
Weight	X																Weight to be used to calculate the study treatment dose.
Randomization		Pre-dose															
Induction of blister	X				X				X								
Aspiration of blister fluid		X				X				X							Aspiration 21 hours (+/- 3 hours) after induction of blister.
CCI [redacted]																	
Study treatment dosing		X															
AE assessment	<---------->															X	
SAE assessment	<---------->															X	
Concomitant medication review	<---------->															X	

1.3.5. Part B

Study 207804 - PART B

PROCEDURE	SCREEN	[a] TREATMENT PERIOD (8 Wks)															[b] FOLLOW-UP (~12 Wks)					Early withdraw	See two footnotes. NOTES a) Treatment Period = Day 1 to 57. b) Follow-Up Period = Day 57 to 141. c) Day 141 (End of Study Visit) is ~13 wks since last dose on Day 50.
DAY	Day -4[1]	1	2	5	8	15	22	23	26	29	36	37	43	50	51	57	71	85	99	120	[c]141		Visit Windows: 1) Within 96 hours of Day 1 Days 15 to 71 (±1). Days 85 to 141 (±2).
Out-patient visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Tel.	X	X	Tel = telephone contact to check AEs and ConMeds (Day 120).
Discharge from clinical unit		X[1]			X[1]	X[2]	X[2]			X[2]	X[2]		X[2]	X[2]									1) Day 1: Discharge not sooner than 4 hours post-start of SC injections. 2) Remaining dosing days: discharge not sooner than 2 hours post-start SC injections.
Inc. & Exc Criteria	X	X																					Re-check clinical status before first dose.
Brief Phys. Exam.	X	(X)	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	
Alcohol and drug screen	X	X			X	X	X			X	X		X	X		X							Methods as per standard local practice
12-lead ECG (Triplicate)	X	(X)[1]	X		X[1]	X[1]	X[1]			X[1]	X[1]		X[1]	X[1]		X	X	X			X	X	1) On Dosing Days: pre-dose, and then 30 and 60 mins after post-start of dosing.
Vital signs	X	(X)[1]	X		X[2]	X[2]	X[2]			X[2]	X[2]		X[2]	X[2]		X	X	X			X	X	1) Day 1: pre-dose, and then 30 mins, 1, 2, 3 and 4 hrs post-start of dosing. 2) On other dosing days: pre-dose, 1 h and 2 hrs.
Haematology, clinical chemistry, urinalysis	(X)[1,2]		X		X	X	X			X	X		X	X		X[2]	X	X	X		X	X	Appendix 2. Samples taken prior to dosing, as appropriate. ADDITIONALLY: 1) Complement C3 & C4 (Screening only). 2) BNP (Screening & Day 57 only).
SARS-CoV-2 PCR Mandatory	X[1]															X					X	X	1) SARS-CoV-2 PCR NEGATIVE RESULT to be obtained prior to the 1st dose
SARS-CoV-2 PCR Optional						←[1]					←[1]												1) Recommended optional SARS-CoV-2 PCR test to be obtained ideally four days before the 3rd and 6th dose such that a result is available prior to dosing on those days
Daily Pain (Digital Tool)	See Screen	<----------Daily Pain----------																					N.B. Pain recorded daily using a digital tool (Evenings of Day 1 to Day 84)
WOMAC		(X)			X	X				X			X			X	X	X	X		X	X[3]	WOMAC, PtGA (participant) & PhGA (Physician Global
CCI																							
Randomization		X																					Allow at least 1 hour to thaw vials at room temp (or thaw 18 hours overnight at 2-8ºC).
Dosing (SC injections)		**X**			**X**	**X**	**X**			**X**	**X**		**X**	**X**									
CCI																							
SAE and AE	<----------																				X	X	SAEs recorded throughout. AEs recorded from first SC injection.
Concom. Meds	<----------																				X	X	
Trial Questionnaire	(X)																			X	X	X	Optional trial-based questionnaire for participant completion.

All activities and blood samples are to be acquired *prior to dosing* (on dosing days), unless stated otherwise.
(X) denotes the Baseline Value.

2. INTRODUCTION

2.1. Study Rationale

This study is the first administration of GSK3858279 to humans for which the purpose is two-fold:

Part A: to evaluate the safety, tolerability, pharmacokinetics (PK) and target engagement (TE) of either a single intravenous (IV) or a single subcutaneous (SC) dose of GSK3858279 in healthy males and females of non-reproductive potential. Target engagement in the skin, which is a surrogate for tight tissue compartment, will be assessed via suction blister procedure in certain cohorts [see Schedule of Activities (SoA, Section 1.3) and Section 4.3]. The intention is to provide sufficient confidence in the safety and tolerability of the molecule as well as target engagement to inform progression to the following part of the study.

Part B: to evaluate the safety, tolerability, efficacy, PK, target engagement and immunogenicity of repeat SC dosing of GSK3858279 in participants with osteoarthritis (OA) of the knee.

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 cell types.

GSK3858279 is a high affinity (Kd<1pM), human immunoglobulin G2σ (IgG2σ) (Fc-silenced), first-in-class, monoclonal antibody (mAb), binding specifically to the chemokine CCL17. It functionally inhibits CCL17 from binding to the chemokine receptor CCR4, to prevent downstream consequences of CCR4 signalling.

OA is a debilitating degenerative disease of the large and small joints and the most common form of adult arthritis in the developed world. Alleviating the chronic pain of OA is a major unmet need as current therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) or opioids have significant side effects that prevent their effective use in this population [Thakur, 2014]. OA is a disease of the whole joint and underlining pain mechanisms are poorly understood [Malfait, 2013].

The rationale for CCL17 neutralisation in OA pain has been generated in vivo preclinically in inflammatory and arthritis models. CCL17 has been recently identified as a peripheral mediator of inflammatory pain. Intraplantar injection of recombinant CCL17 resulted in pain in mice [Achuthan, 2013], whilst therapeutic dosing with an anti-CCL17 surrogate mAb inhibited established inflammatory pain [GSK Document Number 2017N327494_00]. Absence of CCL17 ameliorated inflammatory pain in various murine arthritis models [Lee, 2018]. In addition to effects on pain, CCL17 can itself induce arthritis and a lack of CCL17 also protected joints from disease, as evidenced by reduced bone erosion and proteoglycan loss [Achuthan, 2013]. CCL17 was the 6th most

upregulated gene in a chemically-induced, monosodium iodoacetate (MIA) murine arthritis model of chronic joint pain [Dawes, 2013].

CCL17 evokes excitatory effects in mixed neonatal dorsal root ganglia cultures [Oh, 2001]. A relationship has been established between CCL17 and the pain-mediator nerve growth factor (NGF). CCL17-overexpressing mice showed significantly higher serum NGF levels and increased numbers of NGF+ lymphocytes in wounded tissue than wild-type mice [Kato, 2011]. It was also shown that CCL17 could induce NGF production in a mouse T cell hybridoma [Kato, 2011].

Thus, blockade of CCL17 with the mAb GSK3858279 offers the potential to alleviate OA associated chronic pain. There is no literature on CCL17 circulating levels in OA patients.

2.3. Benefit/Risk Assessment

More detailed information about the potential benefits, known potential risks and adverse events of GSK3858279 may be found in the Investigator's Brochure (IB) [GSK Document Number RPS-CLIN-004032].

The risk assessment of GSK3858279 is based on the pre-clinical studies conducted to date and a blinded review of a partial data set from Part A of this first time in human (FTIH) study [GSK Document Number 2020N429762_00], for which summaries can be found in the IB [GSK Document Number RPS-CLIN-004032]. Details of these risks, 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, AE and cardiac monitoring. The study will be run in clinical units which have immediate access to hospital facilities for the treatment of medical emergencies. Participants will be monitored in the clinic as specified in the Schedule of Activities (see Section 1.3.5) 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
Risks of Investigational Product (IP) GSK3858279		
Risk of infection	The intended pharmacologic effect of GSK3858279 may result in an increase in the frequency and/or severity of infection, as a result of changes in immune cell trafficking. **Non-Clinical** No specific studies have been conducted in nonclinical species to investigate the effect of GSK3858279 on response to viral or bacterial infection. CCL17 has an important role in early responses against skin-invading pathogens e.g. CCL17 controls filarial larval entry by limiting mast cell-dependent vascular permeability. Mice deficient for CCL17 had an up to 4-fold higher worm burden compared to controls by day 10 of infection with murine filaria *Litomosoides sigmodontis* (Specht, 2011). Anti-CCL17 has been shown to be protective in a mouse model of invasive aspergillosis [Carpenter, 2005] suggesting decreased infection risk. The role of CCL17 in systemic anti-pathogen responses is unclear. **Clinical** During this FTIH study in healthy participants (Part A), there was no report of an infection related SAE.	**Participant Selection:** Participants with active infections or a history of recent or recurrent infections will not be allowed to enter the study – see Section 5.2 **Participant monitoring:** Participants will be monitored for infection Participants will be instructed in the informed consent form as to the signs and symptoms of infection, and to contact site personnel should they develop.
Hypersensitivity, including injection site or infusion reactions:	The administration of any recombinant protein has the potential to induce local or systemic immunologic reactions, for example, acute allergic reactions (type I) and immune complex disease associated with the formation of anti-drug antibodies (ADA) (type III). **Non-Clinical** In the 13-week study, administration of GSK3858279 by weekly IV infusion at 100 mg/kg, resulted in infusion reactions after	**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 be also excluded. See Section 5.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	dosing on Days 22 and 29, in one female cynomolgous monkey which was successfully managed in subsequent administrations by pre-treating with anti-histamine. In the 26-week study, there were inflammatory vascular changes in multiple organs and mesangioproliferative glomerulopathy in the kidney which is consistent with ICD following the formation of ADA. Nonspecific injection site reactions caused by the subcutaneous dosing route were also noted in some monkeys, which was exacerbated by the immune complex deposition in one male. These findings were considered non-adverse. Animals studies are not predictive for ADA-mediated adverse reactions in humans, including infusion reactions, hypersensitivity reactions or anaphylaxis [Kronenberg, 2017], especially for human proteins such as GSK3858279. In addition, given that GSK3858279 binds a soluble ligand (CCL17) and is Fc disabled, GSK3858279 is not expected to mediate effector functions of antibody dependent cell mediated cytotoxicity or complement dependent cytotoxicity. **Clinical** During this FTIH study in healthy participants (Part A), there was neither a report of hypersensitivity, nor injection site reaction, nor a clinically significant change in urinalysis.	**Participant monitoring:** • Part A participants will remain in an inpatient facility for 48 hours post dosing to allow adequate monitoring by trained site personnel. Emergency resuscitation facilities will also be available. • Part B participants will be monitored for a minimum of 2 hours post dosing. • 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	Monoclonal antibodies may induce ADAs, which have the potential to induce adverse reactions (mentioned above) or affect the PK and pharmacodynamics (PD) properties of the drug. GSK3858279 is a human antibody, with a lower potential for ADA formation than a chimeric antibody.	**Participant monitoring:** 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Non-Clinical In the nonclinical studies a significant number of monkeys treated with GSK3858279 had confirmed ADA, but mostly the presence of ADA did not affect the systemic exposure or PK parameters for GSK3858279; however, there was no impact on clinical observations apart from the animal which had findings consistent with an infusion-related reaction and on the chronic toxicology study, vascular changes consistent with ICD were seen (mentioned above). In general, the incidence and titre of ADA in nonclinical studies are not predictive of human. **Clinical** The FTIH study in healthy participants showed there was low incidence of ADA, low titre, no pattern of increasing incidence of ADAs following single ascending dose (SAD) of GSK3858279 (or placebo) and no apparent difference between 3 mg/kg IV vs. 3 mg/kg SC.	be investigated following unexplained dipstick proteinuria or haematuria.
Vaccination reactions	There is a theoretical risk that GSK3858279 could decrease an individual's immune response to vaccines administered while on therapy or to allow symptoms to develop following the administration of live vaccines. Monkeys dosed with GSK3858279 for 13 weeks did not demonstrate modulation of the immune system as assessed by T-cell Dependent Antibody Response (TDAR), an assessment of humoral immunity, or of peripheral blood lymphocyte populations as assessed by flow cytometry.	**Participant selection and non-permitted medications:** Attenuated live should not be administered to participants from 30 days prior to the first dose of study drug and for five half-lives after dosing. If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered whilst receiving study drug based on an assessment of the benefit:risk (e.g. risk of decreased responsiveness). See Section 5.2
Cardiac risks	**Non-Clinical** In the 4-week study, review of the heart data (Electrocardiogram [ECG], blood pressure, heart rate, organ weights and histopathology), in monkeys at doses up to 100 mg/kg/week IV	**Participant Exclusion** Participants with a history of cardiac disease or cardiac abnormalities that in the opinion of the investigator would compromise cardiac safety will be excluded from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and 30 mg/kg/week SC to n=2/sex/group, did not identify any changes compared to controls. In the 13-week study, higher heart weights were noted compared to controls, without any histopathological or functional (ECG, blood pressure, heart rate) correlate. The heavier heart weights were not dose related and generally did not show a consistent pattern of increased absolute weights, relative to body weight or brain weight. Refer to IB [GSK Document Number RPS-CLIN-004032] for further details. In the 26-week study, a thorough evaluation to investigate the potential for cardiotoxicity which included ECG, echocardiogram (ECHO), telemetry (blood pressure, heart rate), serum cardiac troponin I, N-terminal proBNP, heart weight and histopathology, did not identify any treatment-related effects on the heart following doses up to 100 mg/kg/week SC. Therefore, the potential effect on heart weights noted in the 13-week study was not reproducible following 26 weeks chronic dosing and is not considered to be clinically significant. GSK3858279 did not bind to human heart in the tissue cross-reactivity studies and there is no known pharmacological mechanism following administration of an anti-CCL17 that would lead to an increase in heart weight. **Clinical** During this FTIH study in healthy participants (Part A), none of the abnormal findings in the ECG parameters were judged to be clinically significant.	Investigations during screening include ECG, Echocardiogram and cardiac troponin T and NT-proBNP. Troponin T and NT-proBNP will be monitored after dosing. See Section 5.2 In addition, telemetry was performed in FTIH study (207804) in healthy participants.
Bleeding risk	CCR4, the receptor for CCL17 is expressed on platelets and both CCL17 and CCL22 activate platelets *in vitro*. A potential risk of impaired platelet activation and blood clotting exists with CCL17 antagonism although at this stage this is theoretical; there are 2 conflicting reports describing the ability of anti-CCR4 antibodies, to either block CCL17/CCL22- mediated platelet aggregation ex vivo [Gear, 2001] or to not block platelet function *in vitro*/*ex vivo*	**Participant exclusion** • Participants with a previous or current history of bleeding diathesis will be excluded see Section 5.2 • Use of anti-coagulants or anti-platelet agents will be prohibited.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	assays [Hagemann, 2014]. Clinical data with direct inhibitors of CCR4, such as mogamulizumab (approved in Japan for treatment T cell lymphoma), are not associated with increased bleeding risk. **Non-Clinical** Although platelet function has not been specifically assessed preclinically; no effects on platelet counts or clotting times were observed in the monkey studies. Neither were there reports of excessive bruising nor difficulties in clotting after blood sampling. **Clinical** There were no reports of any bleeding events during the FTIH study in healthy volunteers.	• In addition, use of NSAIDs will be prohibited in healthy participants.
Skin reactions	Cutaneous adverse clinical effects have been observed in patients with T-cell lymphomas treated with mogamulizumab (anti-CCR4 antibody) including Stevens-Johnson syndrome. This may reflect depletion of immune regulating cells called "Regulatory T cells" within the skin compartment predisposing to cutaneous inflammatory or autoimmune responses. Given that GSK3858279 will only block CCL17, the alternative ligand, CCL22, should offer redundancy to maintain T cell migration. Relevant to this, CCL22 is highly expressed in skin blister fluid [Bouma, 2017].	**Participant exclusion and monitoring** • Participants with a history of drug induced skin reactions and Steven's Johnsons Syndrome will be excluded; see Section 5.2 • Clinically significant skin reactions will be reviewed by a dermatologist and if appropriate a skin biopsy will be requested for histological analysis.
Study Procedures		
Risk associated with blister induction procedure (Part A only)	Possible risks of this procedure may include discomfort during the application of the negative pressure, skin infection after drawing the blister and hyperpigmentation of the skin at the blister induction site.	Participants with keloids or a history of keloids will be excluded from Part A; see Section 5.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk associated with attending an investigative site during the COVID-19 Pandemic	For Part B, the current COVID-19 (SARS-CoV-2) pandemic may pose a challenge to integrity of the trial, protection of participants' rights, safety and wellbeing and the safety of clinical trial staff. Therefore, risk mitigation strategies have been introduced and will be evaluated on an ongoing basis per each country. Part B will be halted 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 cannot be guaranteed. CCL17 (and CCL22) are ligands for the CCR4 receptor. The CCR4 receptor is predominantly expressed on Th2 cells but is also present on some Th1 cells (Kara, 2014). CCL17 is thus more likely to be involved in extracellular infections (e.g. parasitic, extracellular bacteria and fungi), rather than intracellular infections (e.g. viral such as COVID-19) although we cannot rule out a role for CCL17 in viral infection.	**Participant Selection:** OA participants may fall into a higher risk category for complications of COVID-19 (caused by the SARS-CoV-2 virus). Participants will be counselled regarding the importance of infection control measures such as hand washing, reducing inter-personal contacts as much as possible and of potential COVID 19 symptoms. Site trial staff in direct contact and/or within 1 m distance of study participants will receive additional protection *via* the use of Personal Protective Equipment (PPE) and disinfectants. **Participant monitoring:** Prospective OA participants will be contacted by sites to check on COVID-19-related symptoms prior to being pre-screened (SARS-CoV-2 PCR test) and prior to consenting. Consented participants will also be contacted prior to each scheduled visit. Participants will be screened and monitored periodically throughout the Treatment Period and at the End of Study Visit (or at early withdrawal) as per protocol (see Section 1.3.5). **Protection of Trial Integrity** Adherence to the protocol and investigative site procedures will go towards protecting the integrity of the data collected during this clinical trial, as well as the participants' data protection rights. **COVID-19 Contingency Plan** Any participant presenting with COVID-19-related symptoms and/or having 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.

2.3.2. Benefit Assessment

- There will be no direct benefit to the healthy participants in this trial.
- OA participants may experience benefit in terms of relief of knee pain. Note that participants will be allowed to use paracetamol as analgesic rescue medication to help manage their pain and discomfort associated with OA.
- By enrolling in this study, participants will be contributing to the process of developing new analgesic medications, a significant area of unmet need for patients intolerant or unresponsive to oral NSAID treatments.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures proposed to minimize the risk to study participants (including COVID-19 [SARS-CoV-2] testing at screening, and sparse testing during the study), the potential risks identified with GSK3858279 from 1) pre-clinical studies, 2) the review of safety in Part A of this clinical study [see Section 5 of IB] and 3) those associated with study procedures, are considered minimal and justified for progression to Part B.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Parts A and B To evaluate the safety and tolerability of escalating doses of GSK3858279 following single IV, single SC dosing in healthy participants and repeat SC dosing in OA participants.	Adverse Events (AE) and Serious Adverse Events (SAE). Clinical laboratory measurements, 12-lead ECG and vital signs.
Part B To assess changes in pain in participants with OA of the knee following repeat SC dosing.	Change from baseline in average knee pain intensity, at Week 8. Change from baseline in worst knee pain intensity at Week 8 .
Secondary	
To describe the pharmacokinetics (PK) of GSK3858279 following single IV, single SC in healthy participants and repeat SC dosing in OA participants.	CCI [redacted]

Objectives	Endpoints
	CCI [redacted]
To evaluate the target engagement (TE) of CCL17 by GSK3858279 following single IV, single SC dosing in healthy participants and repeat SC dosing in OA participants.	CCI [redacted]

CCI [redacted]

CCI [redacted]

4. STUDY DESIGN

4.1. Overall Design

This study is a randomized, double-blind, placebo-controlled, two-part trial. A study diagram is included in Figure 1.

Part A is a single ascending dose escalation study to evaluate the safety, tolerability, PK, and target engagement of GSK3858279 in healthy participants. Single IV doses and a single SC dose will be investigated in separate cohorts of participants. Target engagement (CCL17) will be assessed both in blood CCI [redacted] CCI [redacted] (see Section 4.3 and SoA, Section 1.3). Up to five single ascending IV doses of GSK3858279 will be investigated. A single SC dose of GSK3858279 will also be assessed to determine bioavailability, as future studies as well as the target product will likely involve SC administration.

A Dose Escalation Committee (DEC) will review at least 15 days of safety and PK data prior to progression to the next dose level (see Study Rationale Section 4.3). The decision to progress the SC cohort will be based upon understanding the PK and TE data from some IV cohorts. The decision to progress to Part B dosing in OA participants will be based on the safety, PK and TE data following single IV and single SC administrations in healthy participants.

In Part A, sentinel participants will be used in each dosing cohort: two participants will be dosed first, one will be randomised to GSK3858279 and one to placebo. 48-hour post

dose safety data from the sentinel participants will be reviewed by the investigator and the remainder of the cohort will then be dosed if deemed safe to do so. The dose level investigated in Part B will not exceed the highest dose tested in Part A.

Part B will investigate the safety, tolerability, efficacy (pain), PK, TE and immunogenicity of weekly SC dosing for 8 weeks of GSK3858279 or placebo (in a 1:1 ratio) in participants with OA of the knee.

Given the global COVID-19 pandemic, all participants are to be screened and monitored throughout and mitigation steps are incorporated. Sites are to contact participants prior to each clinic visit to check for COVID-related symptoms. Participants consenting to Part B will either have a documented negative SARS-CoV-2 PCR approved test within two days of initial screening OR have a test performed at the time of initial screening. A second mandatory negative COVID test is required before 1st dose of study drug. Mandatory testing will be conducted at the end of the Treatment Period and at the End of Study Visit (for details see Section 8.1.4 and Section 10.2). Recommended optional SARS-CoV-2 PCR tests are to be obtained ideally four days before the 3rd and 6th dose such that a result is available prior to dosing on those dosing visits. In the event that GSK's Guidance on COVID-19 changes, GSK will consult Principal Investigators and a joint decision on how to modify the approach to COVID testing may be taken. The decision would be judged on whether this change would constitute a substantial amendment to the protocol (and requiring submission to the Regulatory Authority(ies) and Ethics Committee(s) or whether documentation v*ia* a formal File Note would suffice.

Safety review: Part B will incorporate an early review of safety, PK, TE and ADA data following administration of repeat doses in OA participants. Close in-stream safety monitoring (AEs, clinical laboratory, vital signs, cardiac monitoring) and a review of PK and TE is intended for the first 8 participants (4 randomized to active treatment) with a detailed review when the 8th participant reaches Day 29.

A Safety Review Team (SRT) is employed for Part B and operates in accordance with the SRT Charter, with country oversight described in the study-specific Safety Management Plan (SMP).

Part B incorporates an interim analysis (see Section 9.4.5) of clinical efficacy, safety, tolerability, PK and TE which will occur once approximately 20 participants have completed the Week 4 assessment.

4.1.1. Treatment Groups and Duration

The total duration of the study (from signing of the informed consent until final follow-up) for each participant will vary between cohorts (see Table 1). The screening period will be of a maximum of 28 days for all cohorts in Part A and a maximum of 42 days in Part B. Final follow-up visits will be scheduled to occur when approximately 5 half-lives of GSK3858279 have elapsed after dosing. Follow-up visits are scheduled earlier for the lowest dose group where PK parameters are expected to be below the lower limit of quantification (LLQ), and are extended by an additional 4 weeks for the top dose cohort where extended pharmacology may be observed (see Table 1 and Schedule of Activities [SoA, Section 1.3]).

In Part A, each participant will receive a single dose of study intervention (GSK3858279 or placebo), either IV or SC. The planned dosing schedule is described in Table 1, although dose levels are subject to change depending on emerging study data. The maximum dose (level) that may be administered in the study will be 10 mg/kg, both for IV and SC cohorts. See Section 4.4 for further details.

In Part B, each participant will receive SC injections weekly for 8 weeks.

Table 1 Dosing schedule and study duration

Part	Cohort	Dose of GSK3858279	Follow up (days post dosing)	Maximum study duration including screening (days)
Part A	Cohort 1 IV	Up to 0.1 mg/kg	84	112
	Cohort 2 IV	Up to 0.3 mg/kg	112	140
	Cohort 3 IV	Up to 1 mg/kg	112	140
	Cohort 4 IV	Up to 3 mg/kg	112	140
	Cohort 5 IV	Up to 10 mg/kg	140	168
	Cohort 6 SC	Between 1 and 3 mg/kg (max 240 mg)	140	168
Part B	Cohort 7 SC	240 mg	56 (Treatment) 84(Follow Up)	182/183

4.2. Number of Participants

In Part A, approximately 48 healthy male and female participants (36 randomised to GSK3858279, 12 randomised to placebo) will be enrolled in the study across a maximum of six cohorts (up to five cohorts for IV dosing and one cohort for SC dosing). In each cohort, eight participants will be enrolled, and will be randomised in a 3:1 ratio to GSK3858279: placebo (six will receive GSK3858279 and two will receive placebo). Five evaluable participants are required per cohort, where a participant is considered evaluable if they complete both the screening period and all their planned visits.

In Part B, approximately 50 (a minimum of 20 up to a maximum of 80) participants with OA will be enrolled and will be randomised to receive either GSK3858279 or placebo in a 1:1 ratio A sample-size re-estimation may be performed, and the sample size may be decreased or increased up to a maximum of 80 participants.

For Part A, if participants prematurely discontinue the study, additional participants may be enrolled as replacements (and assigned to the same intervention) at the discretion of the Sponsor in consultation with the investigator.

For Part B, if randomised participants prematurely discontinue the study prior to dosing, additional participants may be enrolled as replacements (and assigned to the same intervention) following Sponsor approval.

4.3. Scientific Rationale for Study Design

Study population

Part A of this study is the first time GSK3858279 will be given to humans. A healthy population is believed to be appropriate to explore the safety and tolerability of GSK3858279 in a population not currently receiving concomitant therapeutic treatments and whose immune function is not compromised. In the absence of reproductive toxicity data, the study population will be restricted to male participants and females of non-reproductive potential.

Part B of this study will investigate the effects of GSK3858279 on pain. In the absence of human experimental pain models that are CCL17 dependent or accurately predict analgesic effect in OA, and of biomarkers for pain, proof of mechanism is best achieved by assessing clinical endpoints in an OA patient population. Knee OA pain participants will be enrolled because of the high prevalence of the condition and well-established clinical endpoints for pain.

The heightened relative risk of increasing age and BMI to COVID-19 susceptibility and poorer outcomes has been considered [Williamson, 2020]. Inclusion of participants between 40 to 75 years (inclusive) and with a BMI within the range 19-34.9 kg/m^2 (inclusive) will continue to be permitted in this study because these parameters are inherently associated to and therefore largely cover the OA population. All participants are to be screened and monitored throughout for COVID-19, and mitigation steps have been incorporated.

Control and blinding

As the primary objectives of the study are safety and tolerability of single IV and SC doses (Part A) and repeat SC doses of GSK3858279 (Part B), use of a placebo comparator is required for assessment of the safety profile. A placebo arm will also act as a true negative control for target engagement and pain assessments.

To ensure unbiased outcomes, a double-blind approach is preferable.

Part A data will be reviewed blinded by the Investigator and unblinded, if required, by the GlaxoSmithKline (GSK) members of the DEC (GSK Clinical Investigational Lead, GSK medical monitor, GSK Safety and Medical Governance (SMG) representative, GSK pharmacokineticist and GSK statistician). Further details are included in the Dose Escalation Plan (DEP). Part B safety monitoring will be undertaken in a blinded manner by the Sponsor SRT, as described in Appendix 1 Section 10.1.5. The Study Medical Monitor will also regularly review AEs and clinical laboratory tests for individual participants during the conduct of the study to ensure individual participant monitoring (according to the SMP).

Sentinel dosing and dose escalation

This study is the first time GSK3858279 will be administered to humans. To ensure adequate safety precautions, sequential dosing and dose escalation processes will be implemented in Part A.

Once eight participants per each cohort have completed the Day 15 visit, the DEC will review all available safety and PK data. In case of early drop-outs, a minimum of 6 participants completing the Day 15 visit will be required for dose escalation data review. If safety data is satisfactory (see Study stopping criteria in Section 7.1), and the next dose level is anticipated not to exceed PK stopping criteria (mean AUC = 2190 µg.day/mL and mean Cmax = 895 µg/mL, based on 4-fold margin against the no observed adverse effect level (NOAEL) from the 3-month toxicological study), a dose escalation to the next planned dose may occur and the second cohort may be enrolled. Doses may be adjusted based on emergent data, and in any case, will not exceed the maximum planned dose in this study 10 mg/kg. The same process will be implemented in subsequent cohorts.

Upon review of data from the 1 mg/kg IV cohort, the DEC may decide to trigger the SC cohort as well as the 3 mg/kg IV cohort, if data are satisfactory.

In Part A, to mitigate a risk of adverse reactions, sequential dosing will be implemented per each cohort. Two participants will receive study intervention first (one on active, one on placebo) and will be monitored in the clinical unit for approximately 48 hours, which is deemed adequate to observe any acute adverse reaction. If no adverse reaction precludes further dosing, subsequent participants may then be dosed. All participants will remain in the clinical unit for approximately 48 hours after dosing to undergo required study procedures, as per the Schedule of Activities.

Progression into Part B

Once eight participants in the highest dose cohort in Part A have completed the Day 15 visit, the DEC will review all available safety, target engagement (i.e, free and total CCL17 levels) in serum and PK data and decide whether to proceed with Part B of the study. In case of early drop-outs, a minimum of 6 participants completing the Day 15

visit will be required for dose escalation data review. Part B will be triggered if the

CCI [redacted]

CCI Although the decision to progress one or two IV single dose levels in Part B was planned to be based on total CCL17 data, following the review of Part A blinded PK and TE data, it was decided to amend the protocol for subcutaneous administration of repeated doses based on PK and TE data.

CCI [redacted]

4.4. Justification for Dose

4.4.1. Part A

Dose levels for Part A were selected on the basis of PK/PD predictions and preclinical data, which are summarised in Table 2. Please refer to the IB for further details.

A target mediated drug disposition model (TMDD) has been developed to characterise the aCCL17 PK and chemokine kinetics observed pre-clinically, and the model parameters were allometrically scaled to a 70 kg human [CP2015PK-002, 2016]. The estimated chemokine degradation rate (Kdeg=585.6/day) implies a chemokine half-life of approximately 2 minutes, considerably shorter than the 20-30 minutes expected. However, the estimated degradation rate (Kdeg) is derived by the assumption of low levels of serum CCL17 in equilibrium with extra cellular component, hence high accumulation of total (as observed in cynomolgus monkey) is explained by low CCL17 level and extremely high turnover. An alternative hypothesis is to assume a lower degradation rate and a much larger extra-cellular component outside plasma. An alternative model assuming a different chemokine degradation rate with a 10-minute half-life has been also developed. There are no differences in the estimated PK profiles for GSK3858279. The lower chemokine degradation rate also results in a longer return to baseline for the free chemokine profiles and sustained target engagement over a longer period. Predictions and safety margins are summarized in Table 2.

The 'Minimal Anticipated Biological Effect Level' (MABEL), as per Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products [CHMP, 2017] was used to define the starting dose and is defined as the dose level predicted to result in a maximum inhibition in plasma in the 30-50% range. A dose of 0.1 mg/kg was designated the MABEL dose as the maximum predicted PD inhibition was 56%, according to human PK/PD predictions.

According to this model, the highest planned dose 10 mg/kg IV is expected to provide a maximum target engagement of 99% with half of this level being recovered after 9.5 days, and a return to baseline around three weeks post dose. Even at this highest simulated dose, high target engagement was not maintained over a 28-day period.

The cynomolgus monkey study, used in the non-clinical assessment of GSK3858279 pharmacology and toxicology, has provided reasonable assurance that there are no undue or unforeseen risks for the first administration of GSK3858279 to humans, at the dose levels proposed in this study. The highest predicted exposures after IV administration (Cmax 213µg/mL, AUC(0- ∞)=1460 µg*day/mL) are almost 6 fold below the NOAEL (Cmax 3580 µg/mL, $AUC_{Day85-92}$ 8760 µg.day/mL) from the 3 month toxicology study.

Table 2 GSK3858279 Doses, Predicted Exposures and Safety Margin

Dose (mg/kg)	Predicted PK and PK/PD inhibition			Safety Margin	
	Max CCL17 inhibition[a] (%)	Cmax [µg/mL]	AUC [µg*day/mL]	Cmax	AUC
0.1 (IV)	56	2.13	17.8	1680x	494x
0.3 (IV)	86	6.39	52.3	561x	167x
1 (IV)	96	21.3	168	168x	52x
3 (IV)	98	63.8	477	56x	18x
10 (IV)	99	213	1460	17x	6x
1 (SC)	66	8.24	140	37x	12x
3 (SC)	87	22.0	402	14x	4x

a. Average TE in the first 12 hours
Cmax = maximum plasma GSK3858279 concentration, AUC = area under concentration-time curve.

A dose level between 1 to 3 mg/kg SC is anticipated to be pharmacologically relevant and will provide a preliminary assessment of GSK3858279 bioavailability after SC administration.

4.4.2. Part B

The dose to be administered in Part B was revised (protocol amendment 3) according to the actual PK and TE (% reduction from baseline in free CCL17 levels) data obtained from Part A [GSK Document Number 2019N397787_00]. However, re-analysis of the concentration of GSK3858279 in Part A samples using an improved analytical method [see GSK Document Number RPS-CLIN-004032] has led to a further protocol amendment (number 5). The data from Part A and the recommendation of the dose regimen for Part B are summarised here.

CCI

[redacted]

CCI [redacted]

4.5. End of Study Definition

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

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

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:

Part A

AGE
1. Between 18 and 65 years of age inclusive, at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

WEIGHT
3. Body weight within the range 50 – 100 kg and body mass index (BMI) within the range 18-32 kg/m^2 (inclusive).

SEX
4. 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; Appendix 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 Appendix 4.

INFORMED CONSENT
5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Part B

AGE
6. Between 40 and 75 years of age inclusive, at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
7. OA of the index knee as defined by symptoms for ≥6 months with a clinical diagnosis of OA as per American College of Rheumatology (ACR) clinical diagnosis criteria
8. Average of daily pain score ≥4 and ≤9 by the 11-point NRS (0-10) in index knee over 7 days prior to dosing (Day-7 to Day-1). Data should be recorded on at least 5 of 7 occasions by the participant to obtain a valid baseline value.
9. Kellgren and Lawrence (KL) score ≥2 on X-ray obtained during screening (Kellgren, 1957). In addition, for participants with bilateral Knee OA, the index knee is determined at baseline as the patient reported most painful knee over the 4 weeks prior to baseline.
10. A history of insufficient pain relief from, or inability to tolerate, or contraindication to, oral NSAIDs.

11. Participant must be willing and able to understand and participate in all scheduled evaluations and to complete all required tests and procedures including the use of patient diaries. This will be judged by the Investigator during the screening period.
WEIGHT
12. BMI within the range 19-34.9 kg/m^2 (inclusive)
SEX
13. 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 or homosexual 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 o Agree to use a male condom o and should also be advised of the benefit for a female partner to use a highly effective method of contraception (see Appendix 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 Appendix 4.
INFORMED CONSENT
14. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

PART A

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. Lymphoma, leukaemia, or any malignancy 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, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

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
17. Previous history of hypertrophic or keloid scarring

PRIOR/CONCOMITANT THERAPY

18. Intended use of over-the-counter or prescription medication including herbal medications within 7 days prior to dosing until final follow-up visit.
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 study intervention or any other type of medical research within the

last 30 days, 5 half-lives or twice the duration of the biological product before dosing day in the current study.

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 levels out of normal range at screening.
32. Positive pre-study drug/alcohol screen
33. Positive human immunodeficiency virus (HIV) antibody test

OTHER EXCLUSIONS

34. Regular alcohol consumption within 6 months prior to the study defined as:
    - an average weekly intake of >21 units for males and >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
35. Smokerlyzer levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.
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.

Part B

MEDICAL CONDITIONS
Diagnosis of one or more of the following, as per medical records: 38. Significant pain in any joint other than the index knee or any referred pain that would impact ability to assess pain in the index knee as per investigator's judgement (Pain in other locations should be less than pain in target knee). 39. Current inflammatory arthritis such as rheumatoid arthritis, autoimmune disorder affecting joints, seronegative spondyloarthritis, gout or pseudogout in any joint (defined as acute episodic attacks of swollen, painful joint in a patient with X-Ray chondrocalcinosis or calcium pyrophosphate dihydrate [CPPD] crystals). Note: asymptomatic CPPD crystals on X-ray are not an exclusion 40. History of gout or pseudogout in any large joint. 41. History or evidence of infectious arthritis, Paget's disease, ochronosis, Wilson's disease, primary osteochondromatosis, osteonecrosis, avascular necrosis and other causes of significant joint disease osteoarthritis as determined by the investigator 42. History of fibromyalgia 43. Current immunodeficiency diseases 44. Current osteoporosis with symptomatic vertebral or hip fractures 45. Current regional pain syndromes caused by lumbar or cervical compressions with radiculopathy 46. History of significant medical illness in the opinion of the investigator would interfere with the study procedures and / or assessments 47. Symptomatic herpes zoster within 3 months prior to screening 48. Evidence of active or latent TB as documented by medical history, examination and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) QuantiFERON test. NOTES: • The choice to perform a TST or a QuantiFERON test will be made by the investigator according to local licensing and standard of care. The QuantiFERON test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression. • In cases where the QuantiFERON or T-spot 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 or T-spot 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.

49. History of significant allergies to humanized monoclonal antibodies
50. 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 IgA dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis
51. History of 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.
52. Breast cancer within the past 10 years.
53. ALT >1.5x ULN
54. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
55. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
56. QTc >450 msec or QTc >480 msec in participants with bundle branch block

    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. It is either machine-read or manually over-read.
    - The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas 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.

57. History of primary cardiomyopathy and any major cardiac or vascular event within the last 6 months, including and not limited to myocardial infarction, unstable angina, cerebrovascular event, peripheral arterial or venous thrombosis.
58. Current or history of renal disease, or estimated creatinine clearance <60 mL/min/1.73m^2 or serum creatinine >1.5xULN or urine albumin:creatinine ratio of >300mg/g at screening
59. Planned surgical procedure over the duration of the study
60. Previous or current history of bleeding diathesis, excessive bleeding or coagulation disorders.
61. History of Stevens Johnson Syndrome
62. Participants with active, recurrent or chronic infection (e.g., osteomyelitis), who have been receiving treatment within three months prior to dosing or individuals with an active infection.

63. History of significant trauma or surgery to a knee, hip or shoulder within the last 6 months.
64. Radiographic evidence of sub-chondral fractures or radiographic abnormalities not consistent with osteoarthritis of the index knee at screening.
PRIOR/CONCOMITANT THERAPY
65. Attenuated live vaccine(s) (with the exception of recombinant non-human primate adenoviral vector vaccines) within 30 days prior to dosing or plans to receive such vaccines during the study.
66. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.
67. Intra-articular therapy within 3 months prior to signing the informed consent.
68. Immunosuppressants, including corticosteroids (parenteral within 3 months of screening; oral within 1 month of screening).
69. Unable or unwilling to discontinue all pain medication including topical analgesic or adjunctive treatment as per Section 6.5 and Section 6.6.
70. Major surgery (as per investigator's judgement) within 3 months prior to dosing.
PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
71. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days.
72. Exposure to more than 4 new chemical entities within 12 months prior to the dosing day.
73. Current enrolment or past participation in a clinical study of an investigational drug intervention within the last 3 months or 5 half-lives (whichever is longer) of signing consent.
DIAGNOSTIC ASSESSMENTS
74. Positive HIV antibody test.
75. Presence of HBsAg at screening.
76. Presence of HBcAb at screening
77. Positive Hepatitis C antibody test result.
78. 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
79. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention
80. NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.
81. Positive coronavirus (COVID-19: SARS-CoV-2 PCR test of a combined throat and nasopharyngeal swab).

82. Clinically significant abnormal echocardiogram at screening, as assessed by the investigator. 83. Cardiac troponin or NT-proBNP levels out of normal range at screening. 84. A positive pre-study drug/alcohol screen at screening
OTHER EXCLUSIONS
85. Regular alcohol consumption within 6 months prior to signing the informed consent defined as: • an average weekly intake of >14 units for males and >14 units for females. • One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits. 86. Regular use of known drugs of abuse 87. 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 locally at each of the investigative sites to reduce the risk of COVID-19 infections among trial participants and clinical site staff. Measures and procedures are encouraged whenever possible and will at least be to effect social distancing (at least 1 metre apart) during the clinical trial and to wear a face cover during visits to the clinical unit.

5.3.2. Meals and Dietary Restrictions

Not applicable

5.3.3. Caffeine, Alcohol, and Tobacco

For Part A:

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before any clinic visit until discharge at each visit.
- Participants will abstain from alcohol for 24 hours before any clinic visit until discharge at each visit
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches and other delivery devices such as vaporizers) will not be permitted while they are in the clinical unit.

For Part B:

- Participants will abstain from alcohol for 24 hours before any clinic visit until discharge at each visit
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches and other delivery devices such as vaporizers) will not be permitted while they are in the clinical unit.

5.3.4. Physical Activity

- Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants should maintain stable levels of physical activity throughout the duration of screening, treatment and follow up.
- Participants may continue a regimen of therapeutic exercise, provided it has been stable for at least 4 weeks prior to enrolment. No new therapeutic regiments should be implemented during the study. Physical therapy or therapeutic massage should not be initiated during this study
- Heat or ice therapy can be used during the study, except 2 hours prior to eDiary assessments and 24 hours prior to a clinic visit

5.4. Screen Failures

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

5.4.1. Re-screening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Individuals who screen fail due to running out of time in the screening window due to non-medical reasons e.g. for a short notice covid booster vaccine may be rescreened more than once following discussion with the medical monitor. Rescreened participants should be assigned a new participant number. Participants who have tested positive for COVID-19 will not be re-screened.

5.4.2. Re-testing of Clinical Laboratory Values during Screening

If a participant fails any of the laboratory criteria, the test may be repeated once within the screening period. If the participant fails, the laboratory criteria for a second time they will be considered a screen failure.

If a blood sample needs to be repeated due to sample handling problems, breakage or sample integrity, this is not considered a re-testing. Further details regarding the procedure for re-testing may be found in the Study Reference Manual (SRM).

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 product received by the participant as per the study protocol. Study intervention may therefore refer to GSK3858279 or placebo.

Table 3 Study interventions

Product name:	GSK3858279	Diluent/Placebo
Formulation description:	GSK3858279 is formulated in 0.79 mg/mL sodium acetate, 50 mg/mL sorbitol, 0.4 mg/mL polysorbate 20, glacial acetic acid 0.28 mg/mL, water for injection, pH 5.0. GSK3858279 contains no preservative.	Normal Saline (0.9% sodium chloride)
Dosage form:	Solution for injection	Solution for injection
Unit dose level:	50 mg/mL. Each vial has an extractable volume of 3.0 mL (150 mg per vial).	0.9% w/v sodium chloride, placebo level variable.
Route of administration and duration:	IV or SC	IV or SC
Dosing instructions:	IV cohorts 1-5: GSK3858279 will be infused over up to 1 hour. GSK3858279 can be diluted in normal saline prior to administration. SC Cohorts 6 (Part A)[1] and 7 (Part B)[2] The appropriate volume of GSK3858279 will be injected using a syringe at	The appropriate volume of normal saline will be infused (IV) or injected (SC) in the same manner as the corresponding active cohort.

	no more than 1.2 mL per injection.	
Physical description:	The drug product is a brown to yellow solution stored in 5 mL glass vials with a 20 mm rubber stopper and a grey-brown 20 mm Flip-top aluminium overseal.	Commercial presentation
Manufacturer/source of procurement:	Study medication is supplied by GSK.	0.9% w/v sodium chloride is sourced locally by the site.

1) Part A: As a maximum of 4 SC injections will be administered for feasibility reasons, the maximum dose that will be administered to participants weighing >80 kg will be 240 mg.
2) For Part B, all participants are to receive a weekly dose of 240 mg SC (4 x 1.2 mL injections) irrespective of weight.

The doses of GSK3858279 for injection will be prepared at the clinical site by an unblinded pharmacist from the stock solution provided (see Table 3).

6.2. Preparation/Handling/Storage/Accountability

- 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 (ie, 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

At Screening a unique Participant Number (case report form [CRF] number) will be assigned to any participant who has at least one Screening procedure performed, other than informed consent. The unique Participant Number will be used to identify individual participants during the course of the study.

Participants who meet the screening eligibility criteria will be randomised to a treatment group through RAMOS NG. The randomisation is centrally controlled by RAMOS NG. RAMOS NG will confirm the participants CRF number (Participant number) and provide the randomisation number, where:

- A randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other participant in the study.

Part A

Within each cohort, participants will be assigned to either GSK3858279 or placebo in a 3:1 ratio, where the intervention codes are as follows:

Intervention code	**Intervention Description**
A	0.1 mg/kg IV GSK3858279
B	0.3 mg/kg IV GSK3858279
C	1 mg/kg IV GSK3858279
D	3 mg/kg IV GSK3858279
E	10 mg/kg IV GSK3858279
F	SC GSK3858279
P	Placebo

Part B

Participants will be assigned to either GSK3858279 or placebo; where the GSK3858279 dose level to be studied in Part B will be dependent on the Part A data. The randomisation ratio will be 1:1 for GSK3858279: placebo.

Intervention code	**Intervention Description**
G	240 mg SC GSK3858279
P	Placebo

6.3.2. Blinding

This will be a double-blind study with respect to allocation of GSK3858279 or placebo to participants and the following will apply.

- The investigator or treating physician may unblind a participant's intervention assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study intervention is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- The interactive voice response system (IVRS)/ interactive web recognition system (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 participant's 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 treatment 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 CRF, as applicable.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the intervention assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF
- 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 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.
- GSK DEC members may review unblinded safety data from Part A on an as required basis and at the dose escalation meetings, where no-one outside of this committee will be unblinded to the study data. Further details of how this will be managed are included in the DEP.
- Members of the study Interim Data Review Committee (IDRC) and senior GSK leadership may also review unblinded data from Part B at Interim Analyses as described in Section 9.4.5.
- There will be an unblinded site pharmacist to prepare the study intervention; however, they will not have contact with study participants.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- Participants will receive study intervention at the clinical unit directly from the investigator or designee, under medical supervision, via IV or SC route depending on the cohort the participant is enrolled into. 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. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant 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 will be provided with a diary card to record usage of any medications between visits

6.5.1. Permitted Therapies

In Part A, participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) 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.

In Part B, the following medications are permitted if they were used at a stable dose for at least 30 days prior to screening:

- Antidepressant medication including selective Serotonin reuptake inhibitors (SSRI) and Serotonin Noradrenaline reuptake inhibitors (SNRI)
- Nutraceuticals (eg Glucosamine or Chondroitin)
- Aspirin for cardiovascular indications at a maximum dose of 300 mg/day

6.5.2. Rescue Medication (Part B)

In Part B, Paracetamol/Acetaminophen, at doses of ≤3 grams/day, is permitted for use as rescue medication any time during the study except 24 h before a clinical visit. The study site will supply rescue medication.

6.6. Prohibited Medications

The following are prohibited from Day -7 until Day 71. A washout period is required prior to Day -7, consisting of 3 days or 5 half-lives, whichever is longer. Refer to Figure 5.

- All pain medications including anti-neuropathic agents (e.g. Gabapentin and Pregabalin), opioids, NSAIDs, topical analgesics
- Adjunctive therapies

The following are prohibited throughout the entire duration of the study:

- Attenuated live vaccine(s)
- Biologic agents (monoclonal antibodies, therapeutic proteins)
- Antiplatelet or anticoagulant agents
- Immunosuppressants
- Systemic Corticosteroids
- Intra-articular therapy of the index joint

6.7. Dose Modification

Part A: The decision to proceed to the next dose level of GSK3858279 will be made by the DEC. The dose escalation decision will be based on safety, tolerability and preliminary PK data obtained in all participants at that dose level (through 15 days post dose). The actual doses to be administered may be adjusted based on safety, tolerability and preliminary PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose, but will not exceed PK criteria (See Section 4.4 and Section 7.2.3), and the maximum dose administered in this study will not exceed the maximum planned dose of 10 mg/kg. Planned dose levels may also be repeated.

The Principal Investigator and the GSK Medical Monitor will review the following and dosing **will be** halted and progression to the next higher dose level stopped if:

- One (1) or more participants experience a serious adverse event which has a reasonable possibility of being causally related to study drug.
- Two (2) or more participants experience a severe or clinically significant non-serious adverse event (based upon investigator judgment) which has a reasonable possibility of relation to study drug. Three (3) or more participants in a cohort experience the same adverse event of moderate severity which has a reasonable possibility of relation to study drug.

Part B: Please see Dose Adjustment Pharmacokinetic Criteria (Section 7.2.3).

6.8. Intervention after the End of the Study

GSK will not provide treatment after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Study stopping criteria

Recruitment will be halted by the sponsor if any of the following occur in participants receiving GSK3858279:

Part A

- One participant experiences an SAE that is considered to be related to GSK3858279
- One participant experiences a significant clinical or laboratory abnormality that may plausibly relate to GSK3858279 (according to the clinical judgement of the investigator)
- Two participants present with unexpected and clinically significant muco-cutaneous bleeding (according to the clinical judgement of the investigator).

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

Part B

- Two participants experience a SAE that is considered related to GSK3858279. Please also refer to the next Section 8.5 (Adverse Events), Appendix 3 (Adverse Events) and the study-specific Safety Management Plan.
- Two 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 GSK3858279.

Recruitment may be resumed after appropriate positive 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. Discontinuation of Study Intervention

Not applicable for Part A.

In Part B, a participant will be permanently withdrawn from study treatment if any of the following symptoms or abnormalities occur, and an investigation will be carried out as described below. After withdrawal of treatment (under these conditions), where possible participants should complete the Early Withdrawal visit and be followed up for safety monitoring.

Study medications will be discontinued, and the participant withdrawn from the study in the event of any of the following:

- A serious infection (including COVID-19)
- Pregnancy
- Severe or serious hypersensitivity reactions, including anaphylaxis
- If the liver chemistry stopping criteria (Section 7.2.1) or QTc stopping criteria (Section 7.2.2) are met.
- Other serious or severe adverse events, at the discretion of the Investigator, after consultation with the GSK Medical Monitor.

Clinically significant deterioration of index knee pain or requiring recurrent rescue medication beyond the level permitted, at the discretion of the investigator, after consultation with the GSK Medical Monitor.

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.

The Liver Safety Required Actions and Follow up Assessments Section and, Liver Stopping Event algorithm can be found in Appendix 6a and Appendix 6b, respectively respectively.

7.2.2. QTc Stopping Criteria

The QTc should be based on a single (initial reading in Part A) or the average of triplicate (Part B) ECG readings obtained over a brief (e.g., 5-10 minute) recording period. See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

A participant who meets the below QTc stopping criteria (based on the average of triplicate ECG readings) will be withdrawn from study intervention:

QTc >500 msec OR Uncorrected QT >600 msec

- For trial eligibility and discontinuation, ideally the same QT correction formula will be used for *all* participants within a single trial. However, GSK does recognize that because multiple sites from different countries may participate in a single trial, this may not always be possible since QT correction formulae pre-programmed by different manufacturers within ECG machines tend to vary. In these situations, the same QT correction formula must be used throughout the trial for an individual participant

7.2.3. Dose Adjustment Pharmacokinetic Criteria

The following criteria will apply.

7.2.4. Temporary Discontinuation

Not applicable for Part A.

For Part B, if a participant experiences a clinically significant AE that the investigator believes may be possibly, probably or definitely related to investigational product (IP) and could potentially be exacerbated by the next dose, the investigator may delay IP dosing by withholding one dose and should contact the Medical Monitor.

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, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- At the time of study discontinuation, the participant should undergo the assessments for early withdrawal shown in the SOA.

7.4. Lost to Follow Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

After providing informed consent, participants will undergo screening assessments. After a successful Screening Period of up to 28 days (for Part A) during which screening assessments will be performed (screening assessments may be carried out over multiple days), participants will be admitted to the clinical unit on the day prior to dosing. On Day 1 they will receive a single IV or single SC dose of GSK3858279 or placebo then remain in house under supervision until discharged on Day 3. Participants will then return for outpatient visits and a follow up visit. The number of visits and the duration of the follow up period will depend on the dose level that the participant received. Details of the visits and follow up duration can be seen in the Treatment Groups and Duration section. There is a degree of flexibility around certain visits to facilitate scheduling. A visits schematic is included in Figure 1.

For Part B the maximum Screening Period will be up to 42 days (screening assessments may be carried out on multiple days) refer to Section 4.1.1 and Figure 5 for SC treatment frequency and out-patient visits.

- Study procedures and their timing are summarized in the SoA (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 (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.1.1. Physical Examinations

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

8.1.2. Vital Signs

- Temperature, pulse rate, and blood pressure will be assessed following the sites local procedure.
- Blood pressure and pulse measurements will be assessed in a 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 (eg, 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 recorded on the CRF.

8.1.3. Electrocardiograms

- Continuous cardiac telemetry will be performed as per the SoA (Section 1.3). Full disclosures will be reviewed in detail and the review maintained as part of the participant's source documents.

- Triplicate or single 12-lead ECG will be obtained as outlined in the SoA (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 time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 10 minutes.
- ECGs may be generated from telemetry.

8.1.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3). for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests, with values considered clinically significantly abnormal during participation in the study 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.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.1.5. 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.

8.1.6. 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.

8.2. Pharmacokinetics

8.2.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analysis of GSK3858279 will be collected at the time points indicated in SoA (Section 1.3). The actual date and time of each 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. Blood samples of approximately 3 mL for PK analysis of GSK3858279 will be collected. 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 PK days. The actual date and time of each blood sample collection will be recorded.

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

Samples may be retained for a maximum of 15 years after the last participant completes the study.

8.2.2. Pharmacokinetic Sample Analysis

Serum CCI analysis will be performed under the control of In Vitro/In Vivo Technologies/ Bioanalysis Immunogenicity and Biomarkers (IVIVT/BIB), the details of which will be included in the SRM and CLW as appropriate. Concentrations of GSK3858279 will be determined in serum samples using the currently approved bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g. SRM, CLW) and raw data will be archived in the GSK R&D GLP archives. Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.3. Efficacy Assessments

Efficacy assessments will be conducted in Part B of the study only.

8.3.1. Patient Reported Outcomes

All patient reported outcomes (PROs) should be administered before any laboratory assessments and other procedures or consultations to avoid influencing the participants' perception of OA pain.

8.3.2. Daily pain scores

Participants will record pain scores daily (evening time) in a digital tool for the 7 consecutive days preceding dosing (during screening) and then daily from Day 1 to Day 84 (12 weeks). They will assess, over the past 24 hours, both:

- average knee pain intensity in index knee
- worst knee pain intensity in index knee

using the NRS, scoring pain on an 11-point scale (0-10), with 0= [redacted] and 10= [redacted] [redacted] Participants will be instructed to complete the pain NRS [redacted] mately the same time each day. Participants will also record any rescue paracetamol/acetaminophen for knee OA over the past 24 h on a digital tool.

8.3.3. WOMAC osteoarthritis index

WOMAC Index 3.1 will be completed by participants on paper questionnaires at time points specified in the SOA (Bellamy, 1988). The questionnaire covers pain, stiffness and function related to osteoarthritis in the index knee over the past 7 days. Participants will respond to each question using an 11-point NRS (0-10), with 0=no [redacted] They will be required to take at least 5 minutes to complete the questionnaire.

[redacted]

8.3.7. Joint X-ray

X-ray of the knee will be performed at Screening for eligibility and the radiographs are to be read centrally by the imaging CRO in order to minimise variability of the read. The knee radiographs will be evaluated for exclusion criteria (Section 5.2) and eligibility to confirm a Kellgren Lawrence score ≥2 (see inclusion criterium Section 5.1). Refer to the SRM for details.

8.4. Pharmacodynamics/Biomarkers

Blood samples (Parts A and B) and CCI [redacted] will be collected from participants in this study to investigate target engagement and CCI [redacted] CCI [redacted] associated with pharmacodynamic effects.

Any samples collected during this study may be used to evaluate novel biomarkers related to the pathology of OA or to identify factors that influence the clinical responses and outcomes to dosing with GSK3858279. This approach may also be extended to include the identification of biomarkers associated with AEs.

The timing of sample collections may be adjusted based on emerging PK data or other new information from 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.

Samples may be retained for a maximum of 15 years after the last participant completes the study.

8.4.1. Target Engagement

Serum samples will be collected for the evaluation of the free and total concentrations of CCL17. CCL17 can be detected in circulation and is the biological target for GSK3858279. The intention is to examine the correlation between free and total CCL17 and the effect of administration of GSK3858279 on the free levels of CCL17 in the circulation.

CCI [redacted]

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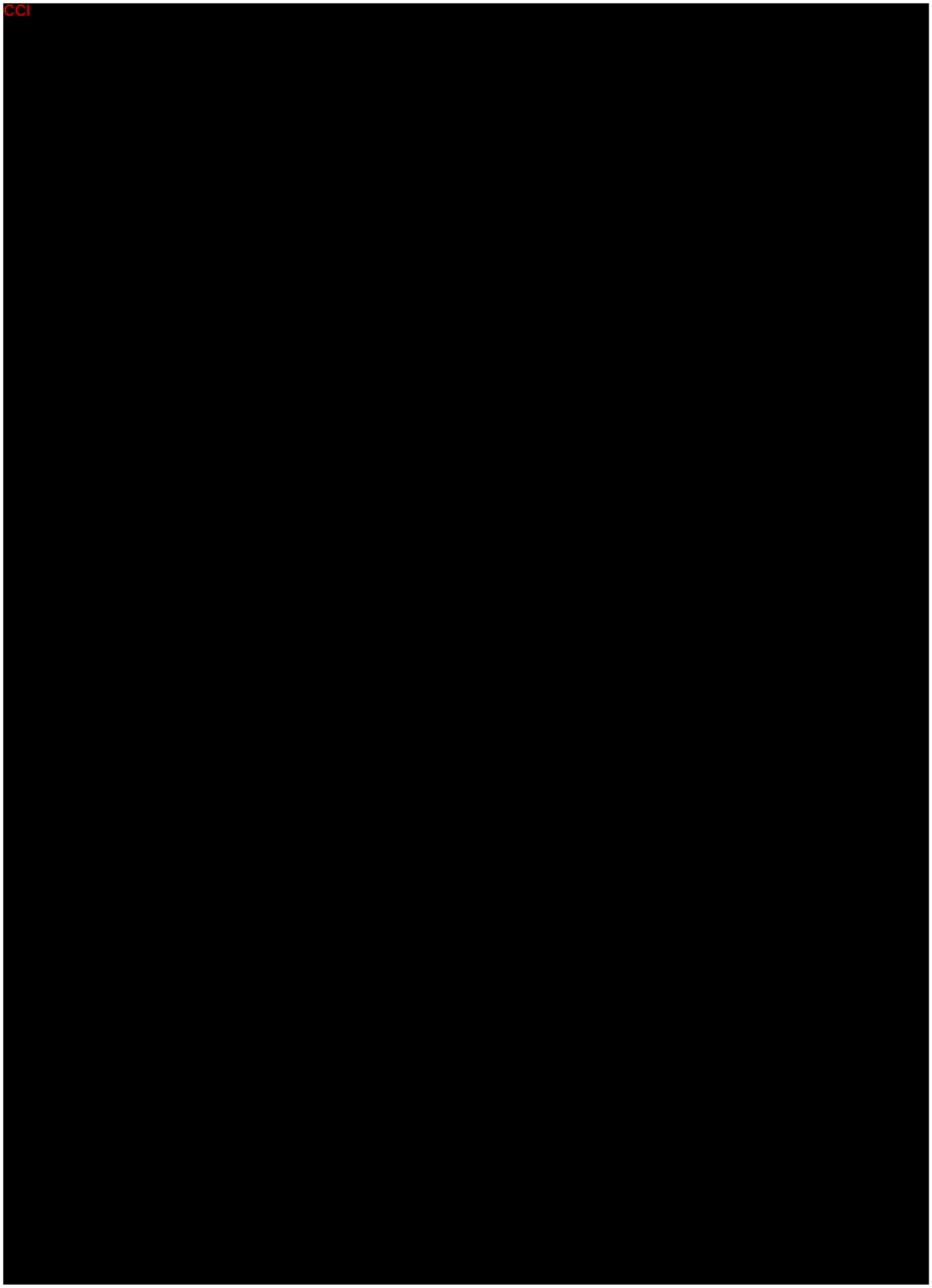

CCI [redacted]

CCI [redacted]

8.5. Immunogenicity Assessments

Serum samples will be collected from all treated participants at pre-dose and various time points post-dosing. The washout samples will be collected at the follow-up visit to minimise interference of circulating drug in the antibody assessments, see SoA (Section 1.3.5). Testing will be performed using the typical tiered approach involving screening, confirmation and titration assays [EMEA, 2017; FDA, 2014], performed by IVIVT, GSK. If sera contain potential anti-GSK3858279 antibodies, they will be confirmed by immune-competition using excess drug, followed by a titration assay.

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

8.6. Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

Consult the Safety Management Plan (SMP: a formal version-controlled document). The SMP describes and serves to *ensure* GSK's overall accountability by maximizing transparency on individual roles and responsibilities for initial and follow up of safety reporting and of the onward reporting responsibilities to regulatory agencies, ethics committees and investigators.

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

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

- All SAEs will be collected from the start of study intervention until the follow-up visit at the time points 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 dose of study intervention until the follow-up visit (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF (not the AE section).
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 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 AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.6.2. Method of Detecting AEs and SAEs

- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.
- Participants will be provided with a diary card to collect any changes in health between clinic visits.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.6.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3.

8.6.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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 (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.6.5. Cardiovascular and Death Events – Part B only

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV medical dictionary for regulatory activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

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

8.6.6. Pregnancy

- The Sponsor will make an effort to collect pregnancy details in female partners of male participants after the dose of study intervention and until 28 weeks after the dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.7. 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.

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[redacted]

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Hypotheses

Part A: As the primary objective of the study is safety, there are no formal hypotheses to be evaluated. An assessment of dose proportionality will be conducted for selected pharmacokinetic endpoints (*i.e.* Cmax, and area under the serum concentration-time curve from zero to time t [AUC(0-t)] or to infinity [AUC(0-∞]) following single IV dose.

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[redacted]

Part B: A comparison between GSK3858279 and Placebo will be made on the pain numerical rating scale. An assessment of the probability of success will also be made comparing GSK3858279 to placebo with respect to the key pain endpoints.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

In Part A, at each dose level studied there will be six participants randomised to each of the GSK3858279 treatment groups. For each dose level, there will also be two participants receiving placebo. The sample size is based on feasibility and will be conducted at one centre.

The primary objective of the study is safety, where the number of safety events would be of interest, for example the number who experience a particular adverse event. At each dose level six participants will receive GSK3858279. If 0/6 of a particular safety event in the GSK3858279 group is observed, using a Bayesian approach to determine the credible interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe 1 safety event in 6 then the posterior distribution would be Beta (2, 6), where we can be 95% certain that the true probability of the safety event lies between 0.04 and 0.58.

A key secondary objective for the study is to determine the pharmacokinetics of the GSK3858279. However, there have been no studies conducted to date within an appropriate population to assess pharmacokinetic precision estimates with six participants per treatment group.

In Part B, approximately 50 participants (minimum of 20 to a maximum of 80) will be randomised in a 1:1 ratio to receive GSK3858279 or placebo. A positive conclusion will be declared if, given the data, there is at least 90% probability that the difference vs placebo is better than 0. A negative conclusion will be declared if, given the data, there is at least 85% probability that the difference vs placebo is worse than -1.0.

For the primary comparison, assuming a change from baseline in participant's assessment of pain score of -1.5 on placebo, and a standard deviation (SD) of 1.8 (Study NCT02683785 and Lane, 2010), with 50 participants, if the true treatment difference is 0 between the two treatments 82% of trials will be declared negative. If the true treatment difference is 1 then 75% of trials will be declared positive. Under these assumptions, the least significant difference between GSK3858279 and placebo would be -0.85.

If the estimated SD during the trial differs from 1.8, then the sample size may be decreased or increased up to a maximum of 80 total participants to ensure robust conclusions can be drawn.

9.2.2. Sample Size Sensitivity

Part A

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates. If the number of participants who completed each active dose reduces, then the true incidence rates of safety events that could not be ruled out would change. These changes are outlined below:

N Completing Cohort	Number of a particular safety event observed with GSK3858279	Upper limit of exact 95%CI indicating that a true incidence rate of x% could not be ruled out
6	2	71%
	3	82%
5	0	46%
	1	64%
	2	78%
4	0	52%
	1	72%
	2	85%

Part B

A sample size sensitivity analysis has been conducted on the primary endpoint in Part B, to investigate a decrease or an increase in SD, current design and prediction highlighted:

N per Arm	SD	Proportion of trials correctly deemed negative if true treatment difference is 0	Proportion of trials correctly deemed negative if true treatment difference is -1	Least Significant Difference
14	1.4	80%	73%	-0.87
	1.8	67%	57%	-1.12
	2	61%	52%	-1.24
	2.2	57%	47%	-1.37
	2.4	53%	43%	-1.49
22	1.4	91%	86%	-0.69
	1.8	79%	71%	-0.91
	2	73%	65%	-1.00
	2.2	68%	59%	-1.11
	2.4	64%	54%	-1.21
25	1.4	93%	89%	-0.65
	1.8	82%	75%	-0.85
	2	77%	69%	-0.94
	2.2	72%	63%	-1.04
	2.4	67%	58%	-1.13
32	1.4	97%	94%	-0.58
	1.8	88%	83%	-0.75
	2	83%	76%	-0.83
	2.2	78%	70%	-0.91

N per Arm	SD	Proportion of trials correctly deemed negative if true treatment difference is 0	Proportion of trials correctly deemed negative if true treatment difference is -1	Least Significant Difference
	2.4	74%	65%	-1.00
40	1.4	98%	97%	-0.51
	1.8	90%	85%	-0.67
	2	88%	83%	-0.74
	2.2	84%	77%	-0.82
	2.4	80%	72%	-0.89

A sample size of up to 14 per arm (28 total) could be used to maintain the acceptable operating characteristics SD of up to 1.4, and thus provide similar operating characteristics as a trial of 50 participants with and SD of 1.8.

A sample size of up to 40 per arm (80 total) could be used to maintain the acceptable operating characteristics SD of up to 2.4, and thus provide similar operating characteristics as a trial of 50 participants with and SD of 1.8.

If the SD is 1.8 then a total of 22 (44 total) per arm completing Week 8 would still provide acceptable operating characteristics.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined, additional analyses populations may be defined in the Reporting and Analyses Plan:

Population	Description
Safety	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant received.
Intent-to-Treat (ITT)	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant was randomized to. • Any participants who receives a treatment randomization number will be considered to have been randomized.
Pharmacokinetic (PK)	• All participants in the Safety population who had at least 1 non-missing serum PK assessment. • This population will be based on the treatment the participant received. • Note: Non-quantifiable [NQ] values will be considered as non-missing values
Per Protocol	• All participants in the ITT population who comply with the protocol. • Protocol deviations that would exclude participants from the PP population are defined in reporting and analyses plan.
Fully treated	• All participants in the Safety population who received at least 80% of planned study treatment. • This population will be identified by review of protocol deviations

9.4. Statistical Analyses

Parts A and B will be reported separately in the outputs.

9.4.1. Efficacy Analyses

All efficacy analyses will be performed on the ITT population.

Endpoint	Statistical Analysis Methods
Primary	The pain scores will be listed for each participant and intervention and summarized descriptively by intervention. A Bayesian repeated measures model using a non-informative prior will be fitted to the pain change from baseline data and probabilities of success will be determined and presented at each timepoint.
Exploratory	Will be described in the reporting and analysis plan

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library standards.

9.4.3. Pharmacokinetics Analyses

All PK analyses will be performed on the Pharmacokinetic Population.

Endpoint	Statistical Analysis Methods
CCI [redacted]	

Endpoint	Statistical Analysis Methods
	CCI

CCI

9.4.5. Interim Analyses

Part A: No formal interim statistical analyses are planned. However, dose escalation meetings will occur at a relevant timepoint after each dose level; including between Parts A and B.

The decision to proceed to the next cohort, and next dose strength to be studied, will be made by the DEC based on assessment of safety and serum GSK3858279 pharmacokinetic data obtained in all participants at the prior dose level. Individual safety data (AEs, laboratory safety tests, ECGs and vital signs) will be reviewed. In addition, un-blinded preliminary PD data may be reviewed by the DEC during the study; where the GSK biology lead will join the DEC in these discussions. Once sufficient safety, PK and target engagement data is collected from the top IV dose and SC cohorts, a data review will take place and a decision to proceed with Part B of the study may be made. Further details are included in the DEP.

Unblinded data from Part A may be reported out in full following the last subject last visit in this part of the study and prior to the conclusion of Part B.

Part B: An interim analysis will occur once approximately 20 participants have completed the Week 4 assessment. A second interim analysis and an unblinded sample size re-estimation may occur prior to enrolling the 50th participant, where the sample size could be decreased to a minimum of 20 or increased to a maximum of 80 participants.

Additional interim analyses may occur in order to inform internal decision making. Full details of all interim analyses will be prospectively outlined in the interim analyses charter.

At the interim analyses, treatment group level, efficacy, safety, PK, TE, rescue medication and ADA data may be reviewed by a list of people included in the IA charter, including the Project Leader and Independent Internal Review Board and internal governance boards as required. Individual participant data may be reviewed at the request of the project leader, but subject identification numbers will be removed to maintain the blind.

If there are interactions with regulatory agencies, any interim data presented will be at the treatment group level unless individual participant data is requested. Unblinded safety information may be presented at an individual level

Dependent on the results observed, the study could be stopped for futility, based on pre-specified futility criteria defined in the IA charter, or via the sample size re-estimation which may result in the sample size being decreased or increased.

The Reporting and Analysis Plan will describe the planned statistical analyses performed at the interim analyses in greater detail.

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 International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (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 to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study 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 the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

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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.
- 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

Oversight of safety for Part A: The DEC will make the decision to proceed to the next dose level of GSK3858279 at the end of each cohort; along with assessing the interim analysis data for Part B of the study. For details of the information to be considered as part of this decision-making process see the DEP.

Safety and PK stopping criteria will be strictly applied. Details of these criteria can be found in Section 7.2. There will be an open and closed part to the dose escalation meeting. At the beginning of the meeting blinded data will be discussed in an open forum with the investigator in attendance. If required, the data will then be reviewed in an unblinded fashion by the unblinded members of the DEC. These unblinded members include the Medical Monitor, GSK SMG representative, GSK statistician and GSK pharmacokineticist. A DEP will be written outlining in detail how the study team will ensure data integrity used in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions, as well as outlining the responsibilities of the investigators and site staff for reporting safety data, participation during dose escalation meetings, and confirmation that the data used for dose escalation are accurate and complete.

Oversight of safety for Part B will be provided by a sponsor SRT. The SRT will conduct in-stream review of blinded safety data including AE, SAEs, vital signs and laboratory data at appropriate intervals during the study. The membership of the SRT will include the GSK Medical Monitor, GSK Statistician and a GSK Safety and Medical Governance representative or appropriate designees.

The SRT may decide to alter the study conduct at any time to ensure participant safety and any such changes to study conduct for safety reasons will be promptly communicated to the appropriate Regulatory Authorities and IRB/IEC. Additional detail regarding the composition and actions of the SRT will be included in the SRT charter.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participant, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the 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 trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in a study specific source document agreement.

10.1.9. Study and Site Closure

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

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

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

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

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 4 will be performed by the local laboratory in Part A and the central laboratory in Part B. Alcohol, Tobacco screens and COVID-19 tests will be performed as per standard local practice in Part B.
- 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 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1,2,3,4]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	[2]Cardiac troponin T [3]NT-proBNP
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination and laboratory quantification of proteinuria (if blood or protein is abnormal on dipstick) • Part B: Alcohol			
Breath	• Part A: Alcohol (breathalyzer)			

Laboratory Assessments	Parameters
Combined throat and nasopharyngeal swab	• COVID-19 (SARS-CoV2) (see SRM for further details)
Other Screening Tests	**Blood (serum)** • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serology (TB test, HIV antibody, HBsAg, HBcAb and hepatitis C virus antibody) • QuantiFERON test • Complement protein C3 and C4 **Urine** • Urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines. • Urine albumin-creatinine ratio (UACR)

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 7.2.1 and Appendix 6a and Appendix 6b All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Troponin T using high sensitivity test.
3. NT-proBNP (N-terminal pro B-type natriuretic peptide) at -Screening and Day 57 visit only.

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.

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

Consult the Safety Management Plan (SMP: a formal version-controlled document). The SMP describes and serves to *ensure* GSK's overall accountability by maximizing transparency on individual roles and responsibilities for initial and follow up of safety reporting and of the onward reporting responsibilities to regulatory agencies, ethics committees and investigators.

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 Meeting the AE Definition

- 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 conditions 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 drug-drug 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.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

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

A SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
○ Results in death
○ 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.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils 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.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

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

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

10.3.3. Definition of Cardiovascular Events – Part B only

Cardiovascular Events (CV) Definition:

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

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

10.3.4. 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 (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study 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 completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- 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 the SRM

SAE Reporting to GSK via Paper CRF

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

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing 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 not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), 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.

- 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.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Males must use the male condom and should be advised of the benefit for a female partner to use a highly effective method of contraception as outlined in Section 10.4.2.

10.4.2. Contraception guidance for female partners of males who are in the study[a]:

• **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*
b. should be consistent with local regulations 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 and female partners of study male participants advised of the benefit to use hormonal contraception in addition 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), spermicides 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 foetal status (presence or absence of anomalies) or indication for procedure.


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

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

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) OR INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention (Part B only)
• Report the event to GSK within 24 hours
• Complete the liver event case report form (CRF), and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver chemistry event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
• Do not restart or rechallenge participant with study intervention (Part B only)
MONITORING:
<u>If</u> ALT≥3xULN AND <u>bilirubin ≥</u> 2xULN <u>or INR</u> >1.5<u>:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, as soon as possible, and at least within 7 days[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 case report form (CRF)
• Record use of concomitant medications on the concomitant medications CRF page including acetaminophen, herbal remedies, other over the counter medications.</td></tr>
</table>

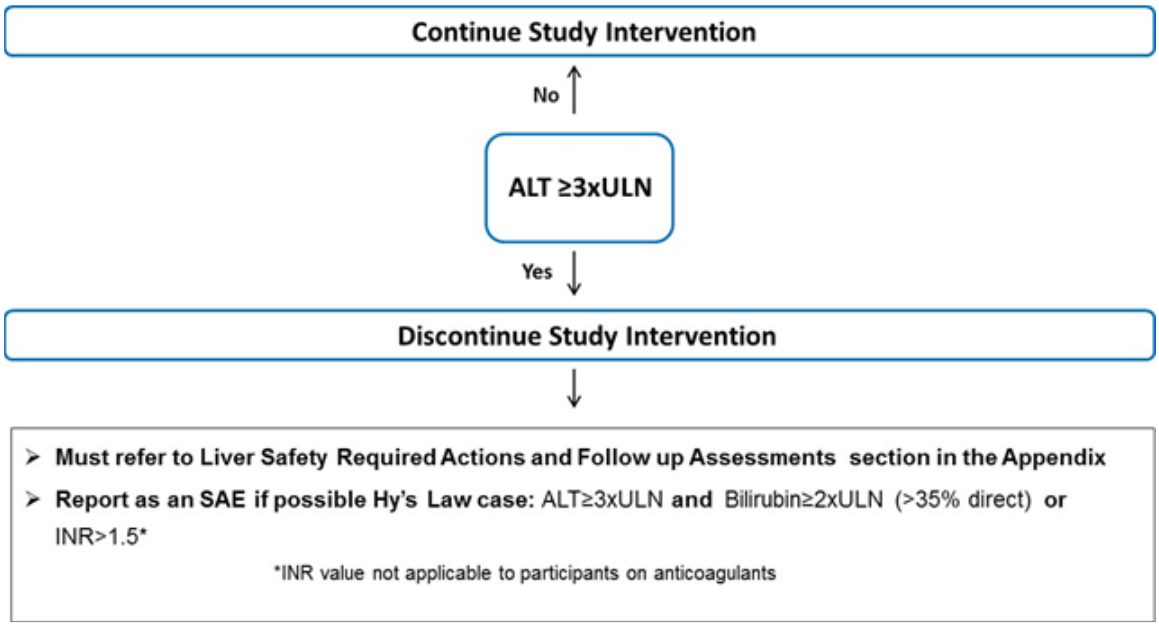
• A specialist or hepatology consultation is recommended **<u>If</u> ALT≥3xULN <u>AND bilirubin</u> < 2xULN <u>and INR</u> ≤1.5<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Record alcohol use on the liver event alcohol intake CRF page **<u>If</u> ALT≥3xULN AND <u>bilirubin ≥</u> 2xULN <u>or INR</u> >1.5<u>:</u>** • 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 participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to 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, do not obtain a PK sample. If a liver event occurs following dose on Day 50 and a PK sample cannot be collected in the time period indicated above, a PK sample should be taken within 84 days post-dose. Instructions for sample handling and shipping are in the SRM

References

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

10.7. Appendix 6b: Healthy Volunteer and Patient Phase I Studies Liver Stopping Event Algorithm



Refer to Appendix 6a for required Liver Safety Actions and Follow up Assessments

10.8. Appendix 7: Efficacy Assessments

10.8.1. Average Pain NRS

Average Pain Severity (Pain NRS)

Please rate your knee pain by selecting the one number that best describes your **knee pain on average** in the **last 24 hours:**

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

10.8.2. Worst Pain NRS

Worst Pain Severity (Pain NRS)

Please rate your knee pain by selecting the one number that best describes your **knee pain at its worst** in the **last 24 hours:**

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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10.9. Appendix 8: Abbreviations and Trademarks

Abbreviations

µg/mL	Micrograms per millilitre
µg*day/mL	Micrograms day per millilitre
ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
AUC(0-t)	Area under the serum concentration-time curve from zero to time t
AUC(0-∞)	Area under the serum concentration-time curve from zero to infinity
AUC(0-tau)	Area under the serum concentration-time curve over the dosing interval
BCG	Bacillus Calmette-Guerin
BL	Baseline
BMI	Body Mass Index
BNP	N-terminal pro B-type natriuretic peptide
BUN	Blood urea nitrogen
CFR	Code of Federal Regulation
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
Cmax	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus strain 19
CPPD	Calcium pyrophosphate dihydrate
CRF	Case Report Form
CSR	Clinical study report
CV	Cardiovascular
DEC	Dose Escalation Committee
DEP	Dose Escalation Plan
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic diary
FTIH	First time in human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GSK	GlaxoSmithKline

h	Hours
HBsAg	Hepatitis B Surface Antigen positive
HBcAb	Hepatitis B core antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDRC	Interim Data Review Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG2	Immunoglobulin G2
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive Web Recognition System
Kdeg	Degradation rate
KL	Kellgren and Lawrence
kg	Kilogram
kg/m^2	Kilograms per square meter
LLQ	Lower Limit of Quantification
mAb	Monoclonal Antibody
MABEL	Minimum Anticipated Biological Effect Level
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mg/day	Milligrams per day
mg/kg	Milligrams per kilogram
mg/kg/week	Milligrams per kilogram per week
MIA	Monosodium iodoacetate
min	Minutes
mL	Millilitre
mm	Millimetre
MSDS	Material Safety Data Sheet
msec	Millisecond
NGF	Nerve Growth Factor
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis

PD	Pharmacodynamics
pH	Potential Hydrogen
PK	Pharmacokinetics
CCI [redacted]	
PGx	Pharmacogenetics
PRO	Patient reported outcome
CCI [redacted]	
PTS	Platform Technology and Science
QTc	Corrected QT
QTcB	Corrected QT using Bazett's formula
QTcF	Corrected QT using Fridericia's formula
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan
RBC	Red Blood cell count
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome– Coronavirus-2
SC	Subcutaneous
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMG	Safety and Medical Governance
SMP	Safety Management Plan
SNRI	Serotonin Noradrenaline reuptake inhibitors
SoA	Schedule of Activities
SRM	Study Reference Manual
SRT	Safety Review Team
SSRI	Serotonic specific reuptake inhibitors
SUSAR	Suspected unexpected serious adverse reactions
TARC	Thymus and activation regulated chemokine
TB	*Mycobacterium tuberculosis*
TDAR	T-cell Dependent Antibody Response
TE	Target engagement
tmax	Time to Cmax
TMDD	Target Mediated Drug Disposition
TST	Tuberculin skin test
t½	Apparent terminal phase half-life
ULN	Upper limit of normal
Vss	Volume of distribution
WBC	Whole Blood Count
WOMAC	Western Ontario & McMaster Universities Osteoarthritis index
WNCP	Women Of Non Childbearing Potential
WOCBP	Women Of Childbearing Potential
w/v	Weight by volume

Trademark Information

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10.10. Appendix 9: Protocol Amendment History

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

10.10.1. Amendment 1 10-APR-2018

Overall Rationale for the Amendment: This is an amendment in response to MHRA feedback. Correction of Cmax value at the highest predicted exposure after 10mg/kg IV administration and addition of dose stopping pharmacokinetic criteria.

Section # and Name	Description of Change	Brief Rationale
Section 4.3 Scientific Rationale for Study Design	CCI [redacted]	
Section 4.4 Justification of Dose		
Section 7.2.3 Dose Stopping Pharmacokinetic Criteria	Added paragraph on Dose Stopping Pharmacokinetic Criteria	For clarity Section 7.2.3 was added

10.10.2. Amendment 2 21-NOV-2018

Overall Rationale for the Amendment: To address the points raised by both the Paul-Ehrlich-Institute (P-E-I letter dated 28-SEP-20018) and the UK Central Ethics Committee (letter dated 12-SEP-2018): principally to clarify the conduct of safety management. Incorporation of non-substantial changes (previously captured in File Notes (details below).

Section # and Name	Description of Change	Brief Rationale
Section 8.5 Adverse Events and Appendix 3	Reference to the study specific Safety Management Plan (SMP) has been included.	PEI's request to define, within the body of the protocol, the processes for prompt communication of SAEs/SUSARs and rapid implementation of corrective and preventive actions between Sponsor, all study sites and investigators.
Table 1.3.1 Schedule of Assessments (Screening)	Addition of Tb-Screening (QuantiFERON test) and FSH and estradiol (in women of non-childbearing potential).	PEI's request to include the screening assessments in the Schedule of Assessments.
Section 7.1 Study stopping criteria	Removal of duplication of "serious." Second bullet modified: "One patient experiences a "significant" clinical or laboratory abnormalilty.	CCI Recruitment will be halted by the sponsor (and may be resumed after appropriate positive review of safety findings and following approval from the regulatory agencies and ethics committees to restart. If deemed appropriate the Informed Consent may be revised.
Figure 2, Figure 3 and Figure 4 and Schedule of Assessments	Weekly (7-day) visit arrangement corrected from Days 112 and 140 to Days 113 and 141, respectively.	Corrected to ensure consistency in scheduling, data collection, analysis and reporting (File Note 4-OCT- 2018).
Section 4.1 and Figure 1	Removal of the interdependency of executing Cohort 7 (single intravenous dose in osteoarthritis patients, Part B) immediately following Cohort 6 (single subcutaneous dose in healthy subjects, Part A).	It is logical to execute Cohort 7 (single intravenous dose in osteoarthritis patients, Part B) following the review of the safety and tolerability of a single intravenous dose administered to healthy subjects in Cohort 5 (Part A).

Section # and Name	Description of Change	Brief Rationale
Figure 1	Removal of the interdependency of executing Cohort 6 (subcutaneous dosing) immediately after Cohort 3 (intravenous dosing).	Cohort 6 (subcutaneous dosing) is not required to run in parallel with Cohorts 4 or 5 and does not inform the decision to progress to Part B which is an intravenous dosing cohort. Therefore, the interdependency has been removed (File Note 3-OCT-2018).
Section 1.3.4 Schedule of Activities	Introduced New Schedule of Activities (Table 1.3.4) for Cohorts 4 – 6 to move the induction blister forward from Days 42/43 to Days 28/29.	PK exposure (observed in Cohort 3) was lower than anticipated so the induction blister was no longer optimally placed for subsequent Cohorts 4 – 6 (File Note 3-OCT-2018).
Section 1.3.4 Schedule of Activities	Correct Side Note for Cohort 6 subcutaneous: to "[2] Cohort 6 Day 1 Vital Signs at Pre-Dose and 1 hour post injection."	Time points for safety evaluation across a 2 hour infusion need to be adjusted for subcutaneous injection (File Note 9-MAY 2018).
Section 1.3.4 Schedule of Activities	Correct Side Note for Cohort 6 subcutaneous: "[2] Cohort 6 Day 1 ECG at Pre-Dose and 1 hour post injection."	Time points for safety evaluation across a 2 hour infusion need to be adjusted for subcutaneous injection (File Note 9-MAY 2018).
Section 1.3.4 Schedule of Activities	Correct Side Note to "final follow-up visit for 1 and 3 mg/kg IV cohorts."	Incorrect dose level used (File Note 3-APR-2018).
Section 1.3.2 Schedule of Activities	Remove the requirement for immune phenotyping of circulating cells.	Immune cell phenotyping in blood is only required for comparison with immune cells in blister fluid (File Note 3-APR-2018).

10.10.3. Amendment 3 18-JUL-2019

Overall Rationale for the Amendment: To adjust the design of Part B from a single intravenous dose to repeat weekly subcutaneous injections over a period of 8 weeks to provide adequate exposure to test the effect on pain in participants with OA of the knee.

Areas of the protocol impacted are: Dose regimen; Treatment Period; Follow-Up Period; Safety Review; Safety Mitigation and Monitoring; Participant Numbers and Interim Analysis; Individual Participant and Study Stopping Rules.

Other areas adjusted are: Patient Population; Patient Global Assessment of Disease Activity, Rescue and Prohibited Medications; PainDETECT; Participant Feedback Questionnaire.

Minor changes and corrections are made throughout to provide refinement and clarification.

MAIN Section # and Name	Description of Change	Brief Rationale
Section 4.4 Justification for Dose	Dose regimen: from a single intravenous dose (two dose levels) to repeat weekly subcutaneous injection of 240 mg (4 injections).	During dose escalation of Part A, a review of pharmacokinetic (PK) and target engagement (TE) data, indicated a much faster clearance of GSK3858279 than was originally predicted. Repeat weekly subcutaneous (SC) dosing is required to provide adequate exposure to test the potential to effect pain in participants with OA of the knee.
Section 3 Objectives and Endpoints	Adjusted the primary objective of Part B for assessment of efficacy following repeat dosing Included rescue medication as a component of the efficacy endpoint.	Both safety and efficacy are evaluated. Rescue medication is a component of the efficacy endpoint.
Section 4.1.1 Treatment Groups and Duration	Treatment Period: from a single dose to 8 weeks of treatment	The secondary objective/endpoint (change from baseline in average weekly Daily Pain NRS) was set at 8 weeks to provide confidence of a clinically meaningful treatment effect *vs* placebo. *Two additional visits* (Day 36 and Day 50) are introduced into the schedule (dosing days). *Day 2 is replaced by Day 4* to optimize pharmacokinetic sampling.
Section 4.1.1 Treatment Groups and Duration	CCI [redacted]	

MAIN Section # and Name	Description of Change	Brief Rationale
	CCI [redacted]	
Section 4.1 Overall Design	Part B Safety review (8 participants): Close in stream monitoring of safety (AEs, clinical laboratory, vital signs and cardiac monitoring) PK and ADAs for the first 8 participants (4 randomized to active treatment) with a detailed review when the 8th participant reaches Day 29.	A review of safety, PK and ADAs will be conducted in a small number of participants following repeat dosing.
Section 4.2 Number of Participants	Part B Participant Numbers:are increased *from* 15 or 20 (one or two single dose levels, respectively) *to* approximately 50 participants will be randomised to receive either repeat doses of GSK3858279 or placebo in a 1:1 ratio.	50 participants are sufficient to investigate efficacy of GSK3858279 with respect to changes in pain versus placebo at Week 8 based on the assumptions listed in Section 9.2. For the secondary comparison (assuming a change from baseline in participant's assessment of pain score of -1.5 on placebo, and a SD of 1.8, the least significant difference between GSK3858279 and placebo would be -0.85.
Section 9 Statistical Considerations Section 9.4.5 Interim Analyses	Section 9 has been adjusted. Part B Interim Analysis: When 20 participants have completed the end of Week 4 assessment.	Alteration of the study design has resulted in adjusted statistical considerations. For futility. A review of PK, TE and ADA will also be conducted. A blinded sample size re-estimation may also occur prior to enrolling the final

MAIN Section # and Name	Description of Change	Brief Rationale
		participant, where the sample size may also be increased to a maximum of 80 participants (if the expected SD is greater than 1.8 or in the case of high dropout). If the sample size is increased a second interim analysis may occur, the timing and size of which will be determined during the sample size re-estimation.
Section 7. Discontinuation of Study Intervention and Participant Discontinuation / Withdrawal. Section 7.1 Study Stopping Criteria Section 7.2 Discontinuation of Study Intervention Section 7.2.1 Liver Chemistry Stopping Criteria Section 7.2.3 Dose Adjustment Pharmacokinetic Criteria Section 7.2.4 Temporary Discontinuation Section 7.5 Participant and Study Completion	Introduction of Section 7 New Text to set out the study rules accordingly for the adjustment from a single to repeat dose regimen. Study Stopping Criteria: Adjusted from *one* to *two* participants. New Text New Text New Text New Text New Text	Individual participant monitoring and withdrawal rules, and study stopping rules are inherent of a repeat dose study design. The study stopping criteria for the Part A FTIH healthy volunteer are adjusted for Part B Osteoarthritis patient study (phase Ib) in light of the satisfactory *blinded* safety profile in Part A (no SAE in 47 subjects,) and to take into account the increased cohort size and study duration.
Section 5.1 Inclusion Criteria	Replaced “body weight 50 -100 kg” with “BMI 19 – 39 kg/m^2” Introduced: History of insufficient pain relief from, or inability to tolerate, or contraindication to, oral NSAIDs. Introduced: X-ray at Screening.	Given the likely maturity of the intended study population, BMI was considered a better means of defining such a population. The patient population was updated to focus on those with significant unmet medical need i.e. unresponsive to NSAIDs Additional requirement for an X-ray (objective measure) of

MAIN Section # and Name	Description of Change	Brief Rationale
		the index knee to confirm Osteoarthritis using a Kellgren and Lawrence (KL) score of ≥2 at study entry and replaces "symptomatic mild to moderate pain" because pain is a subjective and variable measure. Screening period is extended (from 28 to 42 days) to accommodate X-ray assessment.
Section 5.2 Exclusion Criteria	Patient Population: Introduced or Modified Exclusion Criteria Added UACR parameter to the existing renal exclusion criteria. The period within which 500 mL blood may be acquired was reduced from 3 months to 56 days.	To exclude participants whose prior and current medical history renders them unsuitable for this *first* clinical trial GSK3858279. Additional measurement of renal function at screening. Period remains within MHRA/ BfArM guidance.
Section 2.3.1 Risk Assessment.	**Non-clinical 26-week cynomolgus monkey data included:** changes are described (considered non-adverse) which were consistent with the development of ADAs in some animals (immune complex deposition giving rise to inflammatory vascular, and mesangioproliferative changes). **FTIH data included:** blinded partial data from Part A of this Study 207804: There was no report of an infection related SAE, a hypersensitivity or injection site reaction, nor a clinically significant change in urinalysis. **Safety Mitigation and Monitoring:** Duration of the in-house monitoring period: At least 4	Part B is the first instance where repeat subcutaneous injections are to be administered on a weekly basis for 8 weeks, therefore the duration of the in-house period allows close monitoring in case of hypersensitivity or

MAIN Section # and Name	Description of Change	Brief Rationale
	hours at initial dose (Day 1) and at least 2 hours on all remaining dosing days. Cardiac Monitoring: ECHO (Screening) and at any other time (if indicated); Holter: 24 hour at initial Screen (outpatient setting); ECG in triplicate at all visits. Removal of "Disease Exacerbation" from list of Potential Risks.	infusion reactions, and with optimized cardiac monitoring. CCI [redacted]

MAIN Section # and Name	Description of Change	Brief Rationale
Section 8.1.4 Clinical Safety Laboratory Assessments	**Additional Assessments:** • NT-proBNP (N-terminal pro B-type natriuretic peptide [BNP]): Baseline (BL) and Day 57. • Complement proteins C3 and C4 (BL). • Microscopic examination and laboratory quantification of proteinuria (if blood or protein is abnormal on dipstick) throughout. • Urine albumin-creatinine ratio (UACR) at Screening.	Sensitive biochemical measures are now included to obtain a Baseline (BL) value and/or to monitor for early changes in cardiac (NT-proBNP) and renal function (C3, C4, UACR)
Section 4.1 and Section 10.1.5	Safety Management: Safety Review Team (SRT) and Safety Management Plan (SMP)	AEs and clinical laboratory data, will be reviewed in-stream (detailed in the Safety Review Team (SRT) Charter and Safety Management Plan (SMP) to ensure adherence to the Individual Participant and Study Stopping Criteria.
Section 6.5 Concomitant Therapy	**Permitted Therapies:** if used at a stable dose for at least 30 days prior to screening:- antidepressant medication (SSRI, SNRI); Nutraceuticals; Aspirin for cardiovascular indications. **Rescue Medication:** Paracetamol ≤ 3 g/d (*originally ≤ 2 g/d*), except 24 h before an assessment visit.	Maintaining stable doses of the listed therapies is not considered likely to impact on evaluation of either safety, pharmacokinetics or efficacy of GSK3858279 mAb. Daily dose permitted was increased (but remains within accepted limits).
Section 6.6 Prohibited Medications	**Prohibited Medications Added:** Live vaccine; biologic agents (mAbs, therapeutic proteins); antiplatelet or anticoagulant agents; immunosuppressants; systemic corticosteroids; intra-articular therapy of the index joint;. Prohibited Medications up to and including Day 71: pain	

MAIN Section # and Name	Description of Change	Brief Rationale
	medications including anti-neuropathic agents (eg Gabapentin and Pregabalin), opioids, NSAIDs, topical analgesics and Adjunctive therapies	
Section 5.3 Lifestyle Considerations	**Lifestyle Considerations:** Smoking is permitted. Introduced: To continue a regimen of therapeutic exercise, provided that it was stable for at least 4 weeks prior to enrolment. Introduced: Heat and ice therapy may be used.	Clarification. Continuation of regular therapeutic exercise is beneficial for the patient participant and participants will be encouraged to do so throughout (but especially during the initial period of washout of over the counter or prescription medications within 7 days prior to dosing). Heat and ice therapy may be beneficial for the patient participant, but participants will be asked to refrain within 2 hrs of the eDiary assessment and within 24 hrs of a clinic visit).
CCI [redacted]		
Section 8.3.6 Feedback Questionnaire	Feedback Questionnaire (Start of study and last visit) was introduced	To collect participants' experience of this GSK trial to improve future study considerations and designs.

MAIN Section # and Name	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints,	Secondary Efficacy Endpoint: Daily Pain NRS (average and worst knee pain intensity) CCI [redacted]	Clarified that the measures are "change from baseline" and are the averaged over the 7 days prior to each assessment visit. Correction
Section 2.3 Benefit/Risk Assessment	Investigator Brochure version number updated from 00 to 01. Removed "challenge agent"	Investigator Brochure updated to include the blinded safety review of Part A clinical data [GSK Document Number 2019N397787] and the six month GLP cynomolgus monkey study data [GSK Document Number 2019N397648 (P32090G)]. Both studies support this substantial amendment #3 of Part B. Correction: No challenge agent is used in this study.
Throughout the protocol	Changed "Subject" to "Participant." Removed "sponsor open"	To reflect current GSK and International standards To clarify that the sponsor is blinded
Section 5.4 Screen Failures	Screening (Failures): Participants may be re-tested once within the screening window. Screen failures may return for subsequent screening once.	Clarification: Introduction of the standard approach.
Section 1.3.5 Schedule of Activities	New added: C3 and C4 (BL); BNP (BL & Day 57); UACR (Screening) Moved: Pharmacogenetic Sample *from* Day -1 *to* pre-dose on Day 1.	Safety Monitoring incorporated. Pharmacogenetic samples only required from participants who will be randomized to treatment.

MAIN Section # and Name	Description of Change	Brief Rationale
Section 2.2 Background	Removed "without potentiating disease progression."	Removed this inaccuracy, as no clinical data have been obtained to substantiate that GSK388279 will not potentiate disease progression.

10.10.4. Amendment 4 14-NOV-2019

Overall Rationale for the Amendment 4 (for Part B): To address the concerns from the Ethics Committees' review of Amendment 3 (Part B).

Section # and Name	Description of Change	Brief Rationale
Section 3: Objectives and Endpoints	Corrected the *row structure* of the table	To properly reflect our intent to evaluate both safety and efficacy as the primary objectives for Part B.
Section 5.1 Inclusion Criteria	Reduce the upper limit of BMI from 39.9 kg/m^2 to 34.9 kg/m^2	To exclude participants of > Grade 1 Obesity (and so to reduce the risk.
Section 5.2 Exclusion Criteria (No. 57, 60, 62 and 69)	No. 57: To also exclude participants with a history of primary cardiomyopathy No. 60: To clarify that participants who have a history of excessive bleeding or coagulation disorders, will also be excluded. No. 62: To also exclude participants with recurrent infections No. 69: To exclude participants who are unwilling to discontinue all pain medication	To better define the participant population and achieve consistency with the Benefit/Risk Assessment.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Study stopping criteria	Included links to SAE reporting and to the Safety Management Plan. Removed "the same," so that any 2 related SAEs would trigger the stopping of the study.	To highlight the coordination of S/AE reporting and the conditions of SAE reporting.
Section 7.2 Discontinuation of Study Intervention	Included "clinically significant deterioration of index knee pain."	Clinically significant deterioration of index knee pain warrants discontinuation of study treatment.
Throughout the document	Change "patients" to "participants."	Consistent use of terminology

10.10.5. Amendment 5: 07-SEP-2020

Overall Rationale for Amendment 5 (for Part B):

Two main reasons: 1) To introduce COVID-19 safety management and to adjust the visit schedule to accommodate SARS-Cov2 testing. 2) To report on the revised safety margin and introduce additional PK sampling timepoints (resulting from an improved PK bioanalytical methodology).

Minor changes are: CCI [redacted]

Minor edits/corrections are made throughout to provide refinement and clarification.

Section # and Name	Description of Change	Brief Rationale
Appendix 2 (Clinical Laboratory Tests) and throughout, as appropriate Section 4.1. Overall Design. Section 4.3. Scientific Rationale (Study Population).	Added: "COVID-19" Test (SARS-CoV-2) Included the rationale for why participants between 40 to 75 years (inclusive) and with a BMI within the range 19-34.9 kg/m^2 (inclusive) will continue to be permitted into the trial	To screen (and exclude) participants for the presence of SARS-CoV-2 virus and to monitor during the Treatment Period and at the End of Study. Although increasing age and BMI are both associated with a heightened relative risk for COVID-19 susceptibility and poorer outcomes, [Williamson, 2020] these

Section # and Name	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria (Diagnostic Assessments). Section 5.3.1. Lifestyle Considerations (COVID-19 related)	(despite the COVID-19 pandemic). Added: Note that refusal of any COVID test following the first dose of study treatment would not constitute a protocol deviation.	same parameters are inherently associated to and largely encompass the OA population under study. To cover the event that a participant may decide to refuse COVID testing whilst participating in 207804 (this will be tracked).
Section 1.3.1. Part B Schedule of Activities (Screening)	Added: COVID-19 Test Moved: Day -1 screening tests either *to* Day -4 *or to* immediately prior to first dose, as appropriate.	At least 72 (up to 96) hours is required to obtain the result of the COVID-19 test (up to Day -4). Day -4 is to be used for a repeat of haem/chem (to obviate the need to return to the clinic at Day -1). For clarity of importance, Baseline measurements are denoted as (x) on the Schedule of Activities, since these are divided between Day -4 and immediately prior to dosing on Day 1.
Section 1.3.5. Part B Schedule of Activities (Treatment and Follow-Up Period)	**COVID-19:** Monitoring is introduced after 2, 5 and 8 weeks during the Treatment Period, at the End of Study Visit (Day 141), and in case of early withdrawal. **PK/TE:** Additional Visits to site were included: Days 5, 23, 26, 51 and 99 for *at*	**COVID-19:** Sparse testing introduced to reduce the chance of dosing GSK3858279 in the case of pre- or asymptomatic COVID-19. **PK/TE**: Additional sampling is required to better understand the disposition of

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted]	
	End of Study Visit was moved from Day 113 to Day 141 A telephone contact was included at Day 120. CCI [redacted]	CCI [redacted] To extend the period of observation since last dose of study treatment.
Section 1.2 Schema	Replaced.	Updated to better reflect the dose regimen and maximum number of participants permitted.
Section 2.2. Background	Removed "CCL17 levels would be expected to be higher in inflammatory conditions; however, due to the large variability in healthy human serum CCL17 levels, the systemic exposure of CCL17 in OA patients might be similar to	On reflection, this statement appears speculative. Note that the biological rationale of CCL17 as a target is founded on controlled pre-clinical studies.

Section # and Name	Description of Change	Brief Rationale
	that in a healthy population."	
Section 2.3, Benefit Risk Assessment	Included a reference to the updated blinded review of a partial data set from Part A of this first time in human (FTIH) study.	Part A (remains blinded at this time) completed June 2019.
Section 2.3.1: Risks	Infection: Added that "Anti-CCL17 has been shown to be protective in a mouse model of invasive aspergillosis [Carpenter, 2005] Immunogenicity Data: Discrete pre-clinical data was summarised. Cardiac Data: 13week toxicology summary updated "The heavier heart weights were not dose related and generally did not show a consistent pattern of increased absolute weights, relative to body weight or brain weight." Study Procedures: Evaluated the COVID-19 risk and mitigation strategies as "Risk associated with attending an investigative site during the COVID-19 Pandemic."	To reflect the literature on the potential role of CCL17. Discrete pre-clinical data was summarised. Updated for consistency with IB Update. Mitigation Strategies documented for participants attending investigative sites where COVID-19 virus may be circulating (COVID testing to be performed prior to, during the Treatment Period and at End of Study.

Section # and Name	Description of Change	Brief Rationale
2.3.3. Benefit:Risk Conclusion	Updated the Overall B:R Conclusion with respect to COVID-19.	There are measures proposed to minimize the risk of COVID-19 to study participants and we consider that it remains justified to progress to Part B.
Section 3. Objectives and Endpoints	**Primary Efficacy Endpoints**: Removed excessive detail "24 hr" and "average of 7 days prior" from the change from *both* the average knee pain intensity and worst knee pain intensity, at Week 8. **Secondary PK Endpoints:** CCI [redacted] CCI [redacted]	Primary Endpoint definition for pain was simplified and aligned with that described in pivotal clinical trials in this disease area (details in Section 9.4.1).
Section 4.4.2 Justification for Dose (Part B)	Section Replaced. Reference made to 1) Uses data from the re-analysis of Part A samples 2) Uses data from the 6 month cynomolgus monkey toxicology data to calculate the safety margin	The re-analysis of Part A samples uses an improved bioanalytical method. The definitive 6 month cynomolgus monkey toxicology study supersedes the 3 month study.

Section # and Name	Description of Change	Brief Rationale
	CCI [redacted]	The predicted safety margins (AUC, Cmax) remain acceptable and the proposed dose regimen and duration of dosing for Part B remain unchanged.
Section 6.3.1. Randomization	Removed "The randomisation may be stratified by site to allow for operational efficiencies for the preparation of the IP."	No longer required.
Section 7.2.2. QTc Stopping Criteria	Clarified/corrected wording that QTc stopping criteria are based on an average of triplicate ECG readings.	Clarification of wording is being applied retrospectively. Part A evaluated a single reading, but in case of any concern, two further readings would need to be obtained to apply the QTc stopping rule (which requires triplicate readings)
Section 7.2.3. Dose Adjustment Pharmacokinetic Criteria	Included: "non-compartmental"	Included: that a non-compartmental analysis may now also be used (or a model-based post-hoc analysis) of the observed concentrations to provide the individual exposure parameters (Cmax, AUC(0-tau)). Revisions are based upon the recent Part A (blinded)

Section # and Name	Description of Change	Brief Rationale
	Revised: Cmax and AUC(0-tau) values and the fold safety margin: "Cmax of 511 µg/mL or the AUC(0-tau) of 2594µg*day/mL based on a 4-fold margin against the NOAEL from the 6-month toxicological study"	PK data and the recent 6-month toxicology study.
Section 8.6. Treatment and Overdose	Replaced "140 days" with "at least 5 half-lives but not less than 90 days" as the monitoring period for AE/SAE and laboratory abnormalities.	140 days was inadvertently carried over from original protocol when Part B was a single dose design.
Section 8.7.3	Proteome Research: Section deleted	Proteome research already encompassed within Section 8.4.2 (Exploratory Biomarkers).
Section 9.3. Populations for Analyses	Included a PK Population:	PK Population (now tailored for a repeat dose study design)
Section 9.4.3. Pharmacokinetics Analyses	Updated the pharmacokinetic parameters in the Statistical Analyses	Improved quality (precision, clarity and transparency)
Section 9.4.5. Interim Analysis	Replaced a blinded sample size re-estimation with that of an unblinded sample size re-estimation. Removed the rationale of sample size re-estimation – "if the expected SD (daily pain NRS) is greater than 1.8 or in the case of high dropout." Removed the timing of the second interim – "a second interim analysis may occur	The sample size re-estimation was made unblinded and combined. with the second interim to avoid the scenario where the sample size could be increased despite the drug potentially meeting futility criteria. As the second interim and the sample size re-estimation have been

Section # and Name	Description of Change	Brief Rationale
	after approximately 28 participants have completed the Week 8 assessment, the exact timing will be determined during the sample size re-estimation or at the first interim."	combined, the timing has been updated to reflect this.
Appendix 6 Liver Safety: Required Actions	Updated Liver Safety Required Actions for Phase I studies to include acquisition of a PK sample	Drug concentrations at the time of a liver event provide important information.

10.10.6. Amendment 6: 12-Nov-2021

Rationale for Amendment 6

To clarify that 1) Baseline CCL17 samples will be taken at day -4; 2) Non-re-screening of COVID positive participants; 3) Participants with Hep B Core Antibody at screening are excluded in Part B 4) Sample size re-estimation will allow for a decrease in sample size as well as the already planned potential increase 5) Additional Interim analyses may be conducted 6) Minor edits throughout to provide clarification.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.5 Schedule of Activities -for Part B	Under the analysis-PK and target engagement, added collection of baselines CCL17 to Day -4 from initial screening visit	To reduce the impact of concomitant medications at initial screening
Section 5.2 Exclusion Criteria	Included exclusion for Hep B for participants enrolled in Part B	To exclude participants with presence of Hep B surface antigen at screening
Section 5.4.1 Re-screening	Added no re-screening of COVID positive participants.	To provide clarity

Section 6.3.2 Blinding	Added the details on review process of unblinded data from Part B at interim analyses	To provide details on review process at interim analysis.
Section 9.2.2 Sample size sensitivity	Added the sample size sensitivity table when the proportion of trials correctly deemed negative.	More details on sample size sensitivity added
Section 9.4.5. Interim Analyses and Section 1.1 Synopsis	Sample size re-estimation may be reduced or increased at interim analysis 2 and potential additional interim analyses may occur during the study	Additional interim analyses may occur to allow interactions with regulatory agencies and/or help inform internal decision making
Throughout	Minor edits throughout the document for consistency and abbreviations updated	For consistency and clarity

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