Protocol

Study ID: 209973

Official Title of Study: A randomized, double-blind, placebo-controlled, three-period two-treatment incomplete-block crossover study to investigate the effects of intravenous GSK3858279 on a battery of evoked pain tests in healthy participants.

EudraCT: 2019-002609-23

Approval Date of Document: 25-MAY-2021

TITLE PAGE

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Protocol Number: 209973/ Amendment 4

Compound Number or Name: GSK3858279

Study Phase: Phase 1

Short Title: GSK3858279 vs PBO, Phase 1, Evoked Pain Tests, Pharmacokinetics and Target Engagement in healthy participants.

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):

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Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY.		
Document	*Date of Issue*	*DNG Number*
Amendment 4	25-MAY-2021	TMF-13778634
Amendment 3	*10-AUG-2020*	2020N405625_03
Amendment 2	*11-FEB-2020*	2019N405625_02
Amendment 1	*23-SEP-2019*	2019N405625_01
Original Protocol	*25-JUL-2019*	2019N405625_00

Amendment 4 25-MAY-21

Overall Rationale for the Amendment:

Amendment to the Interim Analysis sections. An interim analysis may be performed once the last UVB-MITT participant has completed their period 3 final day 15 PainCart assessments. Dependent on the results, the study could be stopped for futility.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis Section 4.1 Overall Design Section 6.3.2. Blinding Section 9.5 Interim Analysis	Included the potential of performing an interim futility analysis when all UVB-MITT participants have been enrolled and completed their period 3, day 15 PainCart assessments.	For futility and internal decision-making. A review of the primary PainCart endpoints, safety, demography, PK and TE will be conducted.
Section 4.4 Justification of dose and washout period	Updates made to reflect emerging data from FTiH study	Updated to reflect information present in the current IB
Throughout	Update to SARS-CoV-2 mitigation measures	To reflect update to site procedures
Throughout	IB, Interim Report and RAP reference and associated citations updated	Updated to reflect the most current version of the documents

Section # and Name	Description of Change	Brief Rationale
Throughout	Enrolment number amended from 30 participants to 'a maximum of 30' participants	To ensure consistency with language already included in Section 09: Statistical analysis

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, double-blind, placebo-controlled, three-period two-treatment incomplete-block crossover study to investigate the effects of intravenous GSK3858279 on a battery of evoked pain tests in healthy participants.

Short Title: GSK3858279 vs PBO, Phase 1, Evoked Pain Tests, Pharmacokinetics and Target Engagement in healthy participants.

Rationale: The purpose of the study is to elucidate the mechanistic basis for the analgesic effects of GSK3858279 in humans by using a battery of experimental pain assessments in healthy participants.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	Primary
To evaluate the effects of IV administration of GSK3858279 in Ultraviolet B (UVB) burn inflammatory test, cold pressor test and electrical pain test in the PainCart	UVB heat pain detection (°C) Cold pressor time to intolerable pain threshold (sec) Electrical pain tolerance threshold (mA) - single stimulus
Safety	Safety
To evaluate the safety and tolerability of GSK3858279 following IV dosing	Adverse Events (AE) and Serious Adverse Events (SAE). Clinical laboratory measurements, 12-lead electrocardiograms (ECG) and vital signs that are considered of potential clinical importance.
Exploratory	Exploratory
To evaluate the pharmacokinetics (PK) of GSK3858279 following IV administration	Serum PK concentrations and parameters including but not limited to: area under the concentration-time curve [AUC], maximum concentration [Cmax], tmax
To evaluate the target engagement (TE) of Chemokine C-C motif ligand 17 (CCL17) by GSK3858279 following IV administration	Free and total CCL17 levels in serum
To evaluate the effects of IV administration of GSK3858279 in additional endpoints in UVB test, cold pressor test and electrical pain test in the PainCart	Heat pain detection on normal skin (°C) Cold pressor time to pain detection (sec) Electrical pain detection (mA) - single stimulus Electrical pain detection and tolerance threshold (mA) - repeat stimulus

Objectives	Endpoints
	For each test Area Under the Curve (AUC)/Area Above the Curve (AAC) and post-test eVAS
To evaluate the effects of IV administration of GSK3858279 in pressure pain test and Conditioned pain modulation (CPM) test of the PainCart	Pressure pain (tolerance and detection) - KPa CPM - (detection and tolerance threshold) – mA For each test AUC/AAC and post-test eVAS
To assess the potential for anti-GSK3858279 antibody formation following IV dosing	To include: incidence, titres, and, for samples with confirmed anti-drug antibodies (ADAs), neutralising activity

Overall Design:

This is a single-centre, randomized, double-blind, placebo-controlled, three-period two-treatment incomplete-block crossover study to investigate the effects of intravenous GSK3858279 on a battery of evoked pain tests in healthy participants.

Disclosure Statement:
This is a cross-over, basic science study with three study periods that is masking the participant and investigator.

Number of Participants:
A maximum of 30 healthy male participants will be enrolled into the study, such that at least approximately 24 participants complete dosing and critical assessments in all three study periods.

An interim analysis may be performed once the last UVB-MITT participant has completed their period 3 final day 15 PainCart assessments. An interim analysis may also be performed once the final participant has completed their period 3 final day 15 PainCart assessments.

For both UVB Heat Pain Detection and Cold Pressor time to intolerable pain threshold, the sample size is higher than that required for the Electrical Pain tolerance threshold test. Therefore, for the UVB-exposed population, from here on referred to as the UVB-MITT population, approximately 18 participants are required to be enrolled to ensure that approximately 15 participants complete all UVB tests of the PainCart assessment on irradiated skin in all three study periods.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

In each study period participants will receive either GSK3858279 or placebo in a 1:1 ratio. During the trial, participants will receive both treatments, either two doses of GSK3858279 and one dose of placebo, or two doses of placebo and one dose of GSK3858279 with equal likelihood. The order of treatment assignments will be randomized.

If participants prematurely discontinue the study, additional replacement participants may be randomized at the discretion of the Sponsor and in consultation with the Principal Investigator in order to ensure sufficient participants complete the study. Replacement participants will be assigned to the same treatment sequence as the participant they are replacing, at the discretion of the Sponsor and in consultation with the Principal Investigator.

Intervention Groups and Duration:

The study duration, including screening and follow-up will be approximately 6 months for all participants in the study:

Screening	Approximately 28 days prior to first dose.
Number of Participants	One Cohort of a maximum of 30 participants (N=30)
Study (Treatment) Period(s)	Will comprise of three study periods, investigating the difference between GSK3858279 (3mg/kg IV) and Placebo in the PainCart assessments. Each participant will be admitted to the unit either two days before dosing (Day-2, UVB-MITT participant) or one day before dosing (Day-1, non-UVB-MITT participant) on each study period. Participants will be dosed on Day 1 and discharged on Day 2 (except if, for medical reasons, participants need to stay longer). The participants will return for an outpatient visits on Day 7 (UVB-MITT participants only), Day 8 and Day 15. The participants will be contacted on Day 25 and asked about their general health.
Washout Period	Will be at least 4 weeks between doses for an individual participant.
Follow-Up	The participants will be contacted on Day 36 by telephone and asked about their general health. Approximately 56 days after the last study administration, a final follow-up visit will occur. If warranted, additional follow-up visits may be scheduled.

Data Monitoring or Other Committee:

There will not be a data monitoring committee or any other committee on this study.

1.2. Schema

Figure 1 Study Design Schematic

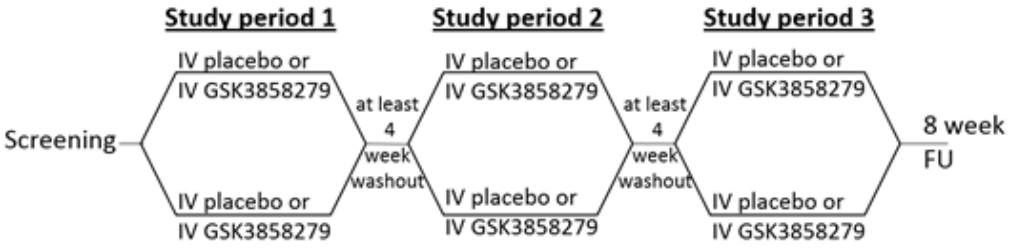


Figure 2 Visit schematic

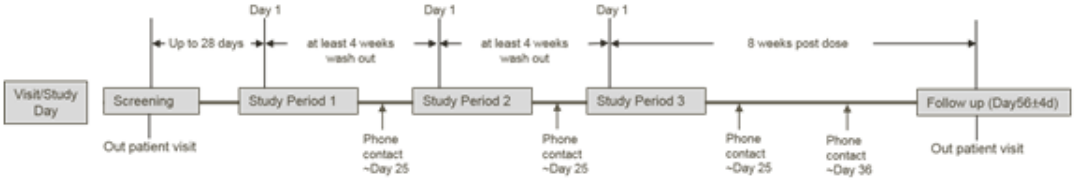
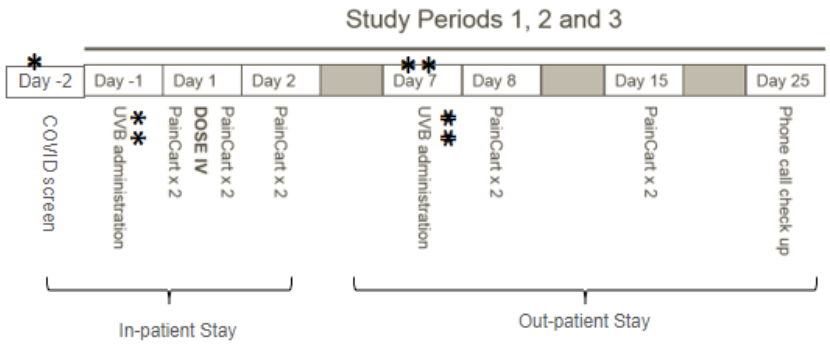


Figure 3 Study Period Details



* Required only in UVB-MITT population

** Optional assessments/study day applicable to UVB-MITT volunteers only

1.3. Schedule of Activities (SoA)

1.3.1. Screening and follow-up

Procedure	Screening (up to 28 days before Day 1)		Follow-up check 36±4 days post last dose	Final follow-up 56±4 days post-last dose	Notes
	Part 1	Part 2			
Out-patient visit	X	X		X	Optional in-clinic stay for participants at the discretion of investigator.
Phone call			X		AE collection - may be out-patient visit at discretion of Investigator for additional checks
Informed consent	X				
Severe acute respiratory syndrome SARS-CoV-2 PCR test or rapid antigen test	X			X	
Temperature check	X	X		X	
Inclusion and exclusion criteria	X				Recheck clinical status before randomization and/or 1st dose of study intervention.
Demography	X				
Full physical examination including height and weight.	X				Weight at screening is used for determination of dose
Fitzpatrick Skin Type	X				Assessments for UVB-MITT population only Assessment to determine applying MED application
Echocardiogram	X				
Medical history (includes substance usage)	X				Substances: Drugs, Alcohol, tobacco and caffeine
Current medical conditions	X				
HIV, Hepatitis B and C	X				
Haematology, clinical chemistry (include liver chemistries) and urinalysis	X			X	Including Troponin-T (hs)
NT-proBNP	X			X	
UrDrug, BrAlc	X			X	
12-lead ECG	T			X	T = Triplicate X = Single
Vital signs	X			X	

Procedure	Screening (up to 28 days before Day 1)		Follow-up check 36±4 days post last dose	Final follow-up 56±4 days post-last dose	Notes
	Part 1	Part 2			
PainCart training	[X]	[X]			May be performed during either part 1 or part 2 (not both)
Minimal Erythema Dose (MED) application	X				Assessments for UVB-MITT population only. Exposure to pre-determined 6 ascending doses of UVB radiation. MED application will be the final assessment on Part 1 of Screening and will only be completed after confirmation of eligibility from available results, e.g. lab data, echocardiogram results may not be available.
MED assessment		X			Assessments for UVB-MITT population only. 24 hours (± 2 hours) after UV exposure
AE/SAE review	X	X	X	X	

- An echocardiogram performed within 3 months prior to first dosing is acceptable for enrolment into the study

- MED determination performed within 6 weeks prior to first dosing is acceptable for enrolment into the study

1.3.2. Study periods 1, 2, 3 and Early Withdrawal

When the following assessments are scheduled to be performed at the same time-point, the order will be as follows:

ECG > vital signs > PK and PD sampling > PainCart

Procedure	Study periods 1, 2, 3 (Days)								Early Withdrawal	Notes
	-2	–1	1	2	7	8	15	25		Allowed visit windows are detailed in the Study Reference Manual (SRM)
Out-patient visit					X*	X	X		X	Optional in-clinic stay for participants at the discretion of investigator. *Day 7 is optional for those participants not receiving UVB.
Admission in clinical unit	X**									Optional in-clinic stay for participants at the discretion of investigator ** If subjects are not UVB-MITT participants, optional admission will be on Day-1 with Day-2 assessments completed on Day-1.
Discharge from clinical unit				X						Except if, the participant needs to remain in the Unit longer for medical reasons.
Phone Call								X		AE collection - may be out-patient visit at discretion of Investigator for additional checks
Brief Physical Examination			X	X		X	X		X	
Haematology, clinical chemistry (include liver chemistries) and urinalysis		X	X	X		X	X		X	Troponin T to be assessed on Day -1, 8, 15 (and EW if needed). **C3/C4 on Day -1 only**
UrDrug, BrAlc		X			X*		X			*for volunteers who do not receive UVB application, the Day 7 Assessments may be performed on Day 8 prior to PainCart
SARS-CoV-2 PCR test or rapid antigen test	X**								X	

Procedure	Study periods 1, 2, 3 (Days)								Early Withdrawal	Notes
	-2	–1	1	2	7	8	15	25		Allowed visit windows are detailed in the Study Reference Manual (SRM)
12-lead ECG		T	X			X	X		X	Day 1: pre-dose (T), 0.5hr, 1hr post start of infusion. On other days a single measure taken prior to 1st PainCart assessment. T = Triplicate X = Single
Vital signs (including temperature)	X**	X	X	X	X-t	X	X		X	Day 1: pre-dose, 0.5hr, 1hr, 2hr post start of infusion. X-t: temperature assessment on Day 7 for UVB-MITT population only On other days a single measure taken prior to 1st PainCart assessment.
Randomization			X							Study period 1 only
Drug/placebo IV infusion			X							Continuous infusion over 1 hour
PainCart			X	X		X	X			Day 1 pre-dose performed twice (baseline) Day 1 performed at 1 and 3 hours post start of IV infusion. Other days performed twice ~2 hours apart at approximately the same time of day in each study period. Day 15 - heat pain detection assessment associated with UVB test performed on normal skin only. Participants not receiving UVB application will not undergo UVB heat pain detection test on irradiated skin. All other paincart assessments including heat pain detection performed on normal skin will still be assessed. See Appendix 7 for details of testing
UVB application		X			X					UVB application (2 x MED) will be performed 24hr (±2hr) prior to start of infusion on Day 1. UVB application (2 x MED) on Day 7 will be performed 24hr (±2hr) prior to PainCart assessment on Day 8. UVB application only applies to those in the UVB-MITT population.

Procedure	Study periods 1, 2, 3 (Days)								Early Withdrawal	Notes
	-2	–1	1	2	7	8	15	25		Allowed visit windows are detailed in the Study Reference Manual (SRM)
AE review	X**	X	←==========→						X	
SAE review	X**	X	←==========→						X	
Concomitant medication review	X**	X	←==========→						X	
Blood samples for PK and PD			X	X		X	X		X	Day 1: pre-dose, 1hr, 3hr post-start of IV infusion. On other days samples taken prior to 1st PainCart assessment.
Blood sample for immunogenicity			X				X		X	Day 1: pre-dose. Day 15: prior to 1st PainCart assessment.

** If subjects are not UVB-MITT participants, optional admission will be on Day-1 with Day-2 SARS-CoV-2 test performed on Day-1.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.
- The planned study assessments on Day 7 (UVB-MITT population only), 8, 15 and 25 may be performed within a ± 24hr window.
- A questionnaire related to COVID-19 is part of each visit and included in the AE review.

2. INTRODUCTION

GSK3858279 is a high affinity, human immunoglobulin G2σ (IgG2σ) (Fc-silenced), first-in-class, monoclonal antibody (mAb) in development for the treatment of pain associated with osteoarthritis with a view to expand to other chronic pain diseases (e.g. neuropathic pain).

2.1. Study Rationale

The purpose of the study is to elucidate the mechanistic basis for the analgesic effects of GSK3858279 in humans by using a battery of experimental pain assessments in healthy participants. Analgesia has been demonstrated in animal models of pain with tool anti-CCL17 antibodies however the mechanistic basis for this effect seen in animal studies is not well understood and, as has been observed for other development assets, may not translate to humans. Clinical studies in pain patients can be challenging because of large placebo responses, and heterogeneity of pain mechanisms within a single disease. Performing the study in healthy participants in a controlled, validated battery of experimental pain tests assessing several pain mechanisms contrasted with historical data of analgesic drugs will inform on pain disease indications to progress.

2.2. Background

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

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 activating the chemokine receptor CCR4, to prevent downstream consequences of CCR4 signalling.

At the time of this protocol, GSK3858279 is being developed for treatment of osteoarthritis pain, however non-clinical data suggests an opportunity to treat other chronic pain conditions including neuropathic pain by targeting this pathway. Alleviating chronic pain is a major unmet need as current therapies (e.g. NSAIDs, opioids) have significant side effects and addiction liabilities that prevent their effective use in treating the patient's pain.

Rationale for CCL17 neutralisation in OA pain has been generated in vivo pre-clinically in inflammatory and arthritis models. CCL17 has been recently identified as a peripheral mediator of inflammatory pain and can itself induce arthritis. Intraplantar injection of recombinant CCL17 resulted in pain in mice in a CCR4-dependent manner [see IB, GlaxoSmithKline Document Number RPS-CLIN-004032

whilst therapeutic dosing with anti-CCL17 surrogate mAb inhibited established inflammatory pain [in house data - see IB, GlaxoSmithKline Document Number RPS-CLIN-004032

Absence of CCL17 ameliorated inflammatory pain in various murine arthritis models.

In parallel, in a preclinical *in vivo* model of nerve injury that recapitulates the mechanical hypersensitivity and thermal allodynia presented by neuropathic pain patients, therapeutic dosing of anti-CCL17 surrogate mAb reverses pain [see IB, GlaxoSmithKline Document Number RPS-CLIN-004032

Importantly, in contrast to inflammatory and arthritic models, chronic neuropathic pain and the rodent nerve injury models tested are largely insensitive to NSAID treatment. As such, the mechanism of action of analgesia induced by neutralisation of CCL17 is potentially applicable to neuropathic pain conditions considered refractory to NSAIDs. The opportunities to treat pain by targeting CCL17 in the context of a variety of conditions and aetiology needs to be explored clinically.

The PainCart is an integrated, multi-modal pain task battery of tests designed to investigate the efficacy of analgesic compounds against several types of pain, including thermal, electrical, chemical and mechanical pain. The models applied in the PainCart have been tested for predictive validity and reliability and can be used repeatedly, quickly, in short succession in healthy participant studies and patient studies.

The translation of findings from animals, through human pain models to patients (and back) is one of the greatest challenges in modern (pain) research. One major disadvantage of many human pain models is that they do not represent the pain aetiology or pain entity when they are translated to patients, i.e. they may mimic aspects of the clinical pain condition, but they cannot reflect the full multidimensionality of a disease. In addition, the main limitation of models of pain is the inability to replicate spontaneous pain, which is one of the main complaints of chronic pain patients and there are currently no human models available to measure this. This being said, experimental pain models may be used to mimic certain aspects of chronic pain condition such as sensitization of the peripheral or central pain processing (windup of nociceptors via repetitive electrical stimulation), or by inducing inflammatory pain responses, additional measures of central sensitization may be taken which portray aspects of neuropathic pain such as touch evoked allodynia and punctate hyperalgesia. By using a combination of methods, the different aspects of nociceptive processing may be teased out and provide mechanistic information to aid decision making. Human experimental pain models can be supportive in understanding the pain mechanisms by exploring the pain system under controlled settings [Standardized stimuli of different modalities (i.e., mechanical, thermal, electrical, or chemical) can be applied to the skin, muscles, and viscera for a differentiated and comprehensive assessment of various pain pathways and mechanisms], the challenge is to match specific treatments to different pain-generating mechanisms.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK3838279 is provided in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number RPS-CLIN-004032]

In light of the global COVID-19 pandemic, all participants will be screened for COVID-19 at the beginning of the study period and will be required to have a negative SARS-Cov-2 test prior to commencing each study period. Please see further details for risk assessment and mitigation strategy below.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3858279 may be found in the Investigator's Brochure (IB) GlaxoSmithKline Document Number RPS-CLIN-004032

The risk assessment of GSK3858279 is based on the pre-clinical studies conducted to date and the ongoing First in Human (FiH) study 207804 – GlaxoSmithKline Document Number 2020N429762_00.

Summaries of findings from these pre-clinical studies and the FiH study can be found in the IB [GlaxoSmithKline Document Number RPS-CLIN-004032]

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

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Hypersensitivity, including injection site and infusion reactions	The administration of any (human) mAb has the potential to induce local or systemic immunologic reactions, for example acute allergic reactions (type I) and immune complex disease (ICD) associated with the formation of anti-drug antibodies (ADA) (type III). **Non-Clinical** In a 13-week study administration of GSK3858279 by weekly IV infusion at 100 mg/kg resulted in infusion reactions after dosing on Days 22 and 29 in one female cynomolgus 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 of three animals (one female at 10 mg/kg/week and one male and one female at 100 mg/kg/week) as well as mesangioproliferative glomerulopathy in the kidney of the males at 10 mg/kg/week or 100 mg/kg/week, which is consistent with ICD following the formation of ADA. Nonspecific injection site reactions caused by the subcutaneous (SC) 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 are not predictive for ADA-mediated adverse reactions in humans, including infusion reactions, hypersensitivity reactions or	**Participant Selection**: Participants with a history of sensitivity to the study medication, or a history of any drug or other allergy that, in the opinion of the investigator, contraindicates their participation, will not be permitted to enter the study. Participants with renal disorders will also be excluded. **Participant monitoring:** In Part A of FiH study (207804), participants remained in the inpatient facility for 48 hours post dosing to allow adequate monitoring by trained site personnel. In Part B of FiH (207804) and in this study (209973), participants will be monitored for a minimum of two hours post dosing. Emergency resuscitation facilities will also be available. Participants will be instructed in the Informed Consent Form (ICF) as to the signs and symptoms of hypersensitivity reactions and be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	anaphylaxis [Kronenberg, 2017]. 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 Part A of the FiH study (207804) in healthy participants, there was neither a report of any relevant hypersensitivity reactions nor any clinically significant changes in urinalysis.	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 PD properties of the drug. GSK3858279 is a human antibody, with a lower potential for ADA formation than a chimeric antibody. **Nonclinical** 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 immune complex disease were seen (mentioned above). In general, the incidence and titre of ADA in nonclinical studies are not predictive of the generation of ADAs in humans.	Samples will be drawn at baseline and at regular intervals to test for immunogenicity, and participants will be monitored for any evidence of adverse reaction as detailed in the hypersensitivity section of this table. Clinical laboratory safety assessments are included in the study. Urine microscopy and laboratory quantification of proteinuria will be investigated following unexplained dipstick proteinuria or haematuria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical In Part A of the FiH study (207804) in healthy participants there was a low incidence of pre-existing ADA and for which titres were low. There was no pattern of increasing incidence or increasing titres of ADAs following escalation of the dose level of GSK3858279 (or placebo) and there was no apparent difference between 3 mg/kg IV vs. 3 mg/kg SC.	
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 potential 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). The role of CCL17 in systemic anti-pathogen responses is unclear. In pre-clinical studies, administration of the anti-CCL17 antibody (GSK3858279) for 13 weeks to monkeys did not result in modulation of the immune system as assessed by T-cell dependent antibody response, an assessment of humoral immunity, or of peripheral blood lymphocyte populations as assessed by flow cytometry (see IB for further details). In addition, we are not aware	**Participant Selection** Participants with active or chronic infections or a history of recent or recurrent infections will not be included in the study – see Section 5.2. **Participant Monitoring** Participants will be monitored for infection. Participants will be instructed in the ICF as to the signs and symptoms of infection, and to contact the site personnel should they develop.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of any pre-clinical in vitro or in vivo data to suggest a potent immunosuppressive effect of CCL17 blockade. There is, however, no data available to our knowledge of the consequences of CCL17 inhibition/ablation in pre-clinical viral infection models. **Clinical** During Part A of the FiH study (207804) in healthy participants, there were no reports of infection-related serious adverse events.	
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. **Non-Clinical** 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 vaccines should not be administered to participants from 1 month prior to dosing of study medication and for five half-lives after dosing of study medication. If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered whilst receiving GSK3858279 based on an assessment of the benefit:risk (e.g. risk of decreased responsiveness).
Cardiac Risks	**Non-Clinical** In the 4-week study, review of the heart data (ECG, blood pressure, heart rate, organ weights and histopathology), in monkeys at doses up to 100 mg/kg/week IV 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	**Participant Exclusion:** Participants with a history of cardiac disease or cardiac abnormalities (including abnormal Troponin T and NT-proBNP) 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
	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 [GlaxoSmithKline 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, telemetry (blood pressure, heart rate), serum cardiac troponin I, NT-proBNP, heart weight and histopathology, did not identify any treatment-related effects on the heart following doses up to 100 mg/kg/week SC. 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 which would lead to an increase in heart weight. Therefore, the potential effect on heart weights noted in the 13-week study in monkey was not reproducible following 26 weeks of chronic dosing in monkey and is not considered to be clinically significant. **Clinical** During Part A of the FiH study (207804) in healthy participants, none of the abnormal findings in the ECG parameters were judged to be clinically significant.	**Participant monitoring:** Investigations during screening include ECG, echocardiogram and troponin T and NT-proBNP. TroponinT and NT-proBNP will be monitored after dosing.
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	**Participant exclusion and non-permitted medication**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	antagonism although at this stage this is theoretical; there are two 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 assays [Hagemann, 2014]. Clinical data with direct inhibitors of CCR4, such as mogamulizumab (approved in Japan for treatment of T cell lymphoma), are not associated with increased bleeding risk. **Non-Clinical** Although platelet function has not been specifically assessed non-clinically; no effects on platelet counts or clotting times were observed in the monkey studies. Neither were there any reports of excessive bruising nor difficulties in clotting after blood sampling. **Clinical** There were no reports of any clinically significant bleeding events during Part A of the FiH study (207804) in healthy participants.	Participants with a previous or current history of bleeding diathesis will be excluded. Use of anti-coagulants or anti-platelet agents will be prohibited.
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** Participants with a history of drug-induced skin reactions and Stevens-Johnson Syndrome will be excluded. **Participant Monitoring** Clinically significant skin reactions will be reviewed by a dermatologist and, if appropriate, a skin biopsy will be requested for histological analysis.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical There were no reports of any clinically significant skin reactions during Part A of the FiH study (207804) in healthy participants.	
Study Procedures		
Events related to UVB irradiation	UV irradiation from sunlight is associated with an increased incidence of skin cancer. UV irradiation is made up of a spectrum of wavelengths with UVB being one of the risk factors for skin cancer. The range of wavelength of UVB used in this study (narrow band range 310-315 nm) is that used for phototherapy to treat skin conditions such as psoriasis. Literature review [Lee, 2005] indicate there was no increased risk of skin cancer in four studies specifically assessing the potential carcinogenic risk of narrow-band UVB, however there is insufficient literature on the number of exposures and risk of long term development of skin cancer at the UVB wavelength to be administered in this study [Hearn, 2008].	**Participant exclusion** Participants with pre-existing risk factor for skin cancer will be excluded (applicable for UVB-MITT population only). Dose of UVB irradiation will be at 2 x MED.
Events related to UVB test	The UVB test may induce a post-inflammatory hyperpigmentation (PIH) in some cases [Siebenga, 2019]. Typically, at centres performing the UVB inflammatory test, 3xMED (Minimum Erythemal Dose) of UVB irradiation is applied to induce sensitisation, however, long-lasting PIH has been associated with 3xMED.	**Participant exclusion** Participants with Fitzpatrick skin type IV, V or VI will be excluded (applicable for UVB-MITT population only). Dose of UV irradiation will be at 2 x MED. **Participant Monitoring** At the follow-up visit, participants will be assessed to monitor the possible occurrence of the hyperpigmentation. Participants will be informed in the ICF as to the risk of forming PIH at the UV irradiation sites.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
SARS-CoV-2	The current SARS-CoV-2 pandemic can pose a challenge to integrity of the trials, protection of participants' rights, safety and wellbeing and the safety of clinical trial staff. Therefore, risk mitigation strategies will be put in place for this trial and will be evaluated on an ongoing basis for the duration of this trial, or until there is a consensus that the period of the SARS-CoV-2 outbreak in the Netherlands has passed. If the dynamics of the SARS-CoV-2 outbreak change in such a way that the safety of the trial participants and clinical trial staff or integrity of the data collected during this clinical trial cannot be guaranteed the trial will be halted. **GSK3858279 on COVID-19 disease** 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 likely to mainly 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. Based on the available information in the Investigators Brochure and outlined in the 'risk on infection' section in this table, above, there is currently no reason to believe that GSK3858279 could 1) increase the susceptibility of trial participants to the SARS-CoV-2 virus, or 2) worsen or mask any COVID-19 signs, symptoms or complications.	**Participant selection and monitoring** Healthy subjects in the current study fall in a low risk category for complications of COVID-19, the disease caused by the SARS-CoV-2 virus. To reduce the risk of SARS-CoV-2 infections among trial participants, measures and procedures based on the advice issued by GSK Global COVID Guidance, the Dutch Centre for Infectious Disease Control (RIVM) and COVID-19 measures declared by the Dutch government will be adhered to as outlined in CHDR SOP GGECOVID. These would include but are not limited to counselling participants regarding the importance of infection control measures such as hand washing, reducing inter-personal contacts as much as possible and participant awareness of potential COVID-19 symptoms. Site trial staff in direct contact and/or within 1.5 m distance of study subjects will receive additional protection via the use of Personal Protective Equipment (PPE) and disinfectants. Guidance for how participants should conduct themselves throughout the study in relation to COVID-19 restrictions are outlined in CHDR SOP GGECOVID

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		All trial subjects will be screened for SARS-CoV-2 with a PCR or rapid antigen test: 1) at screening visit Part 1 2) prior to each admission at the clinical unit with at least one overnight stay (i.e. at Day-2/Day-1); and 3) in case of symptoms possibly related to COVID-19. 4) at the final follow up visit. 5) at times as specified in current COVID-19 guidance of CHDR Healthy subjects may be excluded from the study if they test positive for SARS-CoV-2 from screening to the end of study treatments. In case of a positive SARS-Cov-2 antigen test result after first dose was administered, a SARS-CoV-2 PCR will be performed for confirmation. In case of discordant results, the PCR result is leading Participants >50 years will be excluded from the study. **Protection of Trial Integrity** Adherence to the protocol and CHDR SOP GGECOVID protects the integrity of the data

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		collected during this clinical trial, as well as participants' data protection rights. **COVID-19 Contingency Plan** Any subject that presents with COVID-19-related symptoms and/or has a positive SARS-CoV-2 PCR or rapid antigen test will be excluded from (further) participation in the trial and will receive follow-up medical attention per CHDR SOP GGECOVID

2.3.2. Benefit Assessment

There will be no direct benefit to the healthy participants participating in this clinical trial. By enrolling in this study, participants will be contributing to the process of developing new analgesic medications – a significant area of unmet medical need for patients intolerant or unresponsive to NSAID-related treatments.

2.3.3. Overall Benefit: Risk Conclusion

Taking into consideration the measures taken to minimize the risks to those participating in this study, the potential risks identified in association with GSK3858279 at the dose level to be administered and those associated with the PainCart assessments are considered minimal and are justified.

3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	Primary
To evaluate the effects of IV administration of GSK3858279 in Ultraviolet B (UVB) burn inflammatory, cold pressor test and electrical pain test in the PainCart	UVB heat pain detection (^{o}C) Cold pressor time to intolerable pain threshold (sec) Electrical pain tolerance threshold (mA) - single stimulus
Safety	Safety
To evaluate the safety and tolerability of GSK3858279 following IV dosing	Adverse Events (AE) and Serious Adverse Events (SAE). Clinical laboratory measurements, 12-lead electrocardiograms (ECG) and vital signs that are considered of potential clinical importance.
Exploratory	Exploratory
To evaluate the PK of GSK3858279 following IV administration	Serum PK concentrations and parameters including but not limited to: area under the concentration-time curve [AUC], maximum concentration [Cmax], tmax
To evaluate the target engagement of CCL17 by GSK3858279 following IV administration	Free and total CCL17 levels in serum

Objectives	Endpoints
To evaluate the effects of IV administration of GSK3858279 in additional endpoints in UVB test, cold pressor test and electrical pain test in the PainCart	Heat pain detection on normal skin (°C) Cold pressor time to pain detection (sec) Electrical pain detection (mA) - single stimulus Electrical pain detection and tolerance threshold (mA) - repeat stimulus For each test AUC/AAC and post-test eVAS
To evaluate the effects of IV administration of GSK3858279 in pressure pain test and Conditioned modulatory pain (CPM) test in the PainCart	Pressure pain (tolerance and detection) - KPa CPM - (tolerance and detection) – mA For each test AUC/AAC and post-test eVAS
To assess the potential for anti-GSK3858279 antibody formation following IV dosing	To include: incidence, titres, and, for samples with confirmed anti-drug antibodies (ADAs), neutralising activity

4. STUDY DESIGN

4.1. Overall Design

This study will be a randomized, double-blind, placebo-controlled, three-period two-treatment incomplete-block crossover study in healthy participants to investigate the effects of IV GSK3858279 on evoked pain tests in the PainCart. The study will be performed in a single centre.

In each period, participants will receive either GSK3858279 or placebo in a 1:1 ratio. During the trial, participants will receive both treatments, either two doses of GSK3858279 and one dose of placebo, or two doses of placebo and one dose of GSK3858279 with equal likelihood. The order of treatment assignments will be randomized. (see Section 6.3).

A three period design has been chosen because there is a marked reduction in variability for estimating the direct and residual treatment effects in three-period designs compared to two-period designs even with a large proportion of missing values, the three-period design is far more efficient than the two-period design [Carriere, 1994].

The total duration of the study (from signing informed consent until final follow-up visit) for each participant will be approximately 6 months. Study participation may be prolonged in the event the study is on-hold. Screening period will be a maximum of 28 days prior to study procedures, each study period will be approximately 2 weeks with at least a 4-week wash-out period between dosing (i.e. Day 1) in each of the study periods, final follow-up visit will be at approximately 8 weeks after last dose.

Participants will arrive at the research unit either one or two days before dosing, for the non-UVB-MITT and UVB-MITT group respectively. After arrival, subjects will be tested for SARS-CoV-2. Urine will be screened for the presence of drugs and an alcohol breath test will be performed. For participants with a positive urine drug screen or alcohol breath test, the treatment occasion may be rescheduled at the discretion of the principal investigator and GSK medical monitor. UVB irradiation will be applied approximately 24 hours before dosing in the UVB-MITT population only. ECG and vital signs will also be performed.

Participants will be assigned to receive treatment and pain assessments during either morning or afternoon sessions. They will continue to receive treatment and pain assessments at approximately the same time of day throughout all three study periods.

Meals will be served at the site scheduled times. Safety, PK, PD and PainCart assessments will be performed as outlined in the SoA. Baseline measurements for PainCart (2 baseline measurements) are conducted at each study period prior to dosing.

Phone contact to assess the participant's general health will be conducted as per the SoA, the investigator may invite the participant for a site visit at the investigator's discretion for additional follow-up, as required.

An interim analysis to assess the PD PainCart (three primary endpoints) and safety may occur once the final UVB-MITT participant has completed their final (day 15) PainCart assessments in Period 3. Participant demographics, safety, PK and target engagement may also be assessed at this interim (see Section 9.5 for further information).

An interim analysis to assess the PD PainCart (three primary endpoints) and safety may occur once the final participant has completed their final (day 15) PainCart assessments in Period 3. Participant demographics may also be assessed at this interim (see Section 9.5 for further information).

4.2. Number of Participants

Thirty healthy male participants will be enrolled into the study, such that at least approximately 24 participants complete all activites with the exception of the UVB on irradiated skin assessments, in all three study periods. If participants prematurely discontinue the study, additional replacement participants may be randomized, in order to guarantee that sufficient participants complete all three study periods. Replacement participants will be assigned to the same treatment sequence as the participant that they are replacing, at the discretion of the Sponsor and in consultation with the Principal Investigator.

Of the maximum thirty to be enrolled, approximately 18 healthy male participants are to be enrolled as part of the UVB population such that approximately 15 subjects complete the UVB heat pain detection test of the PainCart assessment on irradiated skin in all three study periods, in addition to the rest of the assessments.

4.3. Scientific Rationale for Study Design

The models allow a mechanistic approach to investigation of new drugs for pain, assessed in a controlled environment and allowing investigation of PK / TE / PD correlations. A number of existing drugs approved for treatment of pain have been used to validate these models [Hay, 2016; Okkerse, 2017] and although there are a few instances where the drugs fail to elicit a predicted response, the refinement/ standardisation of the models has improved this or allowed in part an explanation behind these discrepancies. The models allow investigation of specific pain mechanisms in a quantitative way.

This provides additional information on the translation from animal models to the patients and thus can potentially assist in designing further clinical trials in patients by selection of the best patient population.

The PainCart performed in this study is an integrated, multi-modal pain task battery of tests designed to investigate the efficacy of analgesic compounds against several types of pain, including thermal, electrical and mechanical pain. The models applied in the PainCart have been tested for predictive validity and reliability and can be used repeatedly, quickly, in short succession in healthy participant and patient studies.

The PainCart consists of the following tests (see Appendix 7 for further details):

- UVB burn model of inflammation (primary hyperalgesia)
- Cold pressor test (acute cold-induced ischaemic pain and conditioned pain modulation)
- Electrical pain test of nociceptor activation
- Pressure pain test of muscle nociception

For both UVB Heat Pain Detection and Cold Pressor time to intolerable pain threshold, the sample size is higher than that required for the Electrical Pain Test. Therefore, for the UVB-MITT population approximately 18 participants are required to be enrolled to ensure that approximately 15 participants complete all UVB heat pain detection tests of the PainCart assessment on irradiated skin in all three study periods.

4.3.1. Participant Input into Design

This is a study run in healthy participants. No participant input was taken into the design of this study.

4.4. Justification for Dose and Washout Period

The dose level of 3mg/kg, the 2-week testing duration of each study period, the wash out period of at least 4 weeks, the IV route of administration and the post dose assessment times of Day 1, Day 2, Day 8 and Day 15 are selected for the PainCart study based on:

The dose by IV route is equivalent to the dose of 240mg SC proposed to be administered in an on-going repeat dose study in osteoarthritis patients (207804) and was administered in a healthy participant cohort in that study (3 mg/kg IV).Serum levels of total (complexed, free and partially complexed) GSK3858279 are below the lower limit of quantification (LLQ; 100 ng/mL) after 8 weeks following IV infusion at 3 mg/kg; based on data from a fully validated non-neutralising anti-idiotype capture (NNAIC) assay [GlaxoSmithKline Document Number 2020N429762_00].

- Unbound CCL17 levels in serum have returned to approximately 30% of baseline at 4 weeks post dose.
    - A simulation plan was designed in order to investigate whether the statistical modelling for the PainCart assessments could control the potential properties of carry over effect. The plan details simulating carry over by varying different levels of drug accumulation in to the subsequent period, and the number of days it took for the drug to be eliminated. The results from the simulation showed even in the most extreme scenario (40% accumulation, 2 weeks reduction) the model was capable of extracting the treatment differences while controlling any potential carry over effects.
    - Given the statistical model chosen for analysis, and no increase in risk of safety, the washout period of at least 4 weeks is selected and still considered sufficient (data on file).
- Target engagement (percentage reduction from baseline of free CCL17) is above 90% within 24 hours of dosing IV and continues to 1-week post IV dose of 3 mg/kg. TE falls to 75% after 2 weeks post dose IV.
- t_{max} is at end of IV dose administration allowing PainCart testing to be scheduled at consistent fixed timepoints relative to dosing.

4.5. End of Study Definition

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

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

5. 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:

Age

Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and cardiac monitoring.

Weight

Body weight within 50–100 kg and body mass index (BMI) within the range 18----30kg/m^2 (inclusive).

Sex

Must be Male:

Participants must agree to the following during the intervention period and for at least 90 days after the last 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.

Informed Consent

Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of/significant history of or current 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 as determined by the investigator.
4. Symptomatic herpes zoster within 3 months prior to screening.
5. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, and TB testing: a positive (not indeterminate) QuantiFERON-TB Gold test.

   NOTE: The QuantiFERON-TB Gold 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.
6. Significant allergies to humanized monoclonal antibodies.
7. 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. Those who are at risk of DNA repair diseases or any family history of DNA repair disease.
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. 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 subject will be QTcF. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject 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 an acute, re-current or 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 excessive bleeding or coagulation disorders.
17. Previous history of hypertrophic or keloid scarring.
18. Any current, clinically significant, known medical condition in particular any existing conditions that would affect sensitivity to cold (such as atherosclerosis, Raynaud's disease, urticaria, hypothyroidism) or pain (such as disease that causes pain, hypesthesia, hyperalgesia, allodynia, paraesthesia, neuropathy).
19. Participants indicating pain tests intolerable at screening Participants achieving tolerance at >80% of maximum input intensity for cold pressor and electrical pain tests are to be excluded. If pressure pain test tolerance is >80% of maximum input intensity they may be enrolled as per PI judgement
20. History or presence of post-inflammatory hyperpigmentation. Applicable for the participants in the UVB-MITT population only.
21. Participants with Fitzpatrick skin type IV, V or VI. Applicable for the participants in the UVB-MITT population only.
22. Any of the following on the proposed test area on the back: widespread acne, freckles, tattoos, birthmarks or scarring (investigator discretion may be used to determine if small areas may be avoided in the testing area on the back). Applicable for the participants in the UVB-MITT population only.
23. A minimal erythema dose (MED) higher than 355 mJ/cm^2 at screening. Applicable for the participants in the UVB-MITT population only.

Prior/Concomitant Therapy

24. Past or intended use of over-the-counter or prescription medication including herbal medications within 7 days prior to dosing until after follow-up visit.

25. Live vaccine(s) within 1 month prior to dosing or plans to receive such vaccines during the study.
26. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) or immunosuppressants within 3 months or 5 half-lives (whichever is longer) prior to dosing.
27. Treatment with anti-platelet or anti-coagulant agents within 7 days of dosing.
28. Major surgery (as per investigator's judgement) within 3 months prior to dosing.

Prior/Concurrent Clinical Study Experience

29. Participant has made a blood or plasma donation or has had a comparable blood loss (>450mL) within the last 3 months prior to the Screening Visit. Blood donation during the study is not permitted.
30. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
31. Current enrolment or past participation in any other clinical study involving an investigational study intervention within the last 3 months, 5-half-lives or twice the duration of the biological product before dosing in this current study.

Diagnostic assessments

32. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention.
33. Presence of Hepatitis B core antibody (HbcAb) at screening or within 3 months prior to first dose of study intervention.
34. Positive Hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.

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

    NOTE: Test is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
36. Abnormal clinically significant echocardiogram at screening, as assessed by the investigator.
37. Cardiac troponin T or NT-proBNP levels out of normal range at screening.
38. Positive pre-study drug/alcohol screen.
39. Positive human immunodeficiency virus (HIV) antibody test.
40. Regular use of known drugs of abuse.
41. Estimated glomerular filtration rate (eGFR) of <90 mL/min/1.73 m^2 or serum creatinine >1.5xULN or urine albumin:creatinine ratio of >300mg/g at screening.

42. Positive SARS-CoV-2 PCR or rapid antigen test at screening Participants may be re-screened once they present a negative SARS-CoV-2 PCR or rapid antigen test

Other Exclusions

43. Subjects with known COVID-19 positive contacts in the past 14 days
44. Regular alcohol consumption within 6 months prior to the study defined as:
    - an average weekly intake of >21 units for males. 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.
45. Smoker, smoking history or use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening.
46. Sensitivity to heparin or heparin-induced thrombocytopenia.
47. 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. Meals and Dietary Restrictions

Poppy seed or foods containing poppy seeds are not permitted from 3 days before screening, dosing and until the end of the last study period.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will not be allowed to have excessive caffeine consumption, defined as >800 mg per day from 7 days prior to the first dose of the study drug until 24 hours prior to dosing. Participants will abstain from caffeine-containing products for 24 hours prior to each visit to the study unit. Caffeine quantities defined as: one cup of coffee contains 100 mg of caffeine; one cup of tea, or one glass of cola, or portion of chocolate (dark: 100 g, milk: 200 g) contains approximately 40 mg of caffeine; one bottle of Red Bull contains approximately 80 mg of caffeine.
- Alcohol will not be allowed from at least 24 hours before each scheduled visit, and whilst in the study unit until discharge from the study unit. At other times throughout the study, participants should not consume more than 2 units of alcohol daily on average (one unit is **8** g of alcohol). Participants may undergo an alcohol breath test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products (including e-cigarettes and patches) from the screening visit throughout the study until the final follow-up visit.

5.3.3. Activity

- Strenuous physical activity (e.g., heavy lifting, weight or fitness training) is not allowed from 48 hours prior to each study day (including screening) until discharge from the study unit. Light ambulatory activities (e.g. walking at normal pace) will be

permitted, with the level of activities kept as similar as possible on all days in the study unit.

5.3.4. Exposure to sunlight

Participants, who will form the UVB-MITT population, are asked not to expose their back to excessive sunlight or to sunbathe, including sun tanning in a sun booth and chemical spray tans, between screening and last study period Day 15. This restriction is not required for volunteers who do not receive the UVB application sessions.

5.3.5. SARS-CoV-2 related restrictions

Participants will be required to adhere to the measures and procedures outlined in CHDR SOP GGECOVID, based on the advice issued by the Dutch Centre for Infectious Disease Control (RIVM) and COVID-19 measures declared by the Dutch government, to reduce risk of SARS-CoV-2 infections among trial participants and clinical site staff.

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, any protocol deviations and any serious adverse events (SAEs).

5.4.1. Re-screening

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

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. The urine drug screen can only be repeated for a valid reason (e.g. false positive result due to medication use, poppy seed consumption).

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 or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	Active	Placebo
Intervention Name	GSK3858279	Placebo
Type	Biologic	Placebo
Dose Formulation	Solution for injection. 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.	Solution for injection. Normal Saline (0.9% sodium chloride)
Unit Dose Strength	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.
Dosage Levels	3 mg/kg. Single dose, once per study period.	Single dose, once per study period.
Route of Administration	IV Infusion	IV Infusion
Dosing Instructions	GSK3858279 will be infused over 1 hour. GSK3858279 can be diluted in normal saline prior to administration	The appropriate volume of placebo will be infused over 1 hour.
Use	Experimental	Placebo-control
IMP and NIMP	IMP	Placebo
Sourcing	Study medication is supplied by GSK.	Provided locally by the trial site, subsidiary, or designee.

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

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 labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.
- 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 randomized to a treatment group through RAMOS NG. The randomization is centrally controlled by RAMOS NG.

RAMOS NG will confirm the participants CRF number (Participant number) and provide the randomization number, where:

- A randomization number will be assigned from a randomization 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.

In each period participants will receive either GSK3858279 or placebo in a 1:1 ratio where the intervention codes are as follows:

Intervention code	**Intervention Description**
A	3 mg/kg IV GSK3858279
P	Placebo

During the trial, participants will receive both treatments, either two doses of GSK3858279 and one dose of placebo, or two doses of placebo and one dose of GSK3858279 with equal likelihood, the order of treatment assignments will be randomized. The exact sequences will be blinded to the blinded investigator site staff and participants to prevent bias. Participants will be randomized to a specific sequence on Day 1 of the first study period.

The randomization will be stratified based on whether the pain assessments will be performed in the morning or afternoon.

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 Safety and Medical Governance (SMG) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- There will be an unblinded site pharmacist to prepare the study intervention; however, they will not have contact with study participants.
- There may be two interim analyses performed (see Section 9.5 for details). Unblinded data will be reviewed by members of the GSK3858279 team who do not have direct contact with the study site or 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 route. 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 is receiving at the time of enrolment or receives during the study must be recorded along with:

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

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

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 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.

6.5.1. Permitted Therapies

Paracetamol at doses of ≤3 grams/day, is permitted for use at any time during the study except those times referred to in Section 6.5.2.

Ibuprofen at doses of ≤1.2 grams/day, is permitted for use at any time during the study except those times referred to in Section 6.5.2.

6.5.2. Prohibited Medications

The following restrictions apply from first dose up until the 8-week follow-up visit

Medication	Pre-dose restriction	Other times
Ibuprofen	2 days	For 2 days prior to admission to unit and PainCart assessment (applicable from screening and during study)
Paracetamol	2 days	For 2 days prior to admission to unit and PainCart assessment (applicable from screening and during study)
All other pain medication including topical	1 month	From screening to 8-week follow-up
Live vaccine(s)	1 month	Throughout and for five half-lives after last dose
Biologic agents (monoclonal antibodies, therapeutic proteins)	3 months or 5 half-lives (whichever is the longer)	Throughout
Antiplatelet or anticoagulant agents	7 days	Throughout
Immunosuppressants	3 months or 5 half-lives (whichever is the longer)	Throughout
Systemic corticosteroids (inhaled administration is allowed)	Parenteral: 3 months Oral: 1 month	Throughout

6.6. Dose Modification

No modification of the dose-level is planned on the study.

6.7. 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:

- Two participants experience the same SAE that is considered related to GSK3858279
- 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 Investigator and GSK Medical Monitor and following approval to restart the study from the regulatory agency and ethics committee.

7.2. Discontinuation of Study Intervention

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:

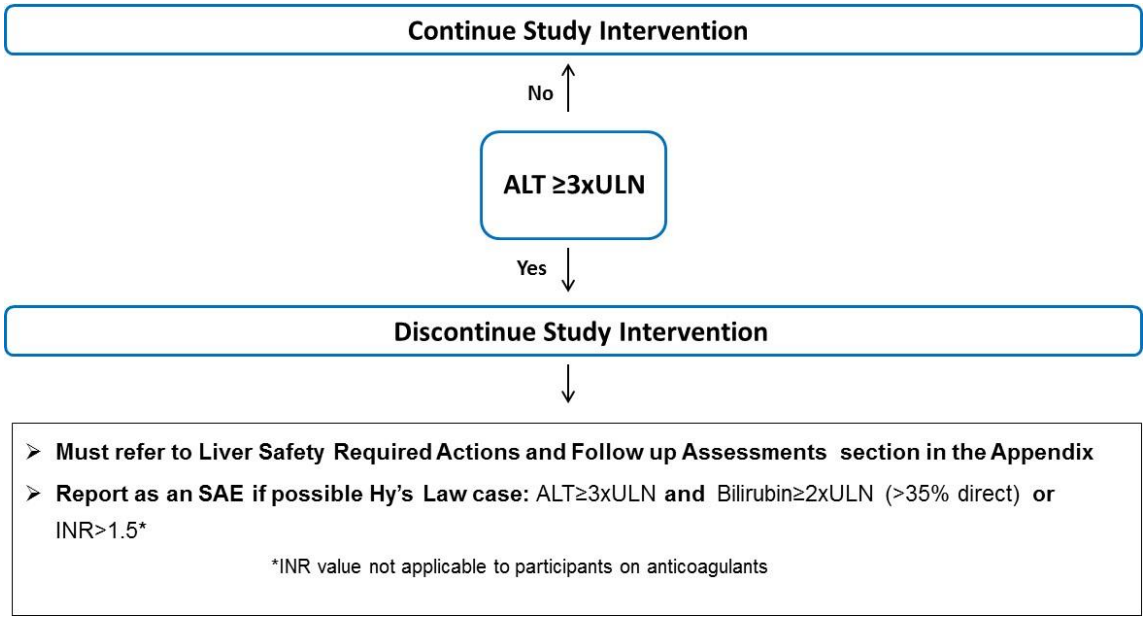
- All serious infections
- Severe or serious hypersensitivity reactions, including anaphylaxis
- If the liver chemistry stopping criteria (Section 7.2.1) or QTc stopping criteria (Section 7.2.2) are met.
- Other serious or severe adverse events, at the discretion of the Investigator, after consultation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

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.

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

- a participant meets one of the conditions outlined in the algorithm.
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.
- Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:



Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm

Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Appendix 5 for required Liver Safety Actions and Follow up Assessments.

7.2.2. QTc Stopping Criteria

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

  - QTcF > 500 msec,
  - Increase from baseline: QTcF > 60 msec
  - In this study as QTcF is used for study eligibility, thus QTcF must be used for discontinuation decisions.
  - QTcF has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (see Section 8.1.3), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.
- If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2.3. SARS-CoV-2 related stopping criteria

If a participant develops COVID-19 like symptoms during the course of the study, procedures as specified in CHDR SOP GGECOVID will be followed.

Withdrawal of participants from the study will be at the discretion of the Principal Investigator, but should first be discussed and agreed with the GSK Medical Monitor. Further dosing and study related procedures except those required for participant safety and well being should be paused until the discussion is complete.

Participants that test positive for a SARS-CoV-2 infection after the first study dose are withdrawn from the study (after discussion with the GSK Medical Monitor and PI) will be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator.

Subjects with a SARS-CoV-2 infection will be followed-up according to SOP GGECOVID.

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. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.4. Lost to Follow Up

A participant will be considered lost to follow-up if he 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, 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening

log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

8.1. Safety Assessments

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

8.1.1. Physical Examinations

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

8.1.2. Vital Signs

- Tympanic body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed supine with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be used in the analysis.

8.1.3. Electrocardiograms

- Triplicate or single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 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.

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 for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 study reference manual or local practice and the SoA.

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.

8.1.6. Skin Reactions

Skin reactions will be recorded as Adverse Events. 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. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and 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 intervention (see Section 7).

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

- All SAEs will be collected from the start of intervention until the follow-up visit at the 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 start of study intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 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 after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.2.2. Method of Detecting AEs and SAEs

- 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.
- 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.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as

defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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.
- For all studies except those utilizing medical devices 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 SAEs) from the sponsor will review and then file it along with the Investigator's Brochure will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5. Pregnancy

- Sponsor will make an effort to collect details of all pregnancies in female partners of male participants, this will be collected after the start of study intervention and until 28 weeks after the last 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.

8.3. Treatment of Overdose

For this study, any dose of GSK3858279 greater than the scheduled dose will be considered an overdose. GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.

Closely monitor the participant for AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 56 days post-last dose of study intervention).

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.

8.4. Pharmacokinetics

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

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

8.4.1. Pharmacokinetic Sample Analysis

Serum (PK) analysis will be performed under the control of GSK Invitro/Invivo Translation (IVIVT). Serum concentrations of GSK3858279 will be determined using approved bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g. SRM) and raw data will be archived in the GSK R&D GLP archives. Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Pharmacodynamics

Blood samples (approximately 3.5mL) will be collected from participants in this study to investigate target engagement, with respect to the data obtained from the PainCart.

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

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

8.5.1. Target Engagement

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

8.5.2. PainCart

Nociceptive pain detection and tolerance thresholds can be measured using the PainCart. This is an integrated range of tests for measuring different modalities of nociception. The PainCart aims to assess as objectively as possible the levels of pain induced in human participants by a variety of potentially noxious stimuli. All measurements will be performed in a quiet room with ambient illumination and temperature. Per session, there will only be one subject in the same room. During nociceptive tasks, participants will be sitting comfortably in a designated chair, with knees supported. The order of the individual PainCart assessments will be identical for all participants and for all time-points. See Appendix 7 for further details.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not planned to be evaluated in this study.

8.8. Immunogenicity Assessments

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

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

8.9. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study will test the null hypothesis that there is no difference between GSK3858279 and placebo versus the alternative hypothesis that GSK3858279 is superior from placebo on the endpoints described: UVB heat pain detection test, cold pressor time to intolerable pain threshold test and electrical pain tolerance threshold test in the PainCart scale. No Adjustment will be made for multiplicity.

9.2. Sample Size Determination

A maximum of 30 participants will be randomized into the study as per Section 6.3.1 such that approximately 24 participants complete all three periods of the study (except UVB assessments on irradiated skin). Approximately18 subjects will undergo the UVB assessments on irradiated skin such that approximately 15 subjects complete the UVB assessments in all three periods.

On each of the three endpoints, a positive conclusion will be declared if, given the data, there is at least 90% probability that the ratio vs placebo is better than 1 (no difference) and a negative conclusion will be declared if, given the data, there is less than 75% probability that the difference vs placebo is better than 1 (no difference).

The coefficient of variation for each endpoint was estimated from Loudon, 2018; Okkerse, 2017; Siebenga, 2019; van Amerongen, 2018, and is shown in Table 1.

Table 1 Coefficient of Variability

UVB heat pain detection (°C)	Cold pressor time to intolerable pain threshold (sec)	Electrical pain tolerance threshold (mA)
3.7%	25.6%	19.1%

With 24 completed participants using a three-period two-treatment incomplete-block crossover design, the probability of declaring a positive outcome on each endpoint where there is no improvement is fixed at 10% by definition (Type I Error). The operating characteristics of each endpoint is provided in Figure 4.

9.2.1. Sample Size Sensitivity

The impact of increases/decreases in the variability of each endpoint from the expected variability is demonstrated in Figure 4 and Figure 5. Subject drop out of 20% is accounted for in the sample size. Operating characteristics and probability of positive outcomes Figure 4 and Figure 5 are based on a sample size of 24 for Electrical pain tolerance and Cold pressor time to intolerable pain threshold, and sample size of 15 for UVB heat pain detection on irradiated skin.

Figure 4 **Operating Characteristics of Study Design. a: Electrical pain tolerance threshold (mA) b: Cold pressor time to intolerable pain threshold (sec) c: UVB heat pain detection (°C)**

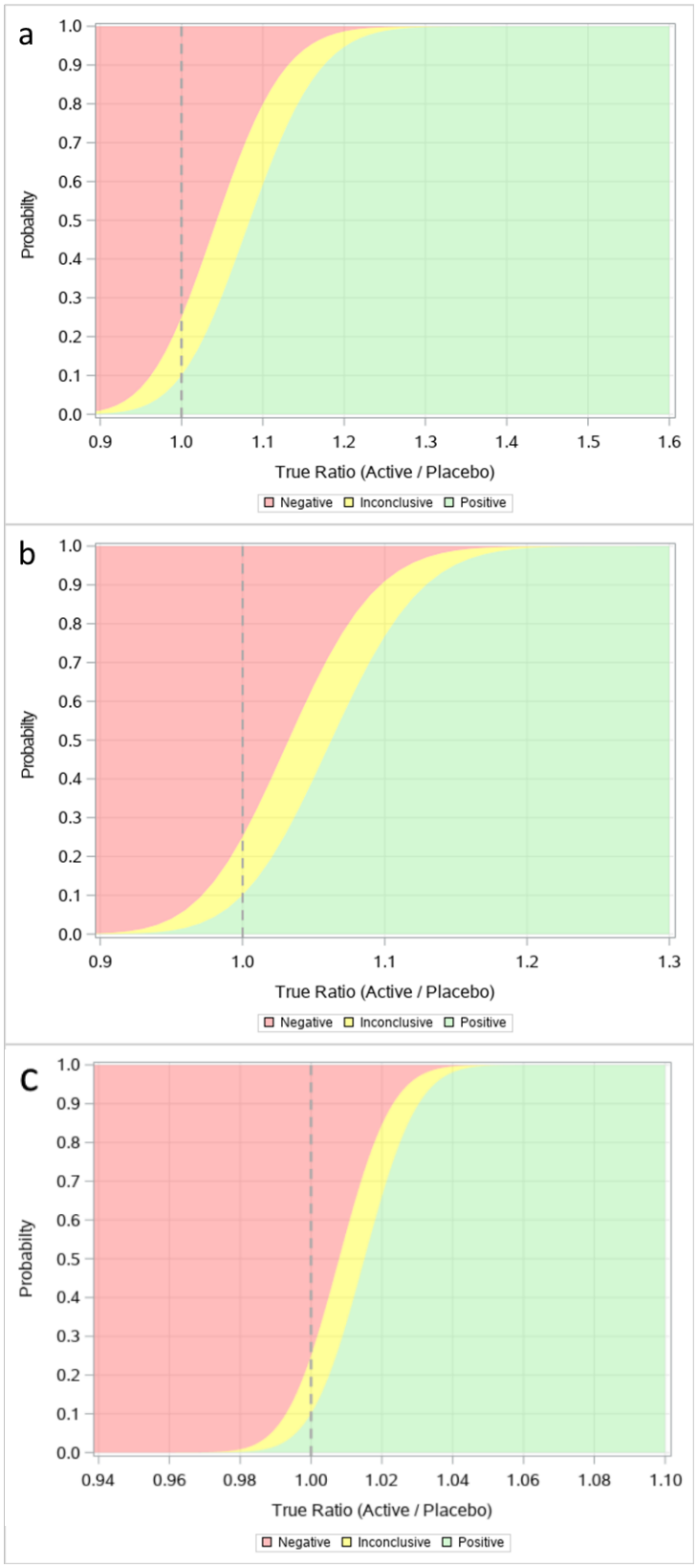
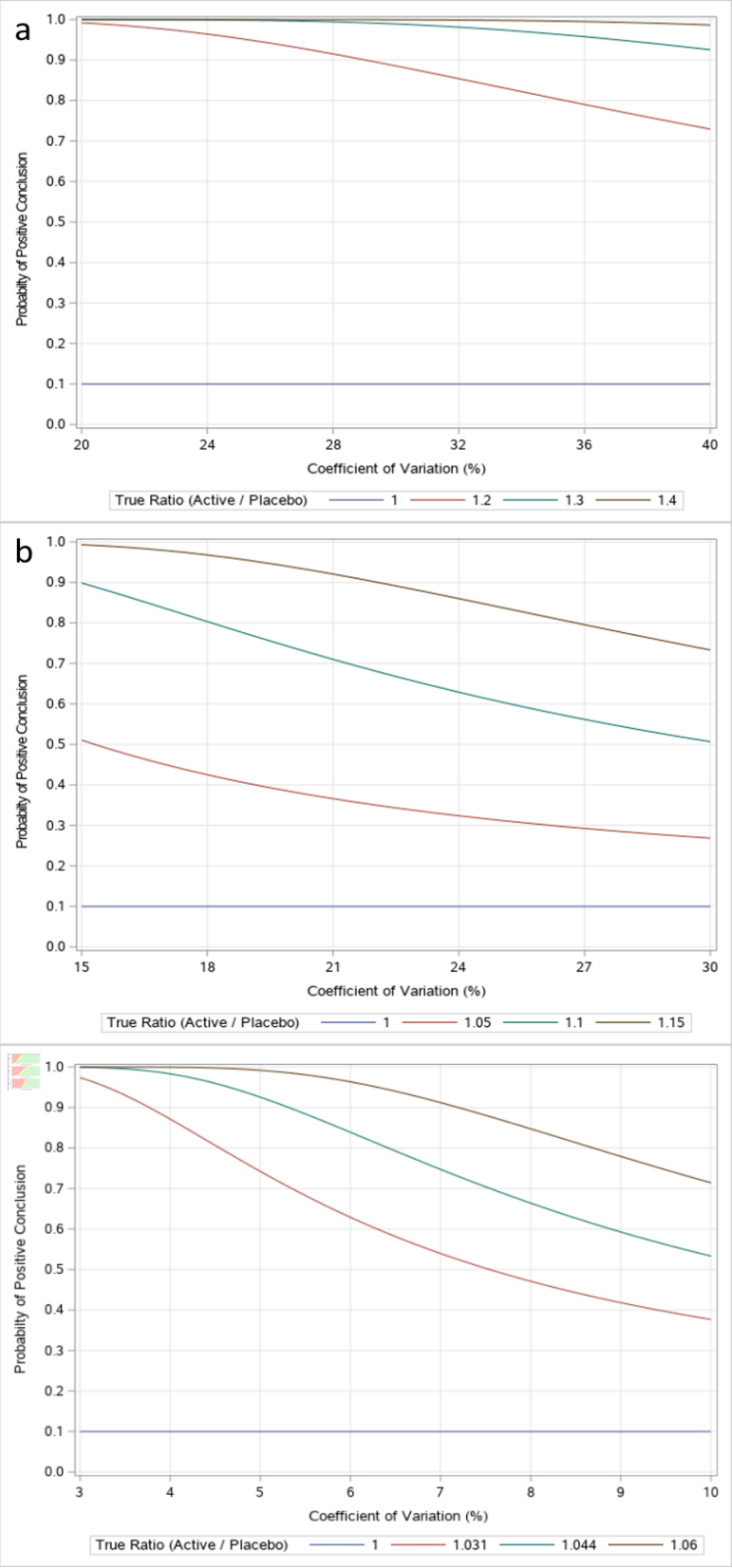


Figure 5 **Probability of positive conclusion based on different assumptions. a: Electrical pain tolerance threshold (mA) b: Cold pressor time to intolerable pain threshold (sec) : UVB heat pain detection (ºC)**



9.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	• All participants who were screened for eligibility
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment the participant was randomized to.
Enrolled	• All participants who passed screening and entered the study. Included are: Run-in Failures; Randomized Participants. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.
Safety	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the subject actually received.
Pharmacokinetic (PK)	• All participants in the Safety population who had at least 1 non-missing serum PK assessment. • Note: Non-quantifiable [NQ] values will be considered as non-missing values
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 subject was randomized to. • Any participants who receives a treatment randomization number will be considered to have been randomized.
Modified Intent-to-Treat (MITT)	• All randomized participants who received at least one dose of study treatment and completed at least one PainCart assessment in at least two study periods. • This population will be based on the treatment the subject was randomized to. • Any participants who receives a treatment randomization number will be considered to have been randomized.
UVB-MITT (UVB)	• Those in the MITT Population who also perform the UVB Heat Pain detection PainCart assessments on irradiated skin.

Population	Description
Completers	• All randomized participants who receive at least one dose of study treatment in all three periods of the trial and completed all scheduled PainCart assessments. • This population will be based on the treatment the subject was randomized to. • Any participants who receives a treatment randomization number will be considered to have been randomized.

9.4. Statistical Analyses

The Reporting and Analysis Plan will be finalized prior to database release (DBR) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

9.4.2. Primary Endpoint(s)

The PainCart measures as described in Section 10.7.2 will be summarized descriptively by intervention. A Bayesian repeated measures model using non-informative priors for each parameter will be fitted to the change from baseline data using an unstructured covariance matrix and, covariates in the model will be detailed in the Reporting and Analysis Plan. Posterior probabilities will be determined and presented at each timepoint.

9.4.3. Secondary/Exploratory Endpoint(s)

Will be described in the Reporting and Analysis Plan.

9.4.4. Other Safety Analyses

All safety analyses will be performed on the Safety Population and will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library standards.

9.4.5. Other Analyses

A post hoc analysis may be carried out to assess the relationship between the observed measures of efficacy and the individual PK exposure or target engagement. If data permits, direct -or indirect response models to link efficacy with PK or TE may be developed. PK and TE data may be integrated in the previous population PK/TE model developed from Part A of study **207804** (GlaxoSmithKline Document Number RPS-CLIN-015095).

9.5. Interim Analyses

Two interim analyses may occur during the conduct of the study:

- An interim analysis may be performed once the final UVB-MITT participant in period 3 has completed the day 15 assessments of the PainCart. At the interim, PainCart, safety, demographics, PK and TE data will be reviewed by the Project Leader and selected members of the Project Team and CPEM Leadership. Dependent on the results observed in the cold pressor and electrical pain single stimulus tolerance endpoints, the study could be stopped for futility. A secondary objective for the interim may be to use the analysis for internal decision-making purposes. An interim analysis may be performed once the final participant in period 3 has completed the day 15 assessments of the PainCart. The interim analyses will be used for internal decision making only, no changes to the study can occur.

Further details of the interim analyses will be provided in the interim charter. The Reporting and Analysis Plan will provide further infomration on the planned statistical analyses performed at the interim analyses.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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 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.

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

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate tick box will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Not applicable.

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 participants, 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 Disclosure 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 30 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- A retention period of 30 years instead of 25 years is used, as the long-term effects of GSK3858279 are still unknown and the to be included healthy volunteers could be of relatively young age; thus still with a long life-expectancy

10.1.8. 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 Start and Closure

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin (direct is only measured if total >1xULN)
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	[3]Complement protein C3 and C4
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Breath alcohol test • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)			

Laboratory Assessments	Parameters
	• HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody [HbcAb] and hepatitis C virus antibody. • QuantiFERON testUrine albumin-creatinine ratio (UACR) • [4]SARS-CoV2 PCR or rapid antigen test The results of each test must be entered into the medical notes.
Other Screening and Follow-Up Tests	• Troponin-T (high sensitivity) • NT-proBNP

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. Complement protein C3 and C4 to be performed **Day -1 only** (as baseline).
4. Combined throat and nasopharyngeal swab; qPCR will be performed by NMDL-LCPL. Approved rapid antigen tests may be used instead of PCR

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (haematology, 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.

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

- Medical or surgical procedure (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:
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 fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) 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. Recording and Follow-Up of AE and SAE

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

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) 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

Males must use the male condom or be long-term sexually abstinent as per Section 5.1 and should be advised of the benefit for a female partner to use a highly effective method of contraception as outlined in Section 10.4.1.

10.4.1. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods 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 That Are User Dependent**

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

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

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), 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)

10.4.2. Collection of Pregnancy Information:

Male participants with partners who become pregnant

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

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

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

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or <u>international normalized ratio (INR)</u> >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
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis as soon as possible, and at least within 7 days, post last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
</table>

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

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

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

10.6. Appendix 6: Abbreviations and Trademarks

Abbreviations

AAC	Area Above the concentration-time Curve
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
AUC	Area Under the concentration-time Curve
BCG	Bacillus-Calmette-Guerin
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA	Competent Authority
CCL17	Chemokine C-C motif ligand 17
CFR	Code of Federal Regulation
CHDR	Centre for Human Drug Research
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimetre
Cmax	Maximum Observed Concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus Disease
CPK	Creatine Phosphokinase
CPM	Conditioned Pain Modulation
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
DBR	Database Release
DNIC	Diffuse Noxious Inhibitory Control
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
eVAS	Electronic Visual Analogue Scale
FDA	Food and Drug Administration
FiH	First in Human
g	Gram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High-Performance Liquid Chromatography
Hz	Hertz

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgM	Immunoglobulin G
INR	International Normalized Ratio
IP	Investigational Product
ITT	Intent-To-Treat
IUD	Intrauterine Device
IRB	Institutional Review Board
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Recognition System
kg	Kilogram
KPa	Kilopascal
LAM	Lactational Amenorrhoea Method
LDH	Lactate Dehydrogenase
mA	MilliAmp
mAb	Monoclonal Antibody
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MED	Minimal Erythema Dose
mg	Milligram
mJ	Millijoule
mL	Milliliter
MSDS	Material Safety Data Sheet
NIMP	Non-Investigational Medicinal Product
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PBO	Placebo
PD	Pharmacodynamics
PK	Pharmacokinetics
PPE	Personal Protective Equipment
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
PDT	Pain Detection Threshold
PTS	Platform Technologies and Science
PTT	Pain Tolerance Threshold
RAMOS NG	Randomization and Medication Ordering System Next Generation
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells

RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SARS-Cov-2	Severe acute respiratory syndrome– Coronavirus-2
SC	Subcutaneous
sec	Seconds
SGOT	Serum Glutamic-Pyruvic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMG	Safety and Medical Governance
SRM	Study Reference Manual
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus and Activation Regulated Chemokine
TB	Tuberculosis
TDAR	T-cell Dependent Antibody Response
TE	Target Engagement
tmax	Time taken to Maximum Observed Drug Concentration
TST	Tuberculin Skin Test
UACR	Urine albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
UV	Ultraviolet
UVB	Ultraviolet B
VAS	Visual Analogue Scale
WBC	White Blood Cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
RAMOS NG

Trademarks not owned by the GlaxoSmithKline group of companies
PainCart
Q-sense
QuantiFERON
Spike2 software

10.7. Appendix 7: PainCart Details

At the Centre for Human Drug Research (CHDR), nociceptive (pain) detection and tolerance thresholds can be measured using the PainCart. This is an integrated range of tests for measuring different modalities of nociception. The PainCart aims to assess as objectively as possible the levels of pain induced in human subjects by a variety of potentially noxious stimuli. All measurements will be performed in a quiet room with ambient illumination and temperature. Per session, there will only be one subject in the same room. During nociceptive tasks, subjects will be sitting in a designated chair, with knees supported.

10.7.1. Individual Assessments

10.7.1.1. UVB model (Thermal pain, normal & UVB exposed skin)

UVB irradiation (TL01 [narrow-band], Philips) is applied at the screening visit in ascending doses (corresponding to different irradiation times) to 6 different 1 x 1 cm areas of skin on the back to determine the individual UVB dose that produces the first clearly discernible erythema (MED). The MED is assessed visually. See Table 3 for the dosing schedule per skin type (mJ/cm^2).

Two times the MED of UVB (assessed at screening) will be applied on the back, 24±2 hours prior to the first pain tasks (the day prior to dosing on all 3 study periods and on day 7 of all study periods). The area of skin irradiated will be 30 x 30 mm. The procedure has been adapted from the methods of Bishop and colleagues [Bishop, 2009], and is according to CHDR SOP CCNUVB with the exception that assessment of MED will be performed at screening only.

To assess inflammatory pain, thermal pain tests will be performed first on normal skin contralateral to the site of UVB irradiation, then on UVB irradiated skin**. On Day 15 thermal pain tests will only be performed on an area of normal skin on the back, not on skin earlier exposed to UVB**

Table 3 UVB dose regimen per skin type (mJ/cm^2).

	Skin Type			
Dose (mJ/cm^2)	**I**	**II**	**III**	**IV**
#1	64	126	176	234
#2	91	177	248	330
#3[a]	128	251	351	467
#4	181	355	496	660
#5	256	502	702	934
#6	362	710	993	1321

a - The mean MED according to Sayre et al. [Sayre, 1981].

10.7.1.1.1. Thermal pain

Thermal pain detection and tolerance thresholds are determined using the Q-sense (Medoc, Israel), which controls a 30 x 30 mm thermode that is placed on the subjects

back. The initial temperature of the thermode will be 32°C and will increase by 0.5°C·s^{-1} until the subject perceives the stimulus as painful (Pain Detection Threshold [PDT] - indicated with pushing a button on a hand-held feedback control) or when a temperature of 50°C is reached. The average of a triplicate measurement will be used to determine pain thresholds.

10.7.1.2. Continuous assessment of pain

Pain intensity will be measured continuously for each of the following nociceptive tasks with subjects rating their pain intensity using a 100% eVAS-slider, with 0 and 100 defined as [redacted] and [redacted], respectively. Equipment is programmed to cease giving stimuli if pain intensity reaches the maximum possible score. Alternatively, all tasks have a maximum safety limit at which the tasks automatically stops.

10.7.1.3. Cold Pressor task (Cold pressor)

The method of cold pressor pain is based on the methods described by Eckhardt and colleagues and Jones and colleagues [Eckhardt, 1998; Jones, 1988]. Subjects place their non-dominant hand into a water bath (minimal depth 200 mm) at 35 ± 0.5 °C for 2 minutes. At 1 minute 45 seconds a blood pressure cuff on the upper-arm will be inflated to 20 mmHg below resting diastolic pressure. At 2 minutes the subject will then move their hand from the warm water bath, directly placing their hand into a similar sized bath at 1.0 ± 0.5 °C. The subjects will be instructed to indicate when pain detection threshold is reached (first change in sensation from cold non-painful to painful) as well as the increase in pain intensity, by moving the eVAS slider. When pain tolerance is reached (sensation is no longer tolerable; eVAS slider at 100 mm), or when a time limit (120 s) is reached, subjects are instructed to remove their hand from the water, at which point the blood pressure cuff will deflate.

10.7.1.4. Electrical stimulation task (Electrical stair)

For cutaneous electrical pain, two electrodes (Ag-AgCl) are placed on clean (scrubbed) skin overlying the left tibial bone 100 mm distal from the caudal end of the patella (middle of the first electrode is placed 100 mm distal the caudal end of the patella and middle of the second electrode 135 mm directly underneath the first). Electrical resistance between electrodes should be less than 2 kΩ.

For single (stair) stimulus, each stimulus (10-Hz tetanic pulse with a duration of 0.2 ms) is controlled by a computer-controlled constant current stimulator. Current intensity increases from 0 mA in steps of 0.5 mA·s-1 (cut-off 50 mA). The pain intensity after each stimulation is measured using the eVAS, until pain tolerance level is reached or a maximum of 50 mA is reached (Adapted from the method of Olofsen and colleagues) [Dahan, 2004; Olofsen, 2005].

For repeated (burst) stimulus, each single stimulus is repeated 5 times with a frequency of 2 Hz. Pain threshold is taken as the value (mA) whereby a subject indicates either: all 5 stimuli are painful, or the train of 5 stimuli started feeling non-painful but ends feeling

painful (VAS > 0) (Adapted from the method of Arendt-Nielsen and colleagues) [Arendt-Nielsen, 2007].

To measure **conditioned pain modulation** (CPM; formerly diffuse noxious inhibitory control [DNIC]), the single stimulus will be repeated within 5 minutes of the end of the cold pressor task.

10.7.1.5. Pressure stimulation task (Pressure pain)

This method of pressure pain induction has been shown to primarily assess nociception generated from the muscle with minimal contribution by cutaneous nociceptors and is based on methods described by Polianskis and colleagues [Polianskis, 2001]; Polianskis, 2002]. Briefly, an 11 cm wide tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany) is placed over the gastrocnemius muscle with a constant pressure rate increase of 0.5 kPa/s controlled by an electro-pneumatic regulator (ITV1030-31F2N3-Q, SMC Corporation, Tokyo, Japan), Power1401mkII analogue–to-digital converter and Spike2 software (CED, Cambridge, UK). The subject sits comfortably with their foot flat on the floor and rates their pain intensity using the eVAS, with 0 and 100 defined as CCI and CCI , respectively. The pneumatic pressure is increased until the subject indicates their pain tolerance threshold, or a maximum pressure of 100 kPa is achieved, at which point the device releases pressure to the tourniquet.

10.7.2. PainCart Endpoints

AAC: Area above the curve from eVAS, AUC = area under the curve from eVAS, PDT = pain detection threshold, PTT = pain tolerance threshold, (e)VAS = (electronic) visual analogue scale

- Thermal Pain (Normal Skin): PDT
- Thermal Pain (UVB skin): PDT
- Cold Pressor: PDT, PTT, AAC, post-test VAS
- Electrical stair (pre-cold pressor): PDT, PTT, AUC, post-test VAS
- Electrical stair (post-cold pressor): PDT, PTT, AUC, post-testVAS
- Electrical burst: PDT, PTT, AUC, post-test VAS
- Pressure Pain: PDT, PTT, AUC, post-test VAS

For PainCart assessments, baseline is defined as the average value prior to dosing in each session.

10.7.3. Order of PainCart assessments

Order of PainCart assessments will be as specified in CHDR SOP

10.8. Appendix 8: Protocol Amendment History

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

Amendment 3 10-AUG-2020

Overall Rationale for the Amendment: Change to Analysis Populations. Populations are now UVB-MITT who undergo all assessments and MITT population who do not receive UVB irradiation (and not perform UVB heat pain detection assessment on irradiated skin). In addition, changes to expand age range and amendment of certain exclusion criteria in order to reduce volunteer burden and aide recruitment.

Risk Benefit Analysis has also been amended in protocol amendment 03 to reflect changes made to the study design and new safety guidance available.

As a result of the worldwide pandemic of COVID-19, throughout the protocol there have been addition of SARS-Cov2 screening and mitigation strategies to ensure the safety of the study participants.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Explanation of UVB-MITT population Clarification of visit days for UVB-MITT population	This is to clarify that not all participants will be required to receive UVB irradiation This is to clarify how the visit days differ for the UVB-MITT population
Section 1.2 figure 3	Clarification of measurements for UVB-MITT population	This is to clarify which of the new analysis populations receive UVB irradiation and assessments
Section 1.3.1 Schedule of Activites	Clarification of assessments for UVB-MITT Population	This is to clarify which of the new analysis populations receive UVB irradiation and assessments
Section 1.3.2 Schedule of Activites	Clarification of assessments for UVB-MITT Population Addition of Day -2	This is to clarify which of the new analysis populations receive UVB irradiation and assessments This is to accommodate a COVID-19 test prior to UVB exposure
Section 1.3.2 Schedule of Activites	Addition of an extra blood sample for PK and PD assessments	This is to allow for a better estimate of Cmax and link to the target engagement

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment	Change to minimum monitoring time post-dose Clarity that UVB irradiation and UVB test risk only applicable to UVB-MITT population Update to participant monitoring for potential risk 'Hypersensitivity, including injection site and infusion reactions Update to summary of rationale for potential risk 'risk fo infection'	To make consistent with other ongoing study (207804) with GSK3858279 Change to Analysis populations Inclusion of additional information from ongoing First in human study. Clarification on immunosuppressive action of CCL17.
4.2 Number of Participants	Addition of analysis populations and detail minimum number to be enrolled into the UVB-MITT population	Change to analysis populations
4.3 Scientific Rationale for Study Design	Clarification given for the number of volunteers needed for UVB-MITT Population	Change to analysis populations
4.4 Justification for Dose and Washout	Update to GSK 3858279 limits of quantification and return to baseline (washout)	New data available on file for GSK3858279 from study 207804
5.1 Inclusion Criteria	1.Extending upper range of age to 50 years	To make consistent with other ongoing study (207804) with GSK3858279
5.2 Exclusion Criteria	19. Subjects failing PainCart assessments on exploratory endpoints (e.g. pressure pain) during screening visit may still be enrolled into study	This is an exploratory measure
5.2 Exclusion Criteria	29- 22 criteria specifically for UVB-MITT population	Change to analysis populations
5.3.4 Exposure to sunlight	Exposure to sunlight restriction lifted for MITT-Population	Restriction only required for volunteers having UVB irradiation in UVB-MITT population
7.2.2 QTc Stopping Criteria	Clarification of QTc recording method	This is to clarify wording on the number of replicate ECGs required to meet the stopping criteria
8.1.3 Electrocardiograms	Amendment to ECG timings	Reduced from 4 to 2 minutes
8.4.1 Pharmacokinetcis Sample Analysis	Amendment to name of the group completing PK sample analysis	Group completing PK analysis have changed name

Section # and Name	Description of Change	Brief Rationale
9,2 Sample Size Determination	Addition of sample size determination for UVB-MITT Population	Change to analysis populations
9.3 Populations for analysis	Addition of UVB-MITT and PK populations	Change to analysis populations
1.2 Schema, 1.3 Schedule of events, 2.2 Background 2.3.1 Risk Mitigation 4.1 Overall Design 5.2 Exclusion criteria 5.3 Lifestyle considerations 5.4.1 Re-screening 7.2 Discontinuation of Study Intervention 10.2 Appendix 2: Clinical Laboratory Tests	Addition of COVID-19 related measures	Minimize risk of COVID-19 pandemic effects on study and subject safety
Throughout the document	Minor changes to clarify meaning of existing text	

Amendment 2 11-FEB-2020

Overall Rationale for the Amendment: Correction to certain exclusion criteria in order to streamline with the other related exclusion criteria. A minor correction to one of the objectives and endpoints, and washout period of few of the prohibited medications.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis & 3. Objectives and Endpoints	Conditioned Modulation Pain (CPM) endpoint units corrected to “mA” from “seconds”	Error in original protocol
Table 1.3.2	Footnote updated to clarify that the planned study assessments on day 25 may also be performed within a ± 24hr window	Omitted in error from original protocol
2.3.1 Risk Assessment	In Vaccination reactions row, Mitigation Strategy column, text has been updated to	Error in original protocol

Section # and Name	Description of Change	Brief Rationale
	reflect washout being effective before dosing and not screening for live vaccination	
5.2. Exclusion Criteria	Exclusion criteria no. 24, 25, 26, 27 and 31 are updated to reflect that prescribed washout periods for over the counter medications, anti-platelet therapies and investigational biologic agents, are till the dosing day in this study rather than screening.	Error in original protocol
6.5.2 Prohibited Medications	Clarification of Prohibited medication washout period applying to the dosing day rather than screening.	Error in original protocol

Amendment 1 23-SEP-2019

Overall Rationale for the Amendment: Feedback from Scientific Review meeting and Ethics Committee following protocol finalisation. Updates to SoA, Table 2 and Appendix 7 for clarity.

Section # and Name	Description of Change	Brief Rationale
1.1. and 3. Objectives and Endpoints	Heat pain detection on normal skin associated with UVB test is added to list of endpoints	Omitted in error from original protocol
1.3. Schedule of Activities	C3/C4. Note added to clarify performed on Day -1 PainCart: Note added to specify thermal test associated with UVB test performed on normal skin Day 15 Study Visit: ±24hr window for study visit on day 7,8 & 15 An echocardiogram performed within 3 months prior to first dosing is acceptable for enrolment into the study MED determination performed within 6 weeks prior to first dosing is acceptable for enrolment into the study	Day of test confirmed to ensure taken as baseline measure No UVB irradiation is performed for Day 15 however testing on normal skin is to be performed on Day 15 Flexibility for study scheduling

Section # and Name	Description of Change	Brief Rationale
5.3.2. Caffeine, Alcohol and Tobacco	One unit of alcohol corrected to 8g of alcohol	Error in original protocol
9.3 Populations for Analyses	Included a new population "Modified Intent-to-Treat" (MITT) and amended the definition of the "Completers" population	MITT is the primary PainCart population. Completers definition updated to reflect all PainCart assessments completed.
9.4.5. Other Analyses 10.1.7 Data Quality Assurance	Study number (207804) added for clarity Study retention changed from 25 to 30 years And sentence added 'A retention period of 30 years instead of 25 years is used, as the long-term effects of GSK3858279 are still unknown and the to be included healthy volunteers could be of relatively young age; thus still with a long life-expectancy'	Omitted in error from original protocol Request to change to comply with Local competent authority guidelines and consistency with protocol
10.1.9. Study and Site Start and Closure	Reason for early closure of study 'Discontinuation of further study intervention development' deleted.	This is not a valid reason for early termination of study
10.2. Protocol Required Safety Laboratory Assessments	Footnote 3 updated to state C3/C4 performed on Day -1 as baseline measure	Day of test confirmed to ensure taken as baseline measure
10.7.1.1 UVB model (Thermal pain, normal & UVB exposed skin)	Sentence added to specify thermal test associated with UVB test performed on area of normal skin of the back on Day 15	No UVB irradiation is performed for Day 15 however testing on normal skin is to be performed on Day 15
10.7.3. Order of PainCart Assessments	Added reference to SOP regarding order of assessments in PainCart	Order of assessments is specified to ensure minimal carry over between assessments

11. REFERENCES

Achuthan A, Cook A, Lee M, Saleh R, Khiew H, Chang M,et.al. Granulocyte macrophage colony-stimulating factor induces CCL17 production via IRF4 to mediate inflammation. *J Clin Invest*. 2013; 126(9); 3453-3466.

Arendt-Nielsen L, Frokjaer JB, Staahl C, Graven-Nielsen T, Huggins JP, Smart TS, et al. Effects of gabapentin on experimental somatic pain and temporal summation. *Reg Anesth Pain Med.* 2007; 32; 382-8.

Bishop T, Ballard A, Holmes H, Young AR, McMahon SB. Ultraviolet-B induced inflammation of human skin: Characterisation and comparison with traditional models of hyperalgesia. *Eur J Pain*. 2009; 13; 524–532.

Bouma G, Zamuner S, Hicks K, Want A, Oliveira J, Choudhury A,et.al. CCL20 neutralization by a monoclonal antibody in healthy subjects selectively inhibits recruitment of CCR6+ cells in an experimental suction blister. *Br J Clin Pharmacol*. 2017; 83(9); 1976-1990.

Carriere KC, Crossover designs for clinical trials. *Stat Med*. 1994; 13; 1063-1069.

Dahan A, Romberg R, Teppema L, Sarton E, Bijl H, Olofsen E. Simultaneous measurement and integrated analysis of analgesia and respiration after an intravenous morphine infusion. *Anesthesiology*. 2004; 101; 1201-9.

Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain*. 1998; 76; 27–33.

EMEA/CHMP/BMWP/14327/2006 Rev 1 Committee for Medicinal Products for Human Use (CHMP) Guideline on Immunogenicity assessment of therapeutic proteins, 18 May 2017.

FDA Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), August 2014.

Gear AR, Suttitanamongkol S, Viisoreanu D, Polanowska-Grabowska RK, Raha S, Camerini D. Adenosine diphosphate strongly potentiates the ability of the chemokines MDC, TARC, and SDF-1 to stimulate platelet function. *Blood*. 2001; 97(4); 937-45.

GlaxoSmithKline Document Number 2020N429762_00. Interim Report of blinded data from Part A of Study 207804: A two-part phase 1 randomised, double blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and target engagement of single intravenous and subcutaneous doses of GSK3958279 in healthy participants. Effective Date 02-SEP-2020

GlaxoSmithKline Document Number RPS-CLIN-004032. GSK3858279 Investigator's Brochure Effective 26 FEB 2021.

GlaxoSmithKline Document Number RPS-CLIN-015095. Reporting and Analysis Plan for the population pharmacokinetic and target engagement modelling of GSK3858279 in healthy participants and participants with osteoarthritis of the knee. Effective Date 09-OCT-2020.

GSK Disclosure Policy: https://www.gsk.com/media/2946/disclosure-of-clinical-trial-information-policy.pdf

Hagemann UB, Gunnarsson L, Geraudie S, Scheffler U, Griep RA, Reiersen H, et al. Fully human antagonistic antibodies against CCR4 potently inhibit cell signaling and chemotaxis. *PLoS One*. 2014; 9(7); e103776.

Hay JL, Okkerse P, van Amerongen G, Groeneveld GJ. Determining Pain Detection and Tolerance Thresholds Using an Integrated, Multi-Modal Pain Task Battery. *J Vis Exp*. 2016; (110); 53800.

Hearn RM, Kerr AC, Rahim KF, Ferguson J, Dawe RS. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol*. 2008; 159(4); 931-5.

Imai T, Baba M, Nishimura M, Kakizaki M, Takagi S, Yoshie O. The T cell-directed CC chemokine TARC is a highly specific biological ligand for CC chemokine receptor 4. *J Biol Chem*. 1997; 272(23); 15036-15042.

Imai T, Yoshida T, Baba M, Nishimura M, Kakizaki M, Yoshie O. Molecular cloning of a novel T cell-directed CC chemokine expressed in thymus by signal sequence trap using Epstein-Barr virus vector. *J Biol Chem*. 1996; 271(35); 21514-21521.

Jones SF, McQuay HJ, Moore RA, Hand CW. Morphine and ibuprofen compared using the cold pressor test. *Pain*. 1988; 34(2);117–22.

Kara E, Comerfield I, Fenix K, Bastow C, Gregor C, McKenzie D, McColl S. Tailored Immune Responses: Novel Effector Helper T Cell Subsets in Protective Immunity. *PloS Pathogens*. 2014; 10: 1-15

Kronenberg S, Husar E, Schubert C, Freichel C, Emrich T, Lechmann M, Giusti A & Regenass F. Comparative assessment of immune complex-mediated hypersensitivity reactions with biotherapeutics in the non-human primate: Critical parameters, safety and lessons for future studies. *Regul Toxicol Pharmacol*. 2017; 88: 125-137.

Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. *Int J Dermatol*. 2005; 44; 355-360.

Loudon P, Siebenga P, Gorman D, Gore K, Dua P, van Amerongen G, Butt RP. Demonstration of an anti-hyperalgesic effect of a novel pan-Trk inhibitor PF-06273340 in a battery of human evoked pain models. *Br J Clin Pharmacol*. 2018; 84(2); 301-309.

Okkerse P, van Amerongen G, de Kam ML, Stevens J, Butt RP, Gurrell R, Groeneveld GJ. The use of a battery of pain models to detect analgesic properties of compounds: a two-part four-way crossover study. *Br J Clin Pharmacol*. 2017; 83(5); 976-990.

Olofsen E, Romberg R, Bijl H, Mooren R, Engers F, Kest B, et al. Alfentanil and placebo analgesia: no sex differences detected in models of experimental pain. *Anesthesiology*. 2005; 103; 130-9.

Polianskis R, Graven-Nielsen T, Arendt-Nielsen L. Pressure-pain function in desensitized and hypersensitized muscle and skin assessed by cuff algometry. *J Pain*. 2002; 3; 28-37.

Polianskis R, Graven-Nielsen, T., Arendt-Nielsen, L. Computer-controlled pneumatic pressure algometry – a new technique for quantitative sensory testing. *Eur J Pain*. 2001; 5; 267-277.

Sayre RM, Desrochers DL, Wilson CJ, Marlowe E. Skin type, minimal erythema dose (MED), and sunlight acclimatization. *Am Acad Dermatol.* 1981; 5(4); 439-443.

Siebenga PS, van Amerongen G, Klaassen ES, de Kam ML, Rissmann R, Groeneveld GJ. The ultraviolet B inflammation model: Postinflammatory hyperpigmentation and validation of a reduced UVB exposure paradigm for inducing hyperalgesia in healthy subjects. *Eur J Pain*. 2019; 00; 1-10.

Siebenga PS, van Amerongen G, Okkerse P, Denney WS, Dua P, Butt RP, Groeneveld, GJ. Reproducibility of a battery of human evoked pain models to detect pharmacological effects of analgesic drugs. *Eur J Pain*. 2019; 23(6); 1129-1140.

Specht S, Frank JK, Alferink J, Dubben B, Layland LE, Denece G, Bain O, Förster I, Kirschning CJ, Martin C, Hoerauf A. CCL17 controls mast cells for the defense against filarial larval entry. *J Immunol*. 2011; 186(8); 4845-52.

van Amerongen G, Siebeng, P, de Kam ML, Hay JL, Groeneveld GJ. Effect profile of paracetamol, Δ9-THC and promethazine using an evoked pain test battery in healthy subjects. *Eur J Pain*. 2018; 22(7); 1331-1342.