CLINICAL STUDY PROTOCOL

Primary study intervention(s)	GSK3858279
Other study intervention(s)	Not Applicable
Study identifier	214221
EU CT number	2022-502313-28-00
Pediatric investigational plan number	Not Applicable
Approval date	26 Mar 2024
Title	A multicenter randomized, double-blind, placebo-controlled Phase 2 study to evaluate efficacy, safety, tolerability, pharmacokinetics and target engagement of GSK3858279 in adult participants with chronic Diabetic Peripheral Neuropathic Pain (DPNP) / NEPTUNE-17
Compound number/Name	GSK3858279
Brief title	A Phase 2 study (NEPTUNE-17) to evaluate efficacy and safety of GSK3858279 in DPNP
Sponsor	GSK Research & Development Limited, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Yulia Green Sr. Clinical Development Director

Medical Monitor name and contact information can be found in the local study contact information document.

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Protocol Amendment 2 Investigator Agreement

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the clinical study site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.

Study identifier	214221
EU CT number	2022-502313-28-00
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Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	26 Mar 2024
Amendment 1	24 July 2023
Original Protocol	22 February 2023

Amendment 2

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the safety monitoring of participants and the scientific value of the study.

Overall rationale for Amendment 2:

This protocol had been amended to clarify eligibility requirements and improve representation of the target population. The main changes include:

- Clarification of pain training, pain scoring and rescue medication use for eligibility.
- Screening period was extended from 5 to 6 weeks to allow additional time for medications washout, if needed.
- Modification of exclusion criteria and associated laboratory tests to allow participants who had a previous hepatitis B infection but no evidence of active infection.
- Modification of eGFR measure of renal function for exclusion from <60 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
1.1. Synopsis	Summarized sections of the protocol.	To improve readability and provide descriptive summary.
1.2. Schema	Extended screening period from 5 to 6 weeks and total study duration from 32 to 33 weeks.	Further screening week added to provide additional time for washout, if required.
1.3. Schedule of Activities	Clarified language around pain and device training. Clarified language around pain reporting. Clarified restrictions on rescue medication use. Clarified language around TB testing. Clarified language about ECG measurement. Addition of mandatory (not optional) laboratory urinalysis at Day 1 and Week 12 visits.	To clarify the requirements for pain training, pain reporting and rescue medication during the run-in period of screening. To show what TB testing is available, subject to Sponsor approval. To provide option of triplicate ECG assessment during screening, if required. Addition of urine protein evaluation at baseline and end of treatment.
2.3.1. Risk assessment	Removed monitoring for TB reactivation. Added hepatitis B monitoring and stopping criteria.	To align with exclusion criteria (participants with a history of active TB and/or latent TB are excluded). To add risk management of viral reactivation for participants with previous hepatitis B.

Section # and title	Description of change	Brief rationale
5.1. Inclusion criteria	Clarification of language around recent hospitalization related to diabetes. Clarified restrictions for rescue medication use, recording and evaluation.	To focus hospitalizations to important unplanned medical events related to diabetes and not to routine scheduled hospital care in some countries. To add further clarity on eligibility of participants who are using excess rescue medication during run-in period that could confound pain scoring.
5.2. Exclusion criteria	Clarification of language around TB testing. Reduction of eGFR measure of renal function for exclusion from <60 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2. Addition of exclusion for any previous exposure to GSK3858279. Requirement of a hepatitis B virus DNA test added for participants who have a positive hepatitis B core antibody test result during screening. Clarification of drug screening results.	To show what TB testing is available, subject to Sponsor approval. Reduction of eGFR from 60 mL/min/1.73 m^2 to 45 mL/min/1.73 m^2 to allow a better representation of the target DPNP population. To prevent the unlikely chance of previous exposure to GSK3858279 to allow accurate calculation of exposure numbers. To allow participants who have had a previous hepatitis B infection but no evidence of current infection (HBV DNA and HbsAg negative). To allow clinical interpretation of drug screening based on all regular medications taken by the participant.
5.4. Screen failures	Added option of re-screening due to administrative reasons.	Addition of option for a further re-screen at the discretion of the Medical Monitor, for administrative reason to provide logistical flexibility.

Section # and title	Description of change	Brief rationale
6.1. Study intervention(s) administered	Updated Table 4 to include route and mode of administration, dose, dosage regimen and duration of intervention for all study interventions (i.e. study drug, placebo and rescue medication).	To align with Sponsor standards and country-specific requirements.
6.4. Blinding	Added details of blinding plans.	To improve clarity.
6.9.3. Rescue medicine	Updated restrictions on rescue medication use, recording and sourcing.	Clarification of rescue medication use during the run-in period for evaluation of eligibility.
7.1. Permanent discontinuation of study intervention	Removed 'new latent TB infection'.	To align with exclusion criteria and screening procedures.
7.1.5. Hepatitis B reactivation stopping criteria	Addition of hepatitis B reactivation stopping criteria section	To add risk management for the reactivation of hepatitis B.
8.3.3. Electrocardiograms	Clarified language around ECG measurement and analysis to allow triplicate ECG at screening if needed.	To clarify study procedures and enable more accurate monitoring of cardiac functions.
8.3.6. Hepatitis B reactivation monitoring	Added details for monitoring. Additional monitoring requirements for participants at Japan sites only.	To provide regular monitoring of participants with previous hepatitis B infection for reactivation and advice on management.
8.5.4. AESI	Removed TB reactivation.	To align with exclusion criteria and screening procedures.
8.7. Pharmacodynamics	Updated details of pharmacodynamic analysis.	Clarification of pharmacodynamic analysis.
9.4. Statistical analyses	Minor clarifications around statistical analyses.	To improve reporting.

Section # and title	Description of change	Brief rationale
10.1. Regulatory, ethical, and study oversight considerations	Clarified language around sample collection and storage. Clarified language around data protection and updated details of GSK publication policy.	Administrative changes to align with Sponsor's standards.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

21 CFR	Title 21 of the Code of Federal Regulations
µg/mL	Micrograms per milliliter
µg*day/mL	Micrograms day per milliliter
ADA	Anti-Drug Antibodies
ADP	Average Daily Pain
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC(0-tau)	Area under the Concentration-time curve over the dosing interval
BCG	Bacillus Calmette-Guerin
BIB	Bioanalysis, Immunogenicity and Biomarker
BL	Baseline
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA	Competent Authority
CFR	Code of Federal Regulation
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum concentration
Cmin	Minimum concentration
COA	Clinical Outcome Assessment
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus strain 19
CPPD	Calcium Pyrophosphate Dihydrate
CRF	Case Report Form
Cavg	Average concentration over a dosing interval
CSR	Clinical Study Report
Ctau	Pre-dose (trough) concentration at the end of the dosing interval
CTIS	Clinical Trial Information System
CV	Cardiovascular
DN4	Douleur Neuropathique 4
DPNP	Diabetic Peripheral Neuropathic Pain
DRG	Dorsal Root Ganglion
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EU	European Union
eDiary	Electronic Diary
FTIH	First Time In Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma Glutamyl Transpeptidase

h	Hours
hCG	Human Chorionic Gonadotropin
HbA1c	Glycated Hemoglobin
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBcAb	Hepatitis B Core Antibody
HBV	Hepatitis B Virus
HBV DNA	Hepatitis B DNA
HHS	Home Healthcare Services
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICEs	Intercurrent Events
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDFU	Investigational Directions For Use
IDMC	Independent Data Monitoring Committee
iDRC	Internal Data Review Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG2	Immunoglobulin G2
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IV	Intravenous
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing System
IWRS	Interactive Web Recognition System
Kd	Dissociation Constant
kg/m2	Kilograms per square meter
LAM	Lactational Amenorrhea Method
LDH	Lactate Dehydrogenase
LLQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MAR	Missing At Random
mAb	Monoclonal Antibody
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg/day	Milligrams per day
mg/kg	Milligrams per kilogram
mg/kg/week	Milligrams per kilogram per week

min	Minute
mm	Millimetre
MSDS	Material Safety Data Sheet
msec	Millisecond
Nab	Neutralizing antibody
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGF	Nerve Growth Factor
NOAEL	No Observed Adverse Effect Level
NQ	Non-Quantifiable
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
OA	Osteoarthritis
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
pH	Potential Hydrogen
PK	Pharmacokinetics
PGx	Pharmacogenetics
PRO	Patient Reported Outcome
PtGA	Patient Global Assessment
PTS	Platform Technology and Science
QSS	Quasi Steady State
QTc	Corrected QT
QTcF	Corrected QT using Fridericia's formula
RA	Rheumatoid Arthritis
RBC	Red Blood Cell count
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SMG	Safety and Medical Governance
SMP	Safety Management Plan
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SoA	Schedule of Activities
SRT	Safety Review Team
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TDAR	T-cell Dependent Antibody Response

TE	Target Engagement
THC	Tetrahydrocannabinol
tmax	Time to Cmax
TMDD	Target-Mediated Drug Disposition
TST	Tuberculin Skin Test
t½	Apparent terminal phase half-life
UACR	Urine Albumin Creatinine Ratio
UDS	Urine Drug Screen
ULN	Upper Limit of Normal
UPCR	Urine Protein Creatinine ratio
WBC	White Blood Count
WNCBP	Women Of Non-Childbearing Potential
WOCBP	Women Of Childbearing Potential
w/v	Weight by volume

Term	Definition
Adverse Drug Reaction	An AE where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.
Auxiliary Medicinal Product (AxMP)	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthoried AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004.
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of an SAE. In a double-blind study, the participant, the Investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Home Healthcare Services	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the Investigator is the responsible leader of the team and may be called the Principal Investigator. The Investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Non-IMP	Any products used in a clinical trial (other than the investigational product being tested) which are stipulated to be used to evaluate the efficacy and safety of

Term	Definition
	the investigational drug in the protocol including comparators, co-administration drugs, rescue drugs and premedication drugs. • Non-IMPs products can be approved in Japan or other countries, or can be products that are not approved.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Pharmacogenomics	The ICH E15 Guidance for Industry defines pharmacogenomics as the 'Study of variation of DNA and RNA characteristics as related to drug or treatment response.' Pharmacogenetics, a subset of pharmacogenomics, is 'the study of variations in DNA sequence as related to drug response.' Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not pharmacogenomics.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	This term refers to the visit conducted in the place other than the study site.
Rescue medication	Medicine(s) identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the participant, or to manage an emergency situation.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to denote a set of Investigational Medicinal Product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: 'Study intervention' and 'study treatment' are used interchangeably unless otherwise specified.

Term	Definition
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Sub-cohort	A group of participants for whom specific study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g. ages, vaccination schedule, etc.) at the time of enrollment.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.
Telemedicine	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A multicenter randomized, double-blind, placebo-controlled Phase 2 study to evaluate efficacy, safety, tolerability, pharmacokinetics and target engagement of GSK3858279 in adult participants with chronic Diabetic Peripheral Neuropathic Pain (DPNP) / NEPTUNE-17.

Brief Title:

A Phase 2 study (NEPTUNE-17) to evaluate efficacy and safety of GSK3858279 in DPNP.

Rationale: Diabetic Peripheral Neuropathic Pain (DPNP) is a common chronic pain condition. Several pharmacological treatments are used to manage neuropathic pain; however, considerable variations in treatment plan, dosage and sequencing, may lead to inadequate pain control, with considerable morbidity among patients. GSK3858279 is a high affinity (Kd<1pM), human immunoglobulin G2σ (IgG2σ)(Fc-silenced), first in class, monoclonal antibody (mAb). It binds specifically to the chemokine CCL17 which is implicated in pain pathogenesis. Based on non-clinical and clinical studies, where aCCL17 has demonstrated an efficacy signal in osteoarthritis pain, this study aims to investigate the safety, efficacy, pharmacokinetic and target engagement of GSK3858279 to address the unmet needs of participants with DPNP. Refer to Section 2.1 for details.

Objectives, Endpoints, and Estimands: The primary objective of this study is to estimate the difference in means between GSK3858279 60 mg SC and placebo and GSK3858279 360 mg SC and placebo, in change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS, in adult participants with DPNP, where persistent use of prohibited pain therapy and study treatment discontinuations due to lack of efficacy or adverse events are considered a negative outcome, in the absence of other study treatment discontinuations and regardless of all other use of prohibited pain therapy and use of allowed rescue medication. A negative change from baseline is evidence of improvement in pain. Refer to Section 3 for details.

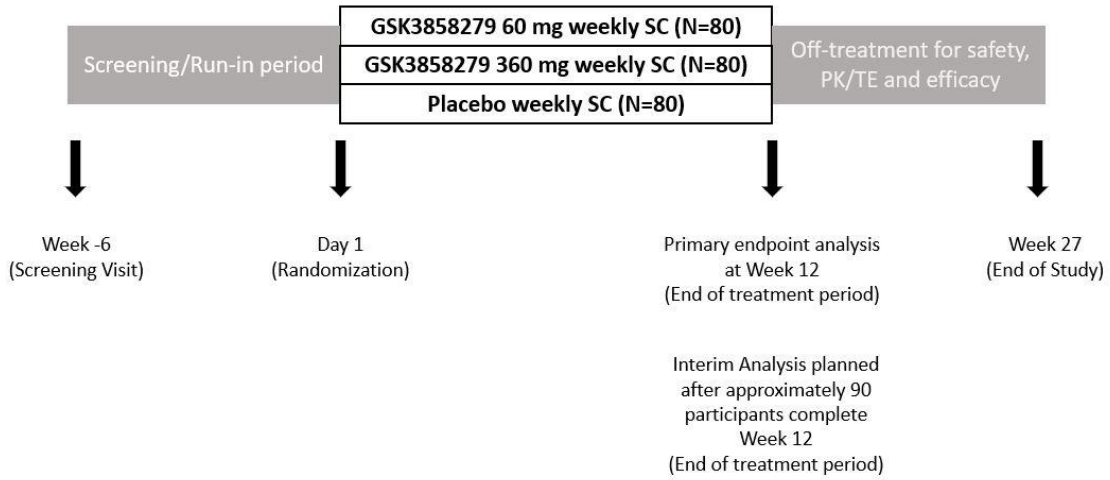
Overall Design: This is a randomized, double-blind, parallel group, placebo-controlled Phase 2 study to evaluate the efficacy, safety, tolerability, PK and TE of GSK3858279 vs. placebo when administered with repeated weekly SC injections in participants with DPNP. After the screening visit and washout period, participants will be stratified based on region and an average of the average daily pain score at baseline and then randomized at 1:1:1 ratio to either GSK3858279 at 60 mg SC weekly or GSK3858279 at 360 mg SC weekly or placebo SC weekly within each stratum. Refer to Section 4.1 for details.

Number of Participants: Approximately 240 participants will be enrolled in this study. The number of participants may be increased by approximately 15% to ensure regional requirements for recruitment are met. Refer to Section 9.6 for details.

Data Monitoring/Other Committee: A Safety Review Team (SRT) is an internal cross-functional team responsible for the ongoing assessment of benefit/risk. An external independent data monitoring committee (IDMC) is implemented in this study to review unblinded data regularly and on an as needed basis. An internal data review committee (iDRC) will review interim analysis data in an unblinded manner for the assessment of futility. Refer to Section 10.1.6 for details.

1.2. Schema

Figure 1 Study design overview



1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities: Screening period

Note: Although there will be more than one site visit during the screening period (the initial screening visit [1a] and a second visit at the beginning of the run-in period [1b]) for the purposes of the SoA these visits will be grouped together and called screening period.

Assessments	Screening period			Notes
Visit	Initial screening (Visit 1a)	Start of washout period (phone call)	Run-in period (Visit 1b)	
Informed consent	X			All screening assessments, with the exception of the informed consent, must be completed within 42 days prior to randomization. Register the participant in IWRS once the ICF is signed. Screening visit assessments could be performed in split visits with prior Sponsor approval. A separate optional Genetic ICF may be signed at Visit 1a, or anytime during the study, if applicable.
Demography	X			
Medical history	X			
DPNP and DPNP treatment history	X			Date of diagnosis of diabetes and DPNP will be recorded along with previous DPNP treatment history.

Assessments	Screening period			Notes
Visit	**Initial screening (Visit 1a)**	**Start of washout period (phone call)**	**Run-in period (Visit 1b)**	
Drug/alcohol/tobacco use history	X			Drug and alcohol use in the last year will be recorded. Tobacco use history in pack years (lifetime) along with the current smoking status in average number of cigarettes smoked per day in the last week will be recorded.
Full physical examination (including height and weight)	X			
DN4 questionnaire / examination	X			Diagnosis of DPNP confirmed by a positive DN4 questionnaire.
Average daily pain score over the past 24 hours	X			
12-lead ECG	X			Single ECG tracing should be obtained. Triplicate ECG can be performed based on Investigator assessment, if required.
Vital signs	X			
Urine drug screen	X			Amphetamines, barbiturates, cocaine, opiates, marijuana (THC), benzodiazepines.
Hematology, clinical chemistry, urinalysis	X			Refer to Section 10.2 for the full list of parameters that will be tested. Urinalysis will be performed locally with the use of dipstick. Urine sample may be sent to the central laboratory for further testing based on Investigator assessment, if required.

Assessments	Screening period			Notes
Visit	**Initial screening (Visit 1a)**	**Start of washout period (phone call)**	**Run-in period (Visit 1b)**	
HbA1c	X			
HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV)	X			See diagnostic assessments in Section 5.2 for country-specific hepatitis B requirement for participants from sites in Japan.
COVID-19 (SARS-CoV-2) test	X			PCR assay.
TB testing	X			QuantiFERON TB Gold Plus Test (or, if unavailable, T-SPOT TB with prior Sponsor's approval).
Pregnancy test (serum in WOCBP) or follicle stimulating hormone (FSH) (in WNCBP as appropriate – see Appendix 4 (Section 10.4)	X			
Rescue Medication: dispense Paracetamol/Acetaminophen	X		X*	Only if ALL initial eligibility criteria were met at the initial screening visit. Participants should be instructed to only use rescue medication provided by sites and to follow dosage and use restrictions. *Additional rescue medication supply should be provided if needed.
Concomitant medication review	X	X	X	All concomitant medications taken within 30 days prior to ICF signature and current DPNP treatment(s) (if applicable) will be recorded along with start and stop dates, doses, routes of administration and reasons for use. Changes in concomitant medications throughout the screening period will also be recorded.

Assessments	Screening period			Notes
Visit	**Initial screening (Visit 1a)**	**Start of washout period (phone call)**	**Run-in period (Visit 1b)**	
Inclusion and exclusion criteria	X	X	X	Recheck clinical status before initiating washout and run-in periods.
Washout period: washout of all pain medications (if applicable)		At least 3 days or 5 half-lives, whichever is longer (according to Investigator and local guidance)		Start the washout period only if ALL eligibility criteria were met at the initial screening besides the average of the average daily pain score. See Section 6.9.1.2 for further details on prohibited analgesics and advice for washout to prevent withdrawal symptoms, if required.
Run-in period: after washout of all pain medications (if applicable)			7 days preceding randomization	Only rescue pain medication is permitted within allowance (Rescue Medication Section 6.9.3). Permitted rescue medication (if needed): Paracetamol/Acetaminophen, administered orally, at doses of ≤3 grams/day and for a maximum of 4 days in a week. Participants exceeding the permitted allowance during the run-in period will not be eligible.
Training on accurate pain reporting	X		X	At initial screening visit prior to initial NRS pain evaluation, a brief training for NRS pain assessment will be provided by PI or site staff. This is based on the Accurate Pain Training video from Investigator meeting. Before the eDiary is dispensed at Visit 1b, participants will be trained on accurate pain reporting course, provided by the third-party vendor WCG. This web-based training to be completed on a site computer/tablet device with supervision.

Assessments	Screening period			Notes
Visit	**Initial screening (Visit 1a)**	**Start of washout period (phone call)**	**Run-in period (Visit 1b)**	
Training on and dispensing of the eDiary			X	eDiary should only be dispensed once the participant passes ALL of the screening assessments besides the average of the average daily pain score and washout of prohibited pain medications has been successful (if applicable). eDiary training to be completed on Clario handheld device at site with supervision.
Average daily, worst daily and nighttime pain scores (eDiary)			Starting 7 days preceding randomization	Scores will be recorded on the eDiary over the 7 consecutive days preceding randomization. Compliance for average daily pain scoring must be a minimum of 6 out of 7 days for eligibility. An average of the average daily pain score will be evaluated for inclusion.
Paracetamol/Acetaminophen intake Diary (eDiary)			Starting 7 days preceding randomization	Recorded on the eDiary over the 7 consecutive days preceding randomization. Compliance of rescue medication data entry must be a minimum of 6 out of 7 days for eligibility. Participants exceeding the permitted allowance during the run-in period will not be eligible. Permitted rescue medication (if required): Paracetamol/Acetaminophen, administered orally, at doses of ≤3 grams/day and for a maximum of 4 days in a week.

Assessments	Screening period			Notes
Visit	**Initial screening (Visit 1a)**	**Start of washout period (phone call)**	**Run-in period (Visit 1b)**	
SAE assessment	X	X	X	All SAEs will be collected from the start of intervention until the final follow-up visit at the time points specified in the SoA. However, any SAEs assessed as related to study participation (e.g. 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.

Table 2 Schedule of Activities: Treatment and Off-treatment Follow-Up period

Assessments	Treatment period																Off-treatment			ED[a]
Week	**Day 1 BL[a]**		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**		**12**	**16**	**20**	**27**	
Visit No	**2**	**3[b]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**15**	**16[b]**	**17**	**18[b]**	**19[b]**	**20**	
Visit window	± 2 days [except for Day 1 (Visit 2) and Visits 3, 11 and 16][c] Minimum 5 days between IMP injections for no more than 2 consecutive dosing visits																**± 7 days**			
Inclusion and exclusion criteria [d]	X																			
Randomization	X																			
Administer: Weekly SC IMP injections [e]	X		X	X	X	X	X	X	X		X	X	X	X						
COAs including PROs																				
Average Daily Pain NRS [f]	<==========X==========>																			X
Worst Daily Pain NRS [f]	<==========X==========>																			X
Nighttime Pain NRS [f]	<==========X==========>																			X
Paracetamol/ Acetaminophen intake eDiary [g]	<==========X==========>																			X

Assessments	**Treatment period**																**Off-treatment**			**ED[a]**
Week	**Day 1 BL[a]**		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**		**12**	**16**	**20**	**27**	
Visit No	**2**	**3[b]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**15**	**16[b]**	**17**	**18[b]**	**19[b]**	**20**	
Visit window	± 2 days [except for Day 1 (Visit 2) and Visits 3, 11 and 16][c] Minimum 5 days between IMP injections for no more than 2 consecutive dosing visits																**± 7 days**			
Dispense Paracetamol/ Acetaminophen if needed	<==========X==========>																			X
PGIS [h]	X					X					X					X				X
PGIC [h]						X					X					X				X
McGill Pain Questionnaire SF2 [h]	X			X		X					X					X	X	X	X	X
Brief Pain Inventory Short Form Domains [h]	X					X					X					X				X
Repeat training on accurate pain reporting[h]											X									
Review eDiary compliance	X		X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X

Assessments	Treatment period																Off-treatment			ED[a]
Week	**Day 1 BL[a]**		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**		**12**	**16**	**20**	**27**	
Visit No	**2**	**3[b]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**15**	**16[b]**	**17**	**18[b]**	**19[b]**	**20**	
Visit window	± 2 days [except for Day 1 (Visit 2) and Visits 3, 11 and 16][c] Minimum 5 days between IMP injections for no more than 2 consecutive dosing visits																**± 7 days**			
Safety Evaluations and Other Assessments																				
Symptom driven brief physical exam	X		X	X	X	X	X	X	X		X	X	X	X		X			X	X
Vital signs	X		X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X
12-lead ECG [i]	X					X					X					X			X	X
Urine pregnancy test [j]	X		X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X
Hematology, clinical chemistry, urinalysis [k]	X		X	X		X		X			X		X			X	X	X	X	X
Fasting lipid panel[l]	X															X			X	X
HbA1c	X															X			X	X[m]
Hepatitis B monitoring (if applicable)						X					X					X			X	X

Assessments	Treatment period																Off-treatment			ED[a]
Week	**Day 1 BL[a]**		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**		**12**	**16**	**20**	**27**	
Visit No	**2**	**3[b]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**15**	**16[b]**	**17**	**18[b]**	**19[b]**	**20**	
Visit window	± 2 days [except for Day 1 (Visit 2) and Visits 3, 11 and 16][c] Minimum 5 days between IMP injections for no more than 2 consecutive dosing visits																**± 7 days**			
TB testing																X			X	X
Tobacco Use History Update [n]																X			X	X
Genetics sample [o, p]	<==========X==========>																			X
SAE/AE review	<==========X==========>																			X
Concomitant medication review	<==========X==========>																			X
PK/TE, Immunogenicity and Biomarker Samples																				
PK/TE blood sample [q]	X	X[c]	X			X				X[c]	X			X	X[c]	X[c]	X	X	X	X
Immunogenicity [q]	X					X					X			X					X	X
Whole blood for RNA or epigenetic analysis [p, q]	X					X										X			X	

Assessments	Treatment period																Off-treatment			ED[a]
Week	**Day 1 BL[a]**		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**	**10**	**11**		**12**	**16**	**20**	**27**	
Visit No	**2**	**3[b]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[b]**	**12**	**13**	**14**	**15**	**16[b]**	**17**	**18[b]**	**19[b]**	**20**	
Visit window	± 2 days [except for Day 1 (Visit 2) and Visits 3, 11 and 16][c] Minimum 5 days between IMP injections for no more than 2 consecutive dosing visits																**± 7 days**			
Serum for protein biomarkers [p, q]	X					X										X			X	
Blood for flow cytometry [q, r]	X					X										X				

a. BL = Baseline, ED = Early Discontinuation/Withdrawal.
b. If country/site and participant agree, this visit can be performed by a home nursing team (Accellacare, a third-party vendor or site personnel). If a home nursing team is utilized, SAE/AE and concomitant medication review should be done by the Investigator over the phone.
c. One post-dose PK/TE sample after visits 3, 11 and 16 is to be taken either at 24-72 hours OR at 96-120 hours post the last IMP dose (based on participant/site preference). PK/TE sample at visit 17 is to be taken approximately 7 days post the last IMP dose at visit 15.
d. Recheck clinical status before randomization.
e. IMP injections must be administered after completion of all the study assessments applicable for the visit. A window of ± 2 days is acceptable between weekly doses (minimum gap of 5 days between each dose, for no more than 2 consecutive dosing visits).
f. NRS pain questions (including average daily pain, worst daily pain and nighttime pain) should be completed on the eDiary on a daily basis.
g. All Paracetamol/Acetaminophen intakes including date, approximate time of dose, dose strength, drug form and reason for use (DPNP or other) should be recorded on the eDiary on a daily basis.
h. Perform PROs before any other assessments or procedures to avoid influencing the participant. Repeat training on accurate pain reporting at Week 8 before PROs are completed.
i. Triplicate ECG measurements will be taken at Baseline (Day 1) visit. Single ECGs will be obtained at all subsequent visits per SoA unless any abnormalities are found during the study or if any of the ECG stopping criteria are met, then triplicate ECG will be obtained.
j. Women of childbearing potential only. Must be completed prior to dosing. Serum pregnancy test should be done if required by local regulations (e.g. country or IRB/EC).
k. Check Section 10.2 for the full list of parameters that will be tested. Urinalysis will be performed locally with the use of dipstick. At Day 1 and Week 12 visits the urine samples must be sent to the central laboratory for further testing. For all other visits, urine samples may be sent to the central laboratory for further testing based on Investigator assessment, if required.
l. Participants are required to fast for a minimum of 10 hours if feasible, as deemed by the Investigator.

m. Only required if the participant is unlikely to return for the final follow-up visit (Week 27) and it has been more than 3 months since the last HbA1c test.
n. Current smoking status in average number of cigarettes smoked per day in the last week will be recorded.
o. Optional. Single sample any time post randomization.
p. Sample not collected in China.
q. Sample collected before IMP dose (on dosing days).
r. Flow cytometry will only be conducted in selected countries.

NOTE: Order of assessments as recommended where possible:

- Any scheduled training and completion of participant reported outcome assessments to be completed first.
- ECG, vital signs, and physical examination should then be followed by blood and urine sampling.
- All assessments (including review of AE/SAEs and concomitant medications) to be completed before any dosing.

If study intervention is permanently discontinued, the participant will be requested to remain in the study and complete the planned visits and assessments for the treatment period (up to the Week 12 visit) per above SoA (except for the weekly SC IMP injections and post-dose [24-72 hours or 96-120 hours] PK/TE sample collection), with a final follow-up visit (Visit 20) approximately 16 weeks from the last dose received.

If a participant wishes to withdraw consent during the study, they will be requested to return for an Early Discontinuation/Withdrawal visit, preferably 1 week from the last dose received (applicable during the treatment period) or as soon as possible after the participant's decision has been communicated to the site staff (applicable during the off-treatment phase), and to return for a final follow-up visit (Visit 20) approximately 16 weeks from the last dose received prior to withdrawal of consent.

In either case the final follow-up visit (Visit 20) will assess all the items per the SoA for the Week 27 visit. Participants should be requested to complete average daily pain, worst daily pain, nighttime pain NRS scoring and Paracetamol/Acetaminophen intake Diary up to the final follow-up visit (Visit 20).

The timing of planned study assessments may change during the study based on emerging data/in-stream data review (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. The timing of PK/TE samples may be altered and/or PK/TE samples may be obtained at additional time points to ensure optimal PK/TE monitoring.

Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic and target engagement data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

The Competent Authority (CA) and Ethics Committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study rationale

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 signaling.

The purpose of this Phase 2 study is to investigate the safety, efficacy, pharmacokinetic (PK) and target engagement (TE) of GSK3858279 in participants with Diabetic Peripheral Neuropathic Pain (DPNP), as the proof-of-concept for this indication. It is the first time that GSK3858279 is tested in DPNP population.

2.2. Background

Diabetic Peripheral Neuropathic Pain (DPNP) is a common complication of diabetes, which affects a wide fraction of participants, and it is likely to increase due to the prevalence of diabetes. Diabetic neuropathy is a complication associated with patient age, illness course and hyperglycemia severity [Hicks, 2019].

DPNP is a common chronic pain condition that can be challenging to treat, particularly for non-specialists. A number of pharmacological treatments are used to manage neuropathic pain outside of specialist pain management services. However, there is considerable variation in how treatment is initiated, the dosages used and the order in which drugs are introduced, whether therapeutic doses are achieved and whether there is correct sequencing of therapeutic classes. A further complication is that a number of commonly used treatments are unlicensed for treating neuropathic pain, which may limit their use. These factors may lead to inadequate pain control, with considerable morbidity. Commonly used pharmacological treatments include antidepressants (tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs] and serotonin-norepinephrine reuptake inhibitors [SNRIs]), antiepileptic (anticonvulsant) drugs, topical treatments and opioid analgesics. In addition to their potential benefits, all of these drug classes are associated with a spectrum of adverse effects [Professional Practice Committee. 4, 2022].

With limited treatment options and comparatively few recent approvals, considerable unmet need remains for participants with neuropathic pain. Physician research indicates that polypharmacy is common and there is strong demand for novel drug classes, with strong uptake expected for successful new agents [Yang, 2015].

2.2.1. The role of C-C class chemokines 17 (CCL17) in neuropathic pain

In vivo preclinical models of nerve-injury-induced neuropathic pain have indicated a role of CCL17 in pain pathogenesis.

The administration of an anti-CCL17 surrogate monoclonal antibodies (mAb), via intraperitoneal or intrathecal routes, inhibits pain-like behavior induced by multiple sciatic nerve injury models, in mice [GSK3858279 Investigator's Brochure RPS-CLIN-034028]. Furthermore, the inhibition of the C-C chemokine receptor 4 (CCR4) using the CCR4 antagonist C021, via intraperitoneal or intrathecal routes, also inhibits neuropathic pain-like behavior associated with sciatic nerve injury, or streptozotocin-induced diabetic pain, in mice [Bogacka, 2020a; Bogacka, 2020b]. The observation that CCL17/CCR4 inhibition causes a reduction in pain-like behavior following both intraperitoneal and intrathecal dosing routes suggests a site of action accessible through both routes of administration, such as the dorsal root ganglion (DRG).

The systemic administration of an anti-CCL17 surrogate mAb had no effect on acute pain behaviors in mice, including acute inflammatory and neurogenic pain caused by formalin or capsaicin injection, respectively, as well as basal pain thresholds to heat, cold and pinprick stimulation. Furthermore, the neutralization of CCL17 had no effect on proprioception as measured by grip strength or motor performance as measured by the Rotarod test [GSK3858279 Investigator's Brochure RPS-CLIN-034028].

In vitro, the direct application of recombinant CCL17 had no effect on calcium flux measured in a mixed culture of murine sensory DRG neurons, or in putative nociceptive DRG neurons sensitive to the transient receptor potential vanilloid type 1 (TRPV1) agonist capsaicin, or the transient receptor potential A1 (TRPA1) agonist allyl isothiocyanate (AITC) [GSK3858279 Investigator's Brochure RPS-CLIN-034028], suggesting that CCL17 does not directly act on sensory neurons.

2.3. Benefit/Risk assessment

The biological treatment with aCCL17 has demonstrated an efficacy signal in osteoarthritis pain [GSK Document Number TMF-14616324]. There is no clinical data of aCCL17 in human patient population suffering from Diabetic Peripheral Neuropathic Pain (DPNP), therefore no benefit/risk assessment can be derived for aCCL17 in this population yet. 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) [GSK3858279 Investigator's Brochure RPS-CLIN-034028].

Participants with DPNP have significant morbidity. Current DPNP treatment options are limited and have associated adverse events. Non-clinical and clinical data support the potential efficacy of GSK3858279 in treating DPNP.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks of Investigational Medicinal Product (IMP) GSK3858279		
Infections	Because of GSK3858279's effects on immune cell trafficking, there is a possibility of increases in the frequency and/or severity of infections including opportunistic infections and tuberculosis. **Non-Clinical Data:** No specific studies have been conducted in non-clinical species to investigate the effect of GSK3858279 on response to viral or bacterial infection. CCL17 has an important role in early responses against skin-invading pathogens e.g. CCL17 controls filarial larval entry by limiting mast cell-dependent vascular permeability. Mice deficient for CCL17 had an up to 4-fold higher worm burden compared to controls by day 10 of infection with murine filaria *Litomosoides sigmodontis* [Specht, 2011]. Anti-CCL17 has been shown to be protective in a mouse model of invasive aspergillosis [Carpenter, 2005] suggesting decreased infection risk. The role of CCL17 in systemic anti-pathogen responses is unclear. **Clinical Data:** While there were reports of infection in the 207804 FTIH Part A and 209973 studies in healthy participants, there were no severe or serious infection AEs.	**Eligibility Criteria:** Exclusion of participants with: • Current immunodeficiency diseases including but not limited to acquired immunodeficiency disorder or immunoglobulin deficiency. • History of infected joint prosthesis, chronic leg ulcers, permanent in-dwelling catheters, chronic sinusitis, recurrent chest infections or recurrent urinary tract infections. • Symptomatic herpes zoster within 3 months prior to screening. • Current or previous active Mycobacterium tuberculosis (TB) regardless of treatment. • Evidence of latent tuberculosis (TB). • Previous close contact with a person with active TB not followed by a satisfactory anti-tuberculosis treatment prior to first dose of study intervention. • Positive human immunodeficiency virus (HIV) antibody test. • Has a positive test for hepatitis B virus (HBV) defined as either: – positive for hepatitis B surface antigen (HBsAg) OR – positive for hepatitis B core antibody (HBcAb) AND positive for HBV deoxyribonucleic acid (DNA). Country-specific requirements for participants from sites in Japan only: additionally, positive for hepatitis B surface antibody (HBsAb) AND positive for HBV DNA. • Positive hepatitis C antibody test result – NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		enrolled, only if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained. • Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. **Monitoring:** • Serious and opportunistic infections and TB are categorized as AESIs. • Monitoring for signs of infection. • Instructions to participants as to the signs and symptoms of infection, and to contact site personnel should they develop. • TB evaluation at screening and monitoring for TB throughout the study. • Hepatitis B reactivation monitoring and stopping criteria throughout the study. **Withdrawal Criteria:** • Temporarily discontinue the study intervention for: – Serious or opportunistic infections, COVID-19 (until the infection has resolved) or suspected TB. • Permanently discontinue the study intervention: – If the temporary hold for serious or opportunistic infections is greater than 2 weeks, Investigational Medicinal Product will be permanently discontinued. The participant will be requested to complete the treatment period (up to the Week 12 visit) with a final follow-up visit approximately 16 weeks from the last dose received. – For active TB infection. – Hepatitis B reactivation, HBV DNA positive OR HBV surface antigen positive.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity	The administration of any monoclonal antibody has the potential to induce local or systemic immunologic reactions. **Non-Clinical Data:** In the 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 and mesangioproliferative glomerulopathy in the kidney which is consistent with immune complex disease following the formation of ADA. Non-specific injection site reactions caused by the subcutaneous dosing route were also noted in some monkeys, which was exacerbated by the immune complex deposition in one male. These findings were considered non-adverse. Animal studies are not predictive for ADA-mediated adverse reactions in humans, including infusion reactions, hypersensitivity reactions or anaphylaxis [Kronenberg, 2017], especially for human proteins such as GSK3858279. In addition, given that GSK3858279 binds a soluble ligand (CCL17) and is Fc disabled, GSK3858279 is not expected to mediate effector functions of antibody dependent cell mediated cytotoxicity or complement dependent cytotoxicity. **Clinical Data:** No serious hypersensitivity reactions have been observed in the Phase 1 completed studies.	**Eligibility Criteria:** Exclusion of participants with: • History of significant allergies to monoclonal antibodies. • Clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA]), dermatosis, toxic epidermal necrolysis or Stevens-Johnson syndrome, and exfoliative dermatitis. • Sensitivity to any of the study interventions, or components thereof. **Monitoring:** • Serious hypersensitivity reactions are categorized as AESIs. • Instructions to participants as to the signs and symptoms of an acute hypersensitivity reaction and to seek immediate medical care should they develop. • Participants will be monitored for a minimum of 2 hours post dosing after the first two SC injection regimens. • Every subcutaneous injection of IMP will be administered by a health professional. **Withdrawal Criteria:** • Permanently discontinue study intervention for serious hypersensitivity reactions.
Injection Site Reactions	Subcutaneous injections, including injections of monoclonal antibodies, may be associated with local reactions such as swelling, induration, or pain.	**Monitoring:** • Investigators will be required to capture all injection site reactions (ISRs) as AEs, ISRs will be categorized as AESIs. • Monitor for injection site reactions throughout study. • ISRs will be captured on a specific eCRF to further characterize the events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Non-clinical Data: No test article-related findings were observed in monkeys at injection sites following doses up to 100 mg/kg/week IV and 30 mg/kg/week SC, following 13 weekly administrations. In the 26-week study, non-adverse and reversible microscopic changes, comprising slight or moderate hemorrhage, inflammatory cell infiltrate, vascular changes and fibrosis, were seen at the SC injection site, in some monkeys at all dose levels (10, 30, and 100 mg/kg/week) and in all dose sites, but more pronounced in one male given 100 mg/kg/week. SC injection site reactions of various degrees of severity are not uncommon by this route of administration. Therefore, these changes are considered non-specific tissue reaction caused by the dosing procedure [Engelhardt, 2008], which were likely exacerbated by immune complex deposition in the male given 100 mg/kg/week. **Clinical Data:** There were no serious injection site reactions in the Phase 1 completed studies evaluating GSK3858279 IV and SC in healthy subjects. In the Phase 1b OA knee pain study, more subjects reported ISRs and there were more total ISRs in the aCCL17 group compared to the placebo group: 10 subjects (42%) experienced 24 ISRs aCCL17 vs. 3 subjects (13%) experienced 4 ISRs placebo. However, there was insufficient safety data to classify this observation as evidence of a causal relationship to GSK2858279. This DPNP Phase 2 study will use a different formulation than used in the Phase 1b OA and overall Phase 1 program.	• The same injection location site (abdomen or thigh) should be used at each weekly dosing visit. • It is recommended that the injections are rotated between different quadrants of the abdomen or different areas of both thighs for each weekly dosing visit. • If the participant is receiving other permitted subcutaneous medication, the IMP in this study should be administered in a different location. For example, if the participant is using their abdomen for the IMP than their SC injection should be on the other side of the abdomen or in the thigh.
Immunogenicity	Monoclonal antibodies may induce ADAs, which have the potential to induce adverse reactions (mentioned above) or affect the PK and pharmacodynamics (PD) properties of the drug. GSK3858279 is a human antibody, with a lower potential for ADA formation.	Blood samples will be drawn for anti-drug antibodies to GSK3858279 analysis according to SoA (Table 2). In addition to scheduled immunogenicity assessments, 'event-driven' testing will be performed in the context of serious hypersensitivity reactions or AEs deemed to be clinically significant, in the opinion of the Investigator, resulting in discontinuation from study intervention.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Non-Clinical Data: In the non-clinical 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 titer of ADA in non-clinical studies are not predictive of human. **Clinical Data:** The 207804 FTIH Part A study in healthy participants showed there was low incidence of ADA, low titer, no pattern of increasing incidence of ADAs following single ascending dose (SAD) of GSK3858279 (or placebo) and no apparent difference between 3 mg/kg IV vs. 3 mg/kg SC. There was no detectable impact on safety. The 207804 FTIH Part B study in participants with OA knee pain showed a low incidence of ADAs. There was 1 (4%) in the placebo group and 5 (21%) ADAs in the GSK3858279 group. The 1 ADA in the placebo group and 4 out of 5 in the GSK3858279 group were detected in the follow-up period after the 8-week dosing period. No pattern of ADA impact on safety was detected. Study 209973 in healthy participants observed incidence of treatment induced ADA was 1/21 (5%) participants, with no detectable impact on safety.	
Vaccine effects	There is a theoretical possibility that GSK3858279 could decrease an individual's immune response to vaccines administered while on therapy. **Non-Clinical Data:** 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.	For participants who are in the screening period, completion of COVID-19 vaccination 14 days prior to first dose of study intervention will be strongly recommended. Live or live attenuated vaccines must not be administered to participants from 30 days prior to first dose of study intervention and for 5 half-lives (16 weeks) after dosing has completed. Investigators should review and update the vaccination status of potential participants as per local guidelines for adult vaccination

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical Data: Vaccine effects have not been formally tested in clinical studies to date.	including against COVID, influenza, herpes zoster and pneumococcus (according to local guidelines) prior to first dose of study intervention. If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered whilst receiving study drug based on an assessment of the benefit/risk (e.g. possible risk of decreased responsiveness). **Eligibility Criteria:** Exclusion of participants: • Who received live or live attenuated vaccine(s) within 30 days prior to first dose of study intervention or plan to receive such vaccines during the study. • With current immunodeficiency diseases including but not limited to acquired immunodeficiency disorder or immunoglobulin deficiency. **Withdrawal Criteria:** Live or live attenuated vaccine use.
Reproductive Toxicity	**Non-Clinical Data:** No reproductive or fertility studies have been conducted in animals with GSK3858279. In the 26-week study mature cynomolgus monkeys did not show toxicities in the reproductive organs (organ weights and histopathology), nor effects on stage dependent evaluation of spermatogenesis in males. In the absence of pathological changes in the male reproductive organs, the biology of anti-CCL17 mAb and the inability of large molecular weight proteins to access pivotal cells in testes, the risk of adverse effects on spermatogenesis in clinical use is considered minimal. **Clinical Data:** No pregnancies have been reported to date and no women of childbearing potential participated in the 207804 FTIH Part A or 209973 studies.	**Eligibility Criteria:** Female participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: • Not a woman of childbearing potential (WOCBP) OR • A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the treatment period and for at least 16 weeks after the last dose of study medication. • Exclusion of female participants who are: – Pregnant (as confirmed by serum pregnancy test), lactating, planning to become pregnant or initiating breastfeeding.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Male participants: A male participant with a partner who is a WOCBP is required to use a condom during sexual intercourse throughout the study and for 16 weeks after the last dose of study medication. **Monitoring:** • Refer to Section 10.4 for further details. • Routine urine pregnancy testing of WOCBP throughout the study (serum if required by local regulations). • Collection of pregnancy information in female participants. • Collection of pregnancy information in female partners of male participants. • Pregnancy to be followed to determine outcome. • Report as AE/SAE any pregnancy complication or elective termination. **Withdrawal Criteria:** • Permanently discontinue study intervention in the event of a pregnancy in a female participant
Study Procedures		
Blood Draws	Venous access in some participants may be problematic and the needles used may cause bruising (ecchymosis) around the access site.	• The whole blood volume that will be collected from each participant over the course of the study is provided in the ICF. • At visits to collect whole blood samples, one or more samples of sufficient volume will be collected and divided into suitable portions for the various analyses such as PD biomarkers. • Whole blood samples for genetic research will only be collected from those consenting to participate in this research. • Whole blood samples will be collected by site personnel or site approved third-party home nurse experienced in phlebotomy.

2.3.2. Benefit assessment

Participants may experience the benefits of pain relief and from extensive monitoring of their disease activity. By enrolling in this study, participants will be contributing to the process of developing new analgesic medications for pain control in DPNP, a significant area of unmet need.

2.3.1. Overall benefit/risk conclusion

Taking into account the measures taken to minimize risk to participants from this study, the potential risks identified in association with GSK3858279 are justified by the anticipated benefits that may be afforded to participants with DPNP.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 3 Objectives and endpoints

Objective(s)	Endpoint(s)
Primary	
To characterize the efficacy of GSK3858279 on pain compared to placebo in participants with DPNP	• Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the Numeric Rating Scale (NRS)
Secondary	
To determine the safety and tolerability of repeated doses of GSK3858279 compared to placebo in participants with DPNP	• Occurrence of AEs, SAEs and AEs of Special Interest (AESIs) • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities
To characterize the PK following repeated dosing of GSK3858279 in participants with DPNP	• Maximum value (Cmax), time of Cmax (tmax), trough value (Ctau), average concentration (Cavg) and area under the curve over the dosing interval (AUC(0-tau)) after the last planned dose
To determine the efficacy of GSK3858279 compared to placebo in various dimensions of pain in participants with DPNP	• Change from baseline in the Short-Form McGill Pain Questionnaire total score over time
To further compare the efficacy of GSK3858279 compared to placebo in pain relief in participants with DPNP	• Change from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS • Occurrence of ≥30% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS • Occurrence of ≥50% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS

Objective(s)	Endpoint(s)
Tertiary	
To determine the effect of GSK3858279 compared to placebo on various dimensions of pain and pain responder rate in participants with DPNP	• Change from baseline in the weekly average of worst daily pain intensity over time, assessed on the NRS • Change from baseline in the weekly average of nighttime pain intensity over time, assessed on the NRS • Occurrence of ≥30% reduction from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS • Occurrence of ≥50% reduction from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS
To determine participant's impression of overall change and severity, as well as clinically meaningful within-patient change in patient reported outcome endpoints in participants with DPNP	• Patient Global Impression of Change (PGIC) over time • Change from baseline in Patient Global Impression of Severity (PGIS) over time
To determine the effect of GSK3858279 compared to placebo on rescue medication use in participants with DPNP	• Usage of rescue medication (occurrence, number of days, amount taken) over time
To determine the effect of GSK3858279 compared to placebo on exploratory biomarkers in whole blood in participants with DPNP	• Change from baseline in peripheral immune cell populations, in particular CCR4-expressing cells, at Weeks 4 and 12 • Change from baseline in serum protein mediators, including but not limited to inflammatory and immune cell activation markers, may be investigated • Whole blood transcriptomics (ribonucleic acid [RNA] sequencing) and epigenetics markers may also be explored
To determine the effect of GSK3858279 compared to placebo on pain severity and pain interference in participants with DPNP	• Change from baseline in Brief Pain Inventory Short Form (BPI-SF) pain severity and interference domains over time
Additional Safety (Tertiary)	
To determine the safety of repeated doses of GSK3858279 compared to placebo in participants with DPNP	• Change from baseline in laboratory parameters, vital signs and ECG
To assess the potential for anti-GSK3858279 antibody formation (ADA and NAb) in participants with DPNP	• Occurrence of ADA and NAb and titers of ADA for samples with confirmed ADA
Additional PK/PD/TE/Biomarkers (Tertiary)	
To characterize the PK following repeated dosing of GSK3858279 in participants with DPNP over time	• Serum PK concentrations of total GSK3858279 over time • Maximum value (Cmax), time of Cmax (tmax), trough value (Ctau), average concentration (Cavg) and area under the curve over the dosing interval (AUC(0-tau)) after the 1st, 4th and 8th dose
To evaluate the CCL17 profile following repeat dosing of GSK3858279 in participants with DPNP over time	• Total and free CCL17 levels in serum over time • Reduction (%) from baseline in free CCL17 over time
To explore the longitudinal dose-exposure-response relationship	• Population parameters for the model describing the relationship between dose, PK and response (assessed on the Numeric Rating Scale [NRS]) pain over time

3.1. Efficacy estimands

Primary estimand for the primary efficacy objective	
Description	Mean change from baseline at Week 12 in the weekly average of average daily pain intensity for GSK3858279 compared to placebo in adult participants with DPNP, where persistent use of prohibited pain therapy and study treatment discontinuations due to lack of efficacy or adverse events are considered a negative outcome, in the absence of other treatment discontinuations and regardless of all other use of prohibited pain therapy and use of allowed rescue medication. Rationale: Interest lies in the treatment effect where participants discontinuing study treatment due to lack of efficacy or adverse events, or persistently taking prohibited pain therapy are reflected in the estimated effect as treatment failures, and irrespective of the use of allowed rescue medication and occasional use of prohibited pain therapy.
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoint	Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuation due to lack of efficacy or adverse events • Strategy: composite; study treatment discontinuation is considered a negative outcome, and post-ICE assessments will be imputed using multiple imputation based on baseline pain scores ICE: other study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: persistent use of prohibited pain therapy • Strategy: composite; persistent use of prohibited pain therapy is considered a negative outcome, and post-ICE assessments will be imputed using multiple imputation based on baseline pain scores ICE: occasional use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included
Population-level summary	Difference in means between each GSK3858279 treatment arm and placebo

Two additional estimands will also be defined as follows:

Additional estimand #1 for the primary efficacy objective	
Description	Mean change from baseline at Week 12 in the weekly average of average daily pain intensity for GSK3858279 and placebo in adult participants with DPNP, in the absence of study treatment discontinuations, prohibited pain therapy and allowed rescue medication. Rationale: This estimand addresses the hypothetical scenario where no intercurrent events occurred, and in particular where all participants continued in the study on treatment and without taking prohibited pain therapy or rescue medication.
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoint	Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS, in the absence of treatment discontinuations, use of prohibited pain medications, and allowed rescue medication
Population	Adult patients with DPNP
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: persistent use of prohibited pain therapy • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: occasional use of prohibited pain therapy • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome ICE: use of allowed rescue medications • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome
Population-level summary	Difference from placebo in mean change from baseline for each GSK3858279 treatment arm
Additional estimand #2 for the primary efficacy objective	
Description	Mean change from baseline at Week 12 in the weekly average of average daily pain intensity for GSK3858279 compared to placebo in adult participants with DPNP, regardless of study treatment discontinuations, use of prohibited pain therapy and use of allowed rescue medication. Rationale: Interest lies in the treatment effect irrespective of study treatment discontinuation, prohibited pain therapy and allowed rescue medication.
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) **compared** to placebo
Endpoint	Change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuation • Strategy: treatment policy; all data collected after the ICE will be included

Additional estimand #1 for the primary efficacy objective	
	ICE: use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included
Population-level summary	Difference from placebo in mean change from baseline for each GSK3858279 treatment arm

The attributes of the primary and additional estimands will be applied to the following continuous secondary efficacy endpoints, using the same strategies to address the same intercurrent events:

- Change from baseline in the Short-Form McGill Pain Questionnaire total score over time
- Change from baseline in the weekly average of average daily pain intensity over time, assessed on the NRS

Primary and additional estimands for the binary secondary efficacy endpoints are described below:

Estimand for the binary secondary efficacy endpoint	
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoints	Occurrence of ≥30% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS Occurrence of ≥50% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs) (**Primary estimand**)	ICE: study treatment discontinuation due to lack of efficacy or adverse events • Strategy: composite; study treatment discontinuation is considered a negative outcome, and post-ICE assessments are set to non-responder ICE: other study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: persistent use of prohibited pain therapy • Strategy: composite; use of prohibited pain medications is considered a negative outcome, and post-ICE assessments are set to non-responder ICE: occasional use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included

Estimand for the binary secondary efficacy endpoint	
Strategy for intercurrent events (ICEs) (**Additional estimand #1**)	ICE: study treatment discontinuations • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: use of persistent prohibited pain therapy • Strategy: hypothetical; data collected after the ICE will not be included, and outcomes will be assumed to be similar to participants who did not experience the ICE ICE: occasional use of prohibited pain therapy • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome used to derive the binary endpoint ICE: use of allowed rescue medications • Strategy: hypothetical; assessments up to 24 hours after the ICE will not be included in the calculation of the change from baseline outcome used to derive the binary endpoint
Strategy for intercurrent events (ICEs) (**Additional estimand #2**)	ICE: study treatment discontinuation • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected after the ICE will be included
Population-level summary	Odds ratio

3.2. Safety estimands

Primary estimand for safety objectives	
Treatment Condition	GSK3858279 (60 mg/week or 360 mg/week) compared to placebo
Endpoints	• Occurrence of Adverse Events (AEs), Serious Adverse Events (SAEs) and AEs of Special Interest (AESIs) • Occurrence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade ≥3 hematological/clinical chemistry abnormalities
Population	Adult participants with DPNP
Strategy for intercurrent events (ICEs)	ICE: study treatment discontinuation • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of prohibited pain therapy • Strategy: treatment policy; all data collected after the ICE will be included ICE: use of allowed rescue medication • Strategy: treatment policy; all data collected will be included
Population-level summary	• AEs, SAEs, AESIs, NCI-CTCAEs: number and % of participants with at least one event by Preferred Term for each treatment arm

4. STUDY DESIGN

4.1. Overall design

This is a Phase 2, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy, safety, tolerability, PK and TE of GSK3858279 vs. placebo when administered with repeated weekly SC injections in approximately 240 enrolled participants with DPNP. The number of participants may be increased by approximately 15% to ensure regional requirements for recruitment are met.

Participants will undergo a screening visit, after which they will go into a washout period of all of their DPNP pain medications (if applicable), consisting of at least 3 days or 5 half-lives, whichever is longer. This is followed by a further 7 days of run-in period to establish an accurate baseline; after which they will first be stratified based on region (Japan, China or the rest of the world) and an average of the average daily pain score at baseline (<7 or ≥7) and then randomized at 1:1:1 ratio to either GSK3858279 at 60 mg SC weekly or GSK3858279 at 360 mg SC weekly or placebo SC weekly within each stratum.

Total study duration will be approximately 33 weeks. Screening will take place within 6 weeks before randomization. Treatment period is up to 12 weeks. Primary endpoint is at Week 12 to determine the efficacy of GSK3858279 at 60 mg SC weekly and GSK3858279 at 360 mg SC weekly on pain compared to placebo in participants with DPNP. Participants will be followed for additional 15 weeks in the off-treatment follow-up period. There will be 2 visits during the off-treatment follow-up period in addition to end-of-study visit at Week 27, where bloods for PK, TE and safety will be collected. Any rescue medication use will be reported by the participant on the electronic diary (eDiary) on a daily basis.

An Interim Analysis for futility will be performed when approximately 30 participants in each treatment arm qualify for Week 12 assessment (by either attending the Week 12 assessment or through missing data imputation strategy, for example in the case that a participant withdraws from the study). Further additional interim analyses may be considered to support internal decision-making and regulatory interactions. An internal data review committee (iDRC) will be set-up for reviewing the results from the interim analyses. Full details of all interim analyses will be prospectively outlined in the iDRC charter.

An external IDMC will regularly review the unblinded study data at scheduled intervals. IDMC reviews will allow ongoing external safety oversight to protect the safety of study participants as the study progresses. Further details on safety monitoring by the IDMC are provided in Section 8.4. Further details of the IDMC composition are highlighted in Section 10.1.6 and full details of activities are provided in the IDMC charter.

4.2. Scientific rationale for study design

The overall study design is well established to assess the efficacy of a novel therapeutic agent in participants with DPNP after they have been unable to sufficiently manage pain despite trying standard of care therapies.

The double-blind, placebo-controlled, randomized study design is considered the gold standard for the safety and efficacy assessment of a new therapy in DPNP both by clinicians and regulatory authorities.

The primary endpoint is change from baseline in the weekly average of average daily pain (ADP) intensity at Week 12, assessed on the Numeric Rating Scale (NRS). ADP on NRS is a validated clinical endpoint widely used in clinical studies of DPNP and is accepted by the regulatory agencies [European Medicines Agency, 2016]. It is a direct and simple way of measuring pain intensity with clear clinical relevance to participants. Pain intensity is the regulator requested key measure of efficacy of an analgesic drug and should always be reported. In long-term studies the weekly averages of the daily measurement compared to baseline, are commonly used as the primary efficacy variable. Change in ADP intensity is further supported by other endpoints such as the change from baseline in the Short-Form McGill Pain Questionnaire and change from baseline in Brief Pain Inventory Short Form (BPI-SF) questionnaire domains that will generate additional evidence to inform how a participant feels and functions.

All participants will have a final follow-up visit 15 weeks after their last visit at Week 12 (16 weeks after their last dose of study intervention at Week 11). This equates to a follow-up period over approximately 5× the apparent terminal elimination half-life for total GSK3858279.

4.2.1. Participant input into design

Feedback on study design was obtained during a participant engagement survey with 56 participants based in Australia, South Africa, Spain, USA and UK in May 2022. The study was well-received overall, and the general design and requirements were acceptable.

It is GSK's intent to continually engage participants whose feedback may influence future study designs for this disease area and may improve the participant experience within clinical research.

4.3. Justification for dose

The doses chosen (60 mg/week and 360 mg/week) allow an exploration of the dose-exposure-response of GSK3858279 in DPNP as the doses are predicted to encompass a range of target engagement (reductions compared to baseline) of the chemokine, CCL17 (Figure 2).

GSK3858279 target engagement has been demonstrated in both healthy and OA of the knee participants. Following single IV (0.1-10 mg/kg) and SC (3 mg/kg) administrations,

there were dose related increases in total (free + complex) CCL17 and reductions (compared to baseline) in free CCL17 (as measured by a semi-quantitative method) over time (207804, Part A, and 209973).

Reductions in free CCL17 (as measured by a semi-quantitative method) were maintained over 8 weeks on repeat weekly dosing (240 mg) to participants with moderate to severe OA of the knee (207804, Part B).

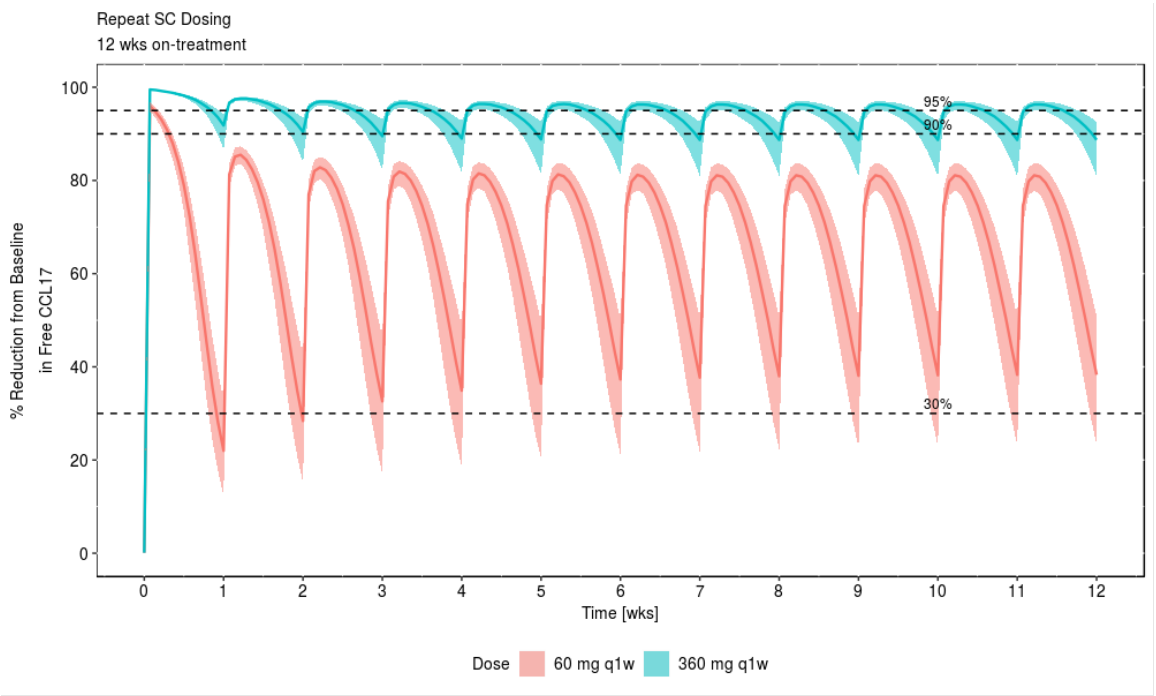
In participants with moderate to severe OA of the knee the 240 mg/week dose demonstrated efficacy on daily average pain (as measured by NRS score). The Phase 1b study (207804, Part B) provides the only prior clinical information on the impact of functional inhibition of CCL17.

The doses (60 mg/week and 360 mg/week) have been selected based on an integration of model predicted target engagement (reductions from baseline in free CCL17) and free concentration-time data [GSK Document Number TMF-14616324]. The target-mediated drug disposition (TMDD) model uses the Quasi Steady State (QSS) approximation and is fitted to total GSK3858279 and total CCL17 data from studies 207804 and 209973 [GSK Document Number TMF-14616324].

The integrated analysis predicts almost complete target engagement (reductions in CCL17 compared to baseline of ≥89%) over the entire dosing interval following the highest dose selected for this study, 360 mg/week (Figure 2). Although SC doses higher than 240 mg weekly have not been studied in human trials, it is considered a low safety risk to proceed with the higher dose of 360 mg SC weekly. The NOAEL based on animal studies is 100 mg/kg/week IV and 100 mg/kg/week SC and the exposure limits based on mean AUC and Cmax in the 26-week cynomolgus study are approximately 45- and 50-fold higher than predicted maximum GSK3858279 AUC and Cmax exposures, respectively, at the proposed 360 mg SC weekly dose in humans. In addition, the single IV dose of 10 mg/kg given in the clinical Phase 1a healthy volunteer study provides a margin over both Cmax (~5.8-fold) and AUC (~2.2-fold) following repeat weekly dosing at 360 mg SC. As there is no rationale for a population effect, translation to DPNP has been assumed.

The lower dose (60 mg/week) is predicted to result in smaller (maximum and trough) CCL17 reductions (Figure 2). Therefore, the selected 6-fold dose range (60 - 360 mg/week) allows for an exploration of the efficacy, safety, and tolerability of GSK3858279 across a range of reductions in target levels and aligns with good practices on understanding efficacy, safety, and tolerability across a wide dose range in Phase 2. This will facilitate selection of dose(s) in Phase 3.

Figure 2 **Model Predicted Reductions (median and 95% CI of the prediction) in free CCL17 following weekly SC dosing with GSK3858279 (60 mg or 360 mg) over 12 weeks [GSK Document Number TMF-14616324].**



4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the off-treatment phase (Week 27 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 enrollment 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
1. 18-75 years of age inclusive, at the time of signing the informed consent. Country-specific requirement: South Korea. Participants from South Korea are required to be aged at least 19 years or greater for entry into the study.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Type I or Type II diabetes with painful, distal, symmetrical, sensory-motor neuropathy attributed to diabetes, of at least 6 months duration; a. Pain must have begun in bilateral distal lower limbs. b. Pain is not related to underlying infection or trauma. c. Diagnosis confirmed by a positive Douleur Neuropathique 4 [DN4] questionnaire at screening. d. Levels of glycosylated hemoglobin A1c (HbA1c) less than 97 mmol/mol (<11%). 3. On a stable anti-diabetic medication regimen (unchanged dose over the last 30 days for diabetes) prior to screening. Adjustment of insulin dose is acceptable, however, resumption of insulin treatment is not allowed since 30 days prior to screening. 4. No recent unplanned (i.e. within the previous 6 months) hospitalizations due to non-compliance or uncontrolled diabetes 5. At screening (Visit 1 a), a pain score ≥4 and ≤9 by the 11-point NRS (0-10) for average daily pain intensity over the past 24. 6. During the run-in period over the preceding 7 days prior to first dose of study intervention; a. An average of the average daily pain score of ≥4 and ≤9 by the 11-point NRS (0-10). Pain scores must be recorded on at least 6 out of 7 days and should not be highly variable (standard deviation ≤1.5). The Investigator will receive confirmation of eligibility if all daily pain score criteria are met. b. Rescue medication use (if required) must be within the permitted allowance. Rescue medication diary must be completed on at least 6 out of 7 days. The Investigator must review the rescue medication diary to confirm eligibility criteria are met. See Section 6.9.3 for details. 7. Documented history of insufficient pain relief from, or inability to tolerate, or contraindication to at least one line of current standard of care therapy, e.g. antidepressants (tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs]), antiepileptic (anticonvulsant) drugs.

8. Participant must be willing and able to understand and participate in all scheduled evaluations and to complete all required tests and procedures including the use of patient eDiary. This will be judged by the Investigator during the screening period.
WEIGHT
9. BMI within the range of 18 to 40 kg/m^2 (inclusive).
SEX
10. Male or Female participant; A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: – Not a woman of childbearing potential (WOCBP) as defined in Section 10.4 OR – Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least 16 weeks after the last dose of study intervention. The Investigator should evaluate potential for contraceptive method failure (e.g. non-compliance, recently initiated) in relationship to the first dose of study intervention. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. See Section 8.3.5. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. A male participant with a partner who is a WOCBP is required to use a condom during sexual intercourse throughout the study and for 16 weeks after the last dose of study intervention.
INFORMED CONSENT
11. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion criteria

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

MEDICAL CONDITIONS

1. History of significant medical illness, including but not limited to cardiovascular, renal, gastrointestinal, lymphatic diseases, which, in the opinion of the Investigator, would interfere with the study procedures and/or assessments.
2. Participant has current painful peripheral neuropathy due to a cause other than diabetes (e.g. pernicious anemia, hypothyroidism, post-herpetic neuralgia).
3. Participant has any lower extremity amputation.
4. Participant has a current or previous foot ulcer within the past 3 months as described by medical history and/or medical examination.
5. Participants who have complications of diseases that are considered to affect the assessment of DPNP. For example, nerve diseases with pain other than DPNP (cervical spondylosis, carpal tunnel syndrome, spinal canal stenosis, and post-herpetic pain), pain diseases other than nerve diseases (collagen diseases, gout, chronic obstructive arteriosclerosis, and arthritis), and other pain at the site of evaluation (skin diseases and traumatic injury).
6. Current immunodeficiency diseases including but not limited to acquired immunodeficiency disorder or immunoglobulin deficiency.
7. History of infected joint prosthesis, chronic leg ulcers, permanent in-dwelling catheters, chronic sinusitis, recurrent chest infections or recurrent urinary tract infections.
8. Symptomatic herpes zoster within 3 months prior to screening.
9. Current or previous active Mycobacterium tuberculosis infection regardless of treatment.
10. Evidence of latent tuberculosis (TB) as documented by medical history, examination and TB testing: either a positive (not indeterminate) QuantiFERON TB Gold Plus test or a positive (not indeterminate) T-SPOT test.

NOTES:

- QuantiFERON Gold Plus test or, if unavailable, T-SPOT TB test (with prior Sponsor's approval) will be performed. The QuantiFERON Gold Plus test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.
- In cases where the QuantiFERON or T-SPOT is indeterminate, the participant may have the test repeated once, but they will not be eligible for the study unless the second test is negative.

- If the participant has had recent close contact with persons who have active TB and did not receive satisfactory anti-tuberculosis treatment prior to first dose of study intervention, they will not be eligible.

11. History of significant allergies to monoclonal antibodies.
12. History, diagnosis, signs or symptoms of any clinically significant psychiatric disorder, including but not limited to: psychotic disorders, somatoform disorders, bipolar disorders, depression with hospital admission within the last 5 years (not expected to require initiation of pharmacological treatment for depression or anxiety for the duration of the study), any other psychiatric illness that, in the opinion of the Investigator, would render a participant as not suitable to participate in the study.
13. History or evidence of clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis or Stevens-Johnson syndrome, and exfoliative dermatitis).
14. Malignancy
    - History of malignancy within the last 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
    - Breast cancer within the past 10 years.
15. Liver
    - Alanine Aminotransferase (ALT) >1.5× ULN at screening.
    - Bilirubin >1.5× ULN at screening (isolated bilirubin >1.5× ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
    - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
16. Hematological laboratory values at screening
    - White Blood Cell (WBC) count $<3.0\times10^9$/L.
    - Hemoglobin <10.0 g/dL.
    - Platelet count $<125\times10^9$/L.
17. Myocardial infarction or unstable angina, or cerebrovascular event within 6 months prior to screening.
18. Unstable or life-threatening cardiac arrhythmia requiring intervention within 3 months prior to screening.
19. New York Heart Association (NYHA) Class III or IV heart failure.
20. Corrected QT interval according to Fridericia's formula (QTcF) >450 msec or QTcF >480 msec in participants with bundle branch block, at screening or Day 1 visit.

21. Evidence of significant renal insufficiency, indicated by an estimated creatinine clearance <45 mL/min/1.73 m2 at screening.
22. Planned surgical procedure over the duration of the study.
23. Major surgery (as per Investigator's judgment) within 3 months prior to first dose of study intervention.
24. Participants with a recurrent or chronic infection (e.g. osteomyelitis), who have been receiving treatment within 3 months prior to first dose of study intervention or individuals with an active infection at screening or Day 1 visit.

PRIOR/CONCOMITANT THERAPY

25. Use of any analgesic medication is prohibited, including those used for DPNP such as gabapentanoids, tricyclic antidepressants, SNRIs, anticonvulsants/antiepileptics, SSRIs (except for well-controlled depression/anxiety), NSAIDs (except for acetylsalicylic acid used for cardiovascular prophylaxis), opioids (including tapentadol), topical analgesics (including transdermal patches), capsaicin products, mexiletine, dextromethorphan, tramadol, cannabinoids and ketamine until completion of the Week 12 visit. These medications must be washed out for at least 3 days or 5 half-lives, whichever is longer, prior to the study's first daily pain assessment (start of run-in period). Before washout a tapered withdrawal can be conducted as deemed clinically necessary to local guidance with the Investigator's supervision.
26. Immunomodulators, including:
    - Corticosteroids (parenteral within 3 months prior to first dose of study intervention; oral within 1 month prior to first dose of study intervention);
    - Biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to first dose of study intervention;
    - Non-biologic agents (e.g. methotrexate, azathioprine, JAK-inhibitors) within 4 weeks or 5 half-lives (whichever is longer) prior to first dose of study intervention;

    are prohibited during the study.
27. Received live or live attenuated vaccine(s) within 30 days prior to first dose of study intervention or plans to receive such vaccines during the study.
28. Use of pain interventions as per Section 6.9.1.4 within 4 weeks of screening.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

29. Current enrollment or past participation in a clinical study of an IMP within the last 30 days or 5 half-lives (whichever is longer) of signing ICF.
30. Exposure to more than 4 new Investigational Medicinal Products within 12 months prior to first dose of study intervention, or any previous exposure to GSK3858279.

31. Participants who are a family member of the Investigator or any associate, colleague, and employee assisting in the conduct of the study (secretary, nurse, technician).
32. Participants who cannot be contacted by phone in an emergency.
33. Participants who are unlikely to comply with the protocol (e.g. uncooperative attitude, inability to return for subsequent visits, inability to complete the eDiary daily etc.) and/or otherwise considered by the Investigator to be unlikely to complete the study.

DIAGNOSTIC ASSESSMENTS

34. Positive human immunodeficiency virus (HIV) antibody test.
35. Has a positive test for hepatitis B virus (HBV) defined as either:
    - positive for hepatitis B surface antigen (HBsAg) OR
    - positive for hepatitis B core antibody (HBcAb) AND positive for HBV deoxyribonucleic acid (DNA).

NOTE: Participants who are positive for HBcAb and negative for HBV DNA can be enrolled in the study provided they follow the requirement of Section 8.3.6 for hepatitis B reactivation monitoring.

Country-specific requirements for participants from sites in Japan only: additionally, positive for hepatitis B surface antibody (HBsAb) AND positive for HBV DNA.

36. Positive hepatitis C antibody test result.

NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained.

37. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention.
38. Active or suspected COVID-19 infection.

Participants who have tested positive for COVID-19 with a PCR assay at screening and who are either asymptomatic or who are symptomatic and uncomplicated require a negative PCR assay after an asymptomatic period of 14 days before they can enroll into the study. Participants who have had a negative PCR assay initially but have since developed clinical features suggestive of COVID-19 or have had known exposure to COVID-19 during the screening period must again test negative with a PCR assay test 14 days after symptoms resolution prior to first dose of study intervention.

39. A positive drug screen at screening.

NOTE: Positive result, such as opiates and benzodiazepines, on the UDS would not automatically exclude participants as long as the results are consistent with the participants current medications use and the washout period will be completed per protocol prior to first dose of study intervention.

OTHER EXCLUSIONS
40. Pregnant (as confirmed by serum pregnancy test) or lactating, or women planning to become pregnant or initiating breastfeeding.
41. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within a year prior to first dose of study intervention.
42. 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

Participants are required to fast for a minimum of 10 hours before visits on which a fasting lipid panel will be drawn when feasible, as deemed by the Investigator. Details are provided as per the SoA.

5.3.2. Caffeine, alcohol, and tobacco

No restrictions are required; however, extensive use of caffeine, alcohol, and tobacco should be avoided. In addition, changes in tobacco usage should also be avoided during the study.

5.3.3. Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.3.4. Other restrictions

Not applicable.

5.4. Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is 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, protocol deviations and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once. A further re-screening for administrative reasons can be approved at the discretion of the Medical Monitor. Rescreened participants are required

to sign a new ICF and should be assigned a new participant number. Previously assigned participant numbers are to be recorded in the participants' eCRF.

5.5. Criteria for temporarily delaying administration of study intervention

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Study intervention SC injections should be administered weekly, preferably on the same day each week. Each participant across all the treatment arms will receive 3 injections at each visit.

The SC injections should be administered to the abdomen or thigh. The same site region of the body (abdomen or thigh) should be used at each weekly dosing visit. The abdomen will be split into 4 quadrants and each thigh into upper and lower parts. All 3 injections should be administered in the same area (quadrant for abdomen, lower or upper half of a thigh) 2-3 cm apart. It is recommended that the injections are rotated between different quadrants of the abdomen or different areas of both thighs for each weekly dosing visit. The IMP injection site should be different from the insulin injection site, if applicable.

A window of ± 2 days is acceptable between weekly doses (except for Visits 2) and a minimum gap of 5 days between each dose, for no more than 2 consecutive dosing visits. Participants should return to their 7-day dosing schedule as soon as possible thereafter.

The SC injections must be performed at the site after completion of study assessments, PK sampling and other blood draws.

All participants must receive general safety monitoring for 2 hours post-injection during the first two dosing visits. Safety monitoring will include monitoring for systemic hypersensitivity and local ISRs.

All participants are to receive a weekly dose of GSK3858279 60 mg SC or GSK3858279 360 mg SC or placebo irrespective of weight.

The doses of GSK3858279 for injection will be prepared at the investigational site by unblinded authorized site staff, from the stock solution provided.

Table 4 Study intervention(s) administered

Intervention Label	GSK3858279	Placebo	Rescue Medication
Intervention description	GSK3858279 is formulated in 20 mM Histidine, 180 mM Trehalose, 40 mM Arginine, 8 mM Methionine, 0.05 mM EDTA, 0.02% PS80, pH 6.0	Normal Saline (0.9% sodium chloride)	Paracetamol/Acetaminophen
Type	Biologic	Placebo	Drug
Dosage form	Solution for injection. The drug product is a brown to yellow solution stored in ISO 2R glass vials with a 13 mm rubber stopper and a grey/violet 13 mm Flip-top aluminium overseal	Solution for injection	Oral dosage form e.g. tablet, capsule, solution
Unit Dose Strength(s)	100 mg/mL. Each vial has an extractable volume of 1.2 mL (120 mg per vial)	0.9% w/v sodium chloride, placebo level variable	Variable
Route of administration and duration	SC Injection, 12 weeks	SC Injection, 12 weeks	Oral
Dosage Level(s)	60 mg/week and 360 mg/week. The appropriate volume of GSK3858279 will be injected using a syringe at no more than 1.2 mL per injection. Dilution instructions will be provided in the Pharmacy Manual	The appropriate volume of normal saline will be injected (SC) in the same manner as the corresponding active cohort	As needed with the following restrictions: No more than 3 grams/day and for a maximum of 4 days in a week
Use	IMP	IMP	Rescue medication
Non-IMP	Not applicable	Not applicable	Non-IMP
Authorized AxMP/Unauthorized AxMP	Not applicable	Not applicable	Authorized AxMP
Sourcing	Study medication is supplied by GSK	0.9% w/v sodium chloride is sourced locally by the site	Paracetamol /Acetaminophen will be provided to sites by GSK or purchased commercially by the site.

Intervention Label	GSK3858279	Placebo	Rescue Medication
Packaging and Labelling	Study intervention will be provided in a single-use vial contained within a carton. Each single-use vial and carton will be labelled as required per country requirement. Dispensed medication will be labelled as required per country requirement.	Study intervention will be purchased commercially by the site and used in its commercial container closure system as single-dose product. Dispensed medication will be labelled as required per country requirement.	Dispensed medication will be labelled as required per country requirement.

Table 5 Study arm(s)

Arm Title	GSK3858279	GSK3858279	Placebo
Arm Type	Experimental	Experimental	Placebo
Regimen number	N/A as parallel group study	N/A as parallel group study	N/A as parallel group study
Arm Description	Participants will receive GSK3858279 (SC) 60 mg once per week for 12 weeks	Participants will receive GSK3858279 (SC) 360 mg once per week for 12 weeks	Participants will receive Placebo (SC) once per week for 12 weeks

6.2. Preparation, handling, storage, and 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, prepare 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 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 site 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 will be available upon request from GSK.

Placebo (0.9% normal saline) will not be supplied by the sponsor. It will be purchased commercially by the study site, subsidiary, or designee and used in its commercial container closure system as single-dose product. The manufacture's drug label instructions and/or packet insert should be followed for handling, dose preparation, and administration. Sites should use the most up to date version of packet insert.

6.3. Assignment to study intervention

All participants will be centrally randomized using an Interactive Web Response System (IWRS). Before the study is initiated, the login information and directions for the IWRS will be provided to each site. Administration of study intervention is summarized in the SoA.

At screening a unique participant 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 eligibility criteria will be randomized to a treatment group centrally through the IWRS. Randomization will be in accordance with a randomization schedule generated by the GSK Randomization Office, prior to the start of the study, using validated internal software.

Once a randomization number and participant number have been assigned to a participant, they will not be reassigned to any other participant in the study.

6.4. Blinding

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

- Participants will be stratified according to region (Japan, China or the rest of the world) and an average of the average daily pain score at baseline (<7 or ≥7), and randomized in a ratio of 1:1:1 to receive GSK3858279 60 mg SC weekly or 360 mg SC weekly or placebo SC weekly within each stratum. Investigators and blinded site staff will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, each syringe will be labelled with yellow 'blinding tape' to mask any visual differences of the liquid between

interventions. The unblinded authorized site staff who prepare the study intervention will not have contact with study participants.

- The unblinded authorized site staff will be responsible for the preparation and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.
- The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant's safety must always be the first consideration in making such determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in source documents and in the eCRF.
- 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 source documents and in the eCRF. The participant will be followed up for safety monitoring if treatment was received.
- GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited safety 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.
- Unblinded site monitors and, in the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately. Unblinded GSK personnel (separate roles outside of the blinded study teams), will also be allowed access to subject level treatment assignments as required to manage the unblinded aspects of study conduct.
- Unblinded personnel independent from GSK will be allowed access to subject level treatment assignments as required to manage IDMC/iDRC conduct.
- The Central Laboratory will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.
- Designated independent representative(s) may be unblinded for preparing population PK and PKPD datasets and for draft PK and PKPD model development/refinement using PK and PKPD unblinded datasets, including but not limited to: concentration-time data, dosing information, baseline demographic characteristics, primary efficacy and PD information.

- Primary reporting will take place after the target number of participants have completed their Week 12 (or Early Withdrawal) visit. GSK staff who have direct contact with sites will remain blinded to individual subject allocation until the end-of-study.

6.5. Study intervention compliance

The Pharmacy Manual should be followed when preparing study intervention for study participants. Participants will receive study intervention at the clinical unit directly from the Investigator or designee, under medical supervision, via SC 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.

6.6. Dose modification

Dose modification is not applicable in this study.

6.7. Continued access to study intervention after the end of the study

Participants will not receive any additional treatment from GSK after completion of the study.

6.8. Treatment of overdose

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

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until the study intervention is predicted to be non-quantifiable systemically (at least 16 weeks). Document the quantity of the excess dose as well as the duration of the overdosing in source documents and in the eCRF.

6.9. Prior and concomitant therapy

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

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

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

6.9.1. Concomitant treatments

Medications prohibited or restricted prior to the study, during the treatment period and/or during the off-treatment follow-up period of the study are listed below, along with any period of exclusion which must be applied.

Whether the participant will need to discontinue IMP, possibly temporarily, will depend on the nature of the prohibited medicine and the risk to participant's safety by continuing IMP.

The Investigator should discuss any such situation with the Medical Monitor and certainly in any situation where a new immunomodulator has been commenced whilst the participant is in the study and receiving IMP.

Should a participant breach the prohibited medicines rules, regardless, the participant should be strongly encouraged to remain in the study.

6.9.1.1. Immunomodulators

Immunomodulators must have been discontinued prior to first dose of study intervention and must not be used throughout the study.

- Corticosteroids: parenteral within 3 months prior to first dose of study intervention; oral within 1 month prior to first dose of study intervention. Inhaled, intranasal, otic, and ophthalmic corticosteroids can be used at any time throughout the study. Topical steroids applied on sites other than the DPNP disease area are also allowed.
- Biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to first dose of study intervention.
- Non-biologic agents (e.g. methotrexate, azathioprine, JAK-inhibitors) within 4 weeks or 5 half-lives (whichever is longer) prior to first dose of study intervention.

6.9.1.2. Analgesics

Use of any analgesic medication is prohibited, including those used for DPNP such as gabapentanoids, tricyclic antidepressants, SNRIs, anticonvulsants/antiepileptics, SSRIs (except for well-controlled depression/anxiety), NSAIDs (except for acetylsalicylic acid used for cardiovascular prophylaxis), opioids (including tapentadol), topical analgesics (including transdermal patches), capsaicin products, mexiletine, dextromethorphan, tramadol, cannabinoids and ketamine until completion of the Week 12 visit. These medications must be washed out for at least 3 days or 5 half-lives, whichever is longer, prior to the study's first daily pain assessment (start of run-in period). Before washout a tapered withdrawal can be conducted as deemed clinically necessary to local guidance with the Investigator's supervision.

Occasional and limited use of an NSAID (including selective COX-2 inhibitors) is permitted only for non-DPNP related pain or self-limiting conditions. However it should be avoided within 24 hours of a study visit or during the last 2 weeks of the treatment period prior to the Week 12 visit. The use of NSAIDs should be restricted to a maximum of 3 days during each 4-week interval. Details of every occasion of NSAID use, including medication name and dose, should be captured in the eCRF. The dose of NSAID should not exceed the locally approved and recommended maximum dose, and combination NSAID products should not be used.

For non-pain related co-morbid conditions, participants will be allowed to take throughout the study the following medications. The dose must be stable for at least 4 weeks prior to screening and will remain stable throughout the study (PRN [as needed] use is not allowed):

- A benzodiazepine, zolpidem, diphenhydramine or related drugs for insomnia.
- A selective serotonin reuptake inhibitor (SSRI) for well-controlled depression/anxiety.
- Oral aspirin (≤325 mg/day) for cardiovascular prophylaxis.

6.9.1.3. Diabetic therapy

Participants must be on a stable anti-diabetic medication regimen (unchanged dose over the last 30 days for diabetes) prior to screening. Adjustment of insulin dose is acceptable, however, resumption of insulin treatment is not allowed since 30 days prior to screening. Participants should remain on the same anti-diabetic medications over the course of the study, unless there is a medical need to adjust anti-diabetic medications.

6.9.1.4. Prohibited concomitant pain interventions

Concomitant use of the following interventions must be discontinued 4 weeks prior to screening and is prohibited until completion of the Week 12 visit:

- Laser therapy
- Acupuncture therapy
- Nerve blocks
- Spinal cord stimulation
- Electrical stimulation therapy
- Other forms of pain reduction interventions that might confound protocol assessments

6.9.2. Vaccinations

Investigators should review and update the vaccination status of potential participants as per local guidelines for adult vaccination including against COVID, influenza, herpes zoster and pneumococcus prior to entering them into the study (refer to American Diabetic Association recommendations where no local guidelines are available [Professional Practice Committee; 12, 2022]), with particular attention to the vaccination status of participants over 65 years of age. All participants may receive inactivated flu vaccines during the study at the discretion of the Investigator.

Live or live attenuated vaccines will need to be given at least 30 days prior to first dose of study intervention and are prohibited throughout the study.

6.9.3. Rescue medicine

Paracetamol/Acetaminophen, administered orally, at doses of ≤3 grams/day and for a maximum of 4 days in a week (the calendar week should be calculated based on Day 1 visit date), is permitted for use as rescue medication any time during the study except within 24 h before and during a clinical visit. Participants will record any Paracetamol/Acetaminophen use over the past 24 h on the eDiary on a daily basis.

For eligibility, all Paracetamol/Acetaminophen use will be recorded in the eDiary from Visit 1b and evaluated during the 7 day run-in period. If participants exceed the permitted allowance during the run-in period, they will not be eligible for the study.

Paracetamol/Acetaminophen will not be supplied by the sponsor, it will be purchased commercially or arranged by the study site. Rescue medicine will be dispensed to study participants who initially meet study criteria at the initial screening visit. Additional supply will be provided when needed during the study by the study site staff. Participants should not be taking their own supply of Paracetamol/Acetaminophen.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Permanent discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of the study intervention. In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will be requested to remain in the study and complete the planned visits and assessments for the treatment period (up to the Week 12 visit) per SoA in Section 1.3 (except for the weekly SC IMP injections and post-dose [24-72 hours or 96-120 hours] PK/TE sample collection), with a final follow-up visit (Visit 20) approximately 16 weeks from the last dose received, unless they also withdraw consent to remain in the study. However, if this is not possible at a minimum participants will be asked to complete all assessments at both the Early Discontinuation/Withdrawal visit, preferably 1 week from the last dose received (applicable during the treatment period) or as soon as possible after the participant's decision has been communicated to the site staff (applicable during the off-treatment phase), and a final follow-up visit (Visit 20) approximately 16 weeks from the last dose received. The final follow-up visit will assess all the items per the SoA for the Week 27 visit. Participants should be requested to complete average daily pain, worst daily pain, nighttime pain NRS scoring and Paracetamol/Acetaminophen intake Diary up to the final follow-up visit (Visit 20).

A participant will be permanently discontinued from study intervention (but may continue to be followed in the study) if any of the following criteria are met:

- Pregnancy
- Serious hypersensitivity reactions assessed as related to study intervention
- Active TB infection
- Liver chemistry, renal function, hematological abnormality, ECG parameters stopping criteria, or hepatitis B reactivation
- Use of prohibited concurrent medication, vaccine, or therapy where the continuation of study intervention would place the participant at risk in the opinion of the Investigator and/or Medical Monitor
- Inability to adhere to protocol-specified restrictions or procedures, at the discretion of the Investigator, after consultation with the GSK Medical Monitor
- Other serious or severe adverse events, at the discretion of the Investigator, after consultation with the GSK Medical Monitor

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the list below:

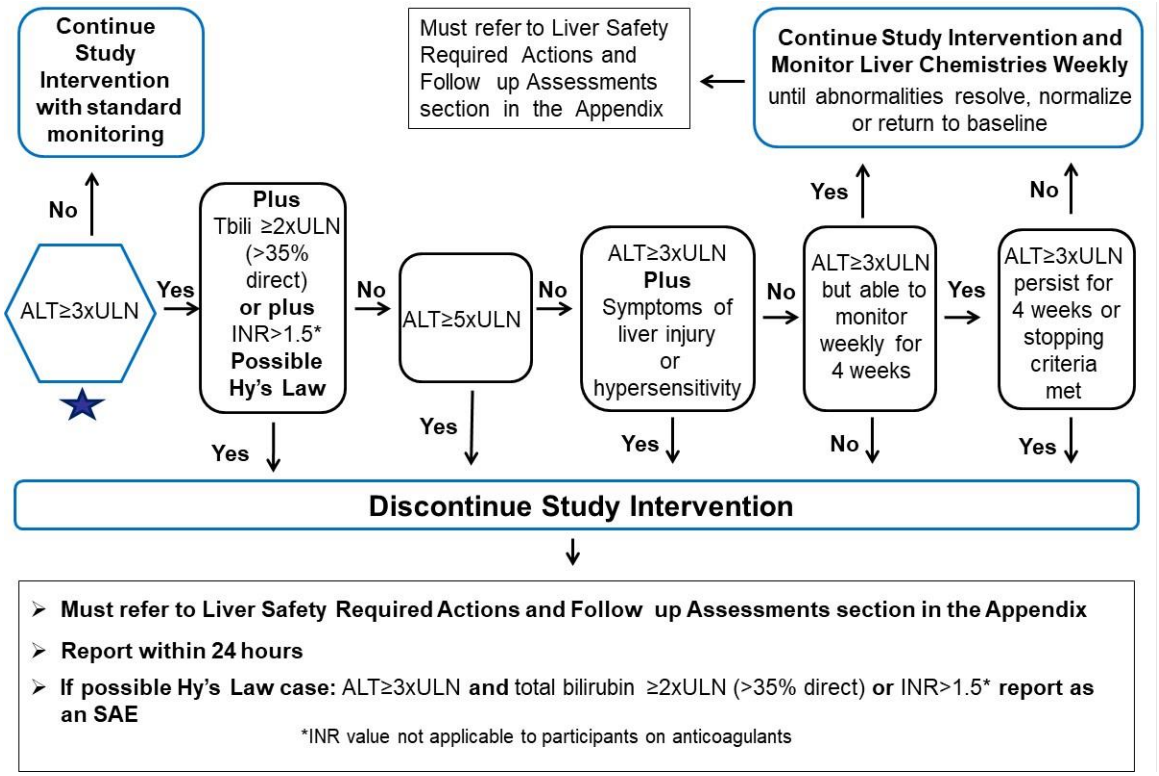
Reasons	Additional items/Sub-reasons
AE	
Lack of efficacy	
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Participant Reached Protocol-Defined Stopping Criteria	Liver chemistry Renal Function Hematological Abnormality ECG parameters Hepatitis B reactivation
Physician Decision	Specify
Pregnancy	
Protocol Deviation	Specify
Site Terminated by Sponsor	Specify
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Pursue Alternative Treatment COVID-19 Pandemic Other, specify
Other	Specify
Death	

AE=Adverse event.

7.1.1. Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

Phase 2 Liver chemistry stopping criteria and increased monitoring algorithm



ALT = Alanine Transaminase; INR = International Normalized Ratio; SAE = Serious Adverse Event; ULN = Upper Limit of Normal; Tbili = Total bilirubin

Refer to Appendix 6 (Section 10.6) for required liver safety actions and follow-up assessments.

7.1.2. ECG stopping criteria

Discontinuation of study intervention for abnormal ECG changes is required by the Investigator. Triplicate ECGs should be performed in case of abnormal ECG findings or if any of the ECG stopping criteria are met. In such cases, an average value from ECG measurements should be used to assess whether IMP administration should be discontinued. For other clinically significant ECG finding or abnormal QTcF result not meeting the protocol-specified stopping criteria, study intervention can be discontinued if the Investigator believes it to be in best interest of the participant. 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.

- Absolute QTcF ≥500 msec
- Absolute QTcF <320 msec (clinically significant QTcF shortening)
- Increase from baseline in QTcF of >60 msec
- Prolongation in repeated ECG interval measurements of PR or QRS of >40 msec from baseline or ventricular arrhythmias (other than occasional premature ventricular contractions)

7.1.3. Renal function stopping criteria

Study intervention will be discontinued if following renal abnormality developed:

- The eGFR decreased >25% compared to baseline, confirmed by a repeat test.
- Participants will not receive any IMP doses whilst awaiting the result of the repeat test.

7.1.4. Hematologic Abnormality stopping criteria

Study intervention will be discontinued for the following hematological abnormalities:

- White Blood Cell Count (WBC) $<2.0\times10^9$/L
- Platelets count $<100\times10^9$/L
- Hemoglobin <8.0 g/dL

7.1.5. Hepatitis B reactivation stopping criteria

Study intervention will be discontinued if the following hepatitis B stopping criteria are met during monitoring of ongoing participants:

- If HBsAg is positive or HBV DNA is detectable, study drug must be discontinued and the participant should be referred for a review by a hepatologist.

7.1.6. Temporary discontinuation

- Serious and opportunistic infections or suspected TB;

  If a serious or opportunistic infection or suspected TB develops, temporarily discontinue IMP until the infection is controlled and discuss further management with the Medical Monitor.

  If the temporary hold for serious or opportunistic infections is greater than 2 weeks, IMP will be permanently discontinued but the participant will be requested to complete the treatment period (up to the Week 12 visit) with a final follow-up visit approximately 16 weeks from the last dose received.

- COVID-19 infection;

  For participants with PCR or antigen proven or presumptive COVID-19 infection, IMP should be withheld until the resolution of the acute symptoms of infection, and IMP should not be re-started until at least 7 days following the resolution of acute symptoms at the Investigator's discretion.

Of note, for subjects who have a positive PCR or antigen test and are asymptomatic, IMP should be withheld for 7 days from the date of the positive test and only resumed if no COVID symptoms developed.

If subjects have IMP withheld for more than 2 weeks, IMP will be permanently discontinued but the participant will be requested to complete the treatment period (up to the Week 12 visit) with a final follow-up visit approximately 16 weeks from the last dose received.

If COVID-19 infection meets the criteria of serious infection, discontinuation guidance for serious infections should be followed.

All confirmed, probable or suspected cases should be reported on AE/SAE eCRFs, as appropriate.

If a participant experiences a clinically significant AE that the Investigator believes may be possibly, probably or definitely related to the IMP and could potentially be exacerbated by the next dose, the Investigator may delay IMP dosing by withholding one dose and should contact the Medical Monitor.

7.1.7. Rechallenge

7.1.7.1. Study intervention restart or rechallenge after liver stopping criteria are met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are not allowed.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an Early Discontinuation/ Withdrawal visit should be conducted, preferably 1 week from the last dose received (applicable during the treatment period) or as soon as possible after the participant's decision has been communicated to the site staff (applicable during the off-treatment phase), and a final follow-up visit (Visit 20) approximately 16 weeks from the last dose received as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal/last contact with the participant will be available for the study analyses. 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, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in source documents and inform the sponsor.

The primary reason for participant discontinuation/withdrawal from the study will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	
Lack of efficacy	
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Physician Decision	Specify
Protocol Deviation	Specify
Site Terminated by Sponsor	Specify
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Pursue Alternative Treatment COVID-19 Pandemic Other, specify
Other	Specify
Death	

AE=Adverse event.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant 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:

1. The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
2. 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/other contact methods, 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.
3. Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. 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. Participants who have signed ICF but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

In the event of a significant study continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the Investigator, as per local health authority/ethics requirements.

The whole blood volume that will be collected from each participant over the course of the study, including any extra assessments that may be required, is provided in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race, and ethnicity in the participant's medical record and the eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and review of the participant's medical record. Record any pre-existing conditions, signs and/or symptoms present prior to study start in the eCRF.

8.2. Efficacy assessments

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

Participants will be provided with the eDiary (Clario, a third-party vendor) on which to record all their patient reported outcomes including Paracetamol/Acetaminophen use. Training on how to use the device and on how to accurately report pain will be provided at the run-in visit (by Clario and WCG respectively, third-party vendors) with the accurate pain reporting training being repeated at the Week 8 visit. eDiary support will be available throughout the trial.

8.2.1. Average Daily Pain NRS

Brief Pain Inventory item 5 is a single item designed to capture information on the self-reported average pain intensity over the past 24 hours. Participants will be asked to mark their pain intensity on a daily basis, using the NRS, on an 11-point scale (0-10), with 0 = no pain, and 10 = pain as bad as you can imagine.

8.2.2. Worst Daily Pain NRS

Brief Pain Inventory item 3 is a single item designed to capture information on the self-reported worst pain intensity over the past 24 hours. Participants will be asked to mark their pain intensity on a daily basis, using the NRS, on an 11-point scale (0-10), with 0 = no pain, and 10 = pain as bad as you can imagine.

8.2.3. Nighttime Pain NRS

Nighttime pain NRS is a single item designed to capture information on the self-reported pain intensity. Participants will be asked to rate their pain intensity between the time they went to bed and the time they woke up. Participants will be asked to mark their pain intensity in the morning, using the NRS, on an 11-point scale (0-10), with 0 = no pain, and 10 = pain as bad as you can imagine.

8.2.4. Brief Pain Inventory Short Form (BPI-SF)

The BPI-SF allows participants to rate the severity of their pain and the degree to which that pain interfered with multiple and common dimensions of feeling and function. The BPI assesses pain severity by measuring pain at its 'worst', 'least', 'average', and 'now'. Furthermore, the BPI measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others and sleep.

The BPI pain interference score is scored as the mean of the seven interference items. This mean can be used if at least four of seven items have been completed on a given administration.

8.2.5. Patient Global Impression of Change (PGIC)

The PGIC is a single item scale that allows participants to rate the change in the disease state from baseline to specified time points during the study. It provides the participant's impression of overall change. It is used as an anchor in analyses to evaluate threshold of clinically meaningful within-patient score change and may be used for additional validation analyses.

8.2.6. Patient Global Impression of Severity (PGIS)

The PGIS is a single item scale that allows participants to rate the overall severity in the disease state. It measures static, current state patient global impression of overall disease severity. It is used as an anchor in analyses to evaluate threshold of clinically meaningful within-patient change and may be used for additional validation analyses.

8.2.7. McGill Pain Questionnaire Short Form 2 (SF-MPQ-2)

The McGill pain questionnaire Short Form 2 is a 22-item questionnaire, which has been developed and validated to evaluate multi-dimensional pain over time. The questionnaire consists of 22 descriptors that are rated on an intensity scale from 0 = none to 10 = worse possible [Dworkin, 2009].

8.2.8. Glycated Hemoglobin (HbA1c)

Given the potential exacerbation of DPNP with extremes of glycemic control, HbA1c will be collected during treatment and follow-up periods in order to explore any relationship with efficacy assessments.

8.3. Safety assessments

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

8.3.1. Physical examination/history, directed physical examination

A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded at the initial screening visit (1a).

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.

8.3.2. Vital signs

Temperature, pulse rate, respiratory rate, and blood pressure will be recorded before blood collection for laboratory tests. All readings will be recorded in source documents and in the eCRF.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. The participant should use the same position throughout all the visits.

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).

At specific visits in the off-treatment phase as specified in the SoA, vital signs may be collected and recorded by a HHS professional.

8.3.3. Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA (see Section 1.3). Participants must be supine for approximately 5-10 minutes prior and during ECG collection.

Single tracing will be obtained at screening visit (triplicate ECGs can be performed based on Investigator's assessment, if required).

Triplicate tracings will be obtained at baseline visit (Day 1). The three tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. All results will be recorded in the eCRF. Eligibility will be assessed based on all ECG readings at screening and the average of the triplicated ECG tracings at baseline.

Single ECG tracing will be obtained at all other visits as outlined in the SoA (see Section 1.3) unless any abnormalities (including ECG stopping criteria) are found during the study, then triplicate ECG measurements will be taken.

The site will use an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT,QTc intervals and QRS axis. Refer to Section 7.1.2 for ECG parameters withdrawal criteria.

If the ECG machine does not automatically calculate the QTc interval according to Fridericia's formula (QTcF), site staff should use the below equation to manually calculate the QTcF and document the result in the participant's medical record.

$$QTcF = \frac{QT}{\sqrt[3]{\frac{60}{HR}}}$$

QTcF result in msec,QT in msec,HR (heart rate) in bpm

All ECGs will be read locally and paper ECGs will be kept at study sites as source documents.

8.3.4. Clinical safety laboratory tests

See Section 10.2 for the list of clinical safety laboratory tests to be performed by Q2 Solutions, a third-party vendor, in accordance with Central Laboratory Manual and the SoA (Section 1.3).

At specific visits in the off-treatment phase as specified in the SoA, if allowed by country regulation/ethics, clinical safety laboratory sampling may be conducted remotely by a HHS professional.

The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 16 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the Investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (see Section 10.3.1 and Section 10.3.2).
- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the sponsor notified.
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g. SAE or AE), then the results must be recorded in the site's source documents. Results and reference ranges will also be recorded in the eCRF for SAEs.

8.3.5. Pregnancy testing

A serum pregnancy test must be performed for all female participants of childbearing potential at screening Visit 1a.

A urine or serum pregnancy test must be performed for all female participants of childbearing potential before the administration of all doses of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to Section 8.5.6 for the information on study continuation for participants who become pregnant during the study.

Refer to Section 5.1 Inclusion criteria for pregnancy testing entry criteria.

Pregnancy testing (urine or serum as required by local regulations) should be conducted per the SoA during study intervention period for all women of childbearing potential (WOCBP). If a urine pregnancy test is positive or cannot be confirmed as negative (e.g. an ambiguous result) a serum pregnancy test is required. In such case, the IMP should be withheld until a negative serum pregnancy test result is available. The participant must permanently discontinue the IMP if the serum pregnancy result is positive.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure (refer to Section 1.3 for details).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulations, to establish the absence of pregnancy at any time during the WOCBP's participation in the study.

8.3.6. Hepatitis B reactivation monitoring

Participants who are positive for hepatitis B core antibody (HBcAb) and negative for HBV DNA can be enrolled in the study provided they follow monitoring assessments for hepatitis B during the trial as follows:

- ALT, AST, HBsAg and HBV DNA will be tested at Week 4 (Visit 7), Week 8 (Visit 12) and Week 12 (Visit 17) and then at end of study, Week 27 (Visit 20) or early discontinuation visit.
- If HBsAg is positive or HBV DNA is detectable, study drug must be discontinued, and the participant should be referred for a review by a hepatologist. See Section 7.1.5 for hepatitis B reactivation stopping criteria.
- ALT elevation in absence of HBV DNA reactivation criteria: refer to protocol-defined increased monitoring and/or stopping criteria (Section 7.1.1). Evaluate for other possible causes of ALT elevation.
- Additional monitoring requirements for participants at Japan sites only [See Appendix 8 (Section 10.8)]:
  - Participants who are HBsAb positive (and negative for HBV DNA), hepatitis B reactivation monitoring will only be needed if vaccination history could not be confirmed.
  - In addition to the hepatitis B reactivation monitoring timepoints above, monitoring will also be tested at Week 16 (Visit 18) and Week 20 (Visit 19).

8.4. Safety monitoring and Data Review Committees

Participant safety will be continuously monitored in a blinded manner by the Medical Monitor and a designated Safety Lead (or delegate) throughout the study. Pertinent findings and conclusions are shared with the product's Safety Review Team (SRT) for review of the overall benefit/risk profile of the product.

Additionally, an external IDMC will be utilized in this study comprised of clinical and statistics experts, none of whom are affiliated with the sponsor (see Section 10.1.6). The IDMC will regularly review the unblinded data and will convene at scheduled intervals to ensure the safety of study participants as the study progresses. The IDMC charter will provide full details of all the activities, including which data will be reviewed and the timing and frequency, the schedule for regular IDMC meetings, and how the integrity of the study will be maintained.

In addition, ad-hoc IDMC meetings will be called at the earliest convenience, if any of the following occurs:

- A death in the study that is considered attributable by the Investigator or GSK safety group to the study drug.
  - Study enrolment and dosing will be paused AND
  - The IDMC will review the unblinded safety data and make a recommendation to:
    - Resume enrolment and dosing and continue the study without modification*, or
    - Continue the study with modification, or
    - Terminate the study.

*To preserve the study continuity and scientific integrity, if the IDMC recommendation is to resume enrolment and dosing without any study modification, this will be implemented immediately.

- Two or more SAEs in separate participants reported in the same active treatment arm (same dose level) that are considered attributable by the Investigator or GSK safety group to GSK3858279.
  - Study enrolment will continue and dosing will **not** be paused AND
  - The IDMC will review the unblinded safety data and make a recommendation to:
    - Continue the study without modification, or
    - Continue the study with modification, or
    - Terminate the study.

Furthermore, an iDRC will be appointed for this study to oversee and review the interim analysis data for futility. No study personnel with direct contact with sites or site staff will be involved in the iDRC. Full details of the data to be reviewed, the frequency of review and members of the committee will be included in the internal Data Review Committee Charter, to be finalized before study start.

8.5. Adverse Events (AEs), Serious Adverse Events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

8.5.1. Time period and frequency for collecting AE, SAE, and other safety information

All SAEs and AEs will be collected from the start of study intervention until the final follow-up visit at the time points specified in the SoA.

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 eCRF, not the AE section. If however this medical occurrence meets the definition of an SAE and is assessed as related to study participation (e.g. protocol-mandated procedures, invasive tests or change in existing therapy) or related to a GSK product, it will be reported as an SAE.

All SAEs will be recorded and reported to the sponsor immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. A post study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in this section.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, after a participant has been discharged from the study, the Investigator must record it in the medical records, per the local country requirements.

If the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the sponsor.

8.5.2. Method of detecting AEs and SAEs

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

8.5.3. 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 and non-serious AESIs (as defined in Section 8.5.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.5.

8.5.4. AESI

The potential risks of GSK3858279 are discussed in Section 2.3.1.

Adverse Events of Special Interest (AESIs) for GSK3858279 include:

- Serious infections
- Opportunistic infections
- TB
- Serious hypersensitivity reactions
- Injection site reactions

Reported AESIs will be adjudicated internally using a pre-defined process.

Routine monitoring for the signs and symptoms of TB will be performed during this study as part of every full or brief physical exam (see SoA in Section 1.3). If at any point during the study, the Investigator suspects that a participant may have new TB infection, an immediate and thorough investigation should be undertaken including consultation with a physician specializing in TB.

The Investigator should discuss such cases with the Medical Monitor and interruption of study intervention should be considered.

8.5.5. Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.5.1 for reporting timeframes.

For SAEs the Investigator must always provide an assessment of causality at the time of the initial report, as defined in Section 10.3.5.3.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review, sign and date, and then file the report in site files and will notify the IRB/IEC, if appropriate according to local requirements.

Investigators have to report to the Sponsor pregnancies, medication errors, abuse and misuse even in absence of AE/SAE as these may be subjected to local regulatory requirements for the Sponsor.

Table 6 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic AEs Report	24 hours*	electronic AEs Report
Pregnancies	24 hours*	paper pregnancy notification report and electronic pregnancy report	24 hours *	paper pregnancy notification report and electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information by the Investigator/site staff.
‡. For each SAE, the Investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.5.6. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the Investigator.

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for post intervention contraception determined in Section 5.1.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy or the female partner's pregnancy of a male participant.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The female participant will be followed to determine the outcome of the pregnancy. Pregnancy data from female partners of male participants who become pregnant will also be collected. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. See Table 6 for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the sponsor as described in Section 8.5.1. While the Investigator is not obligated to actively seek this information in former female study participants he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.5.7. Cardiovascular and death events

For any cardiovascular events detailed in Appendix 3 (Section 10.3) and all deaths, whether or not they are considered SAEs, specific cardiovascular (CV) and death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV event data query prompting its completion.

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

8.5.8. Contact information for reporting SAEs, AESIs, and pregnancies

Table 7 Contact information for reporting SAEs, AESIs, and pregnancies

Study contact for questions regarding SAEs, AESIs, and pregnancies: Contact GSK's local and/or medical contacts
Contacts for reporting SAEs, AESIs, and pregnancies: Available 24/24 hours and 7/7 days uk.gsk-rd-gcsp-ctsm-admin@gsk.com

AESI = Adverse event of special interest; GSK = GlaxoSmithKline Biologicals SA; SAE = Serious adverse event.

8.5.9. Participant card

The Investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the Investigator(s) or their back up. Dispensation of participant card should be documented in source documents.

8.6. Pharmacokinetics

Blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of total GSK3858279 at the time points indicated in the SoA and used to characterize the PK of GSK3858279 in DPNP participants. The actual date and time of each blood sample collection and dose administration will be recorded.

The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure optimal PK monitoring. Each PK sample should be collected as close as possible to the planned time relative to the dose administered to the

participant on dosing days. Details on PK blood sample collection including processing, storage and shipping procedures are provided in the Central Laboratory Manual.

Samples collected for analyses of serum GSK3858279 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis.

Serum analysis will be performed under the control of In Vitro/In Vivo Technologies / Bioanalysis Immunogenicity and Biomarkers (IVIVT/BIB). Concentrations of total GSK3858279 will be determined in serum samples using the validated bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g. CLW). Drug concentration information that may unblind the study will not be reported to investigational sites or blinded personnel until the study has been unblinded.

If allowed by country regulation/ethics, PK sampling may be conducted remotely by a HHS professional.

8.7. Pharmacodynamics

Pharmacodynamics will be evaluated as part of the analyses for TE (Section 8.8), biomarkers (Section 8.10) and immunogenicity assessments (Section 8.11).

8.8. Target (CCL17) concentrations

Blood samples of approximately 3.5 mL will be collected from participants in this study to investigate target engagement at the time points specified in the SoA. The actual date and time of each blood sample collection and dose administration will be recorded. The timing of TE samples may be altered and/or TE samples may be obtained at additional time points to ensure optimal TE monitoring. Each TE sample should be collected as close as possible to the planned time relative to the dose administered to the participant on dosing days. Details on TE blood sample collection including processing, storage and shipping procedures are provided in the Central Laboratory Manual.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis.

Concentrations of total and free CCL17 will be determined in serum samples using the validated bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g. CLW). CCL17 concentration information that may unblind the study will not be reported to investigational sites or blinded personnel until the study has been unblinded.

If allowed by country regulation/ethics, TE sampling may be conducted remotely by a HHS professional.

8.9. Genetics

A 6-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study at any time post - randomization. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. New signed genetic informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis.

See Section 10.5 Genetics for information regarding genetic research. Details of the processing, storage and shipping procedures along with destruction of these samples can be found in Central Laboratory Manual.

If allowed by country regulation/ethics, genetic sampling may be conducted remotely by a HSS professional.

8.10. Biomarkers

Serum and whole blood samples will be collected to determine the effect of GSK3858279 on peripheral exploratory biomarkers in participants with DPNP. Samples will be collected according to the schedule described in the SoA and as detailed in the Central Laboratory Manual. Details on the planned biomarker analysis are provided below. Data analysis will be performed independently of the main study and will form the basis of a separate report.

Collected samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of biomarker and/or other responses to GSK3858279. Further research and analysis will only be conducted in countries where permitted by local regulations and guidelines.

Immunophenotyping

Blood samples will be collected in Cyto-Chex tubes and analyzed by flow cytometry for a panel of immune cell markers. This panel will allow the detection and quantification of T cells (including CD4, CD8, T helper 17 and regulatory T cell subsets), B cells, NK cells, NKT cells and monocytes. The expression of CCR4 in the various cell types will also be analyzed to investigate proximal pharmacological effects. This analysis will only be carried out for subjects in pre-selected countries.

Analysis of serum proteins

Serum samples will be collected for PD exploratory and correlative studies. Immunoassays may be used to measure relevant protein biomarkers, including but not limited to inflammation and immune cell activation markers. Proteomic analysis of a large panel of serum proteins may be performed to identify proteins, pathways and processes regulated by GSK3858279. These protein markers may also be used to identify markers predictive of clinical efficacy or responder patient sub-populations.

Transcriptomic/epigenetic analysis

Whole blood samples will be collected in RNA stabilization tubes for exploratory studies which may include RNA sequencing or the analysis of epigenetic markers.

8.11. Immunogenicity assessments

Serum samples will be collected from all participants administered GSK3858279 according to the SoA table. The actual date and time of each blood draw will be recorded. Details for collecting, processing, storage and shipping of samples are provided in the Central Laboratory Manual.

Sample analysis will be performed under control of BIB, GSK. The presence of anti-GSK3858279 antibodies will be determined in serum samples using validated bioanalytical methods. A tiered analyses approach will include a screening assay, confirmation assay, titration assay, and neutralization assay. A sample that confirms positive in the confirmation assay will be reported as positive for ADA.

Immunogenicity results, including the incidence, titer, and neutralizing activity, will be reported. Additional analysis may be performed to further characterize immunogenicity results.

8.12. Health economics or medical resource utilization and health economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) 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.

Statistical analyses will be performed by, or under the direct auspices of, Biostatistics, GSK. Reporting of study data will be performed in accordance with applicable GSK standards.

9.1. Statistical hypotheses/comparisons

The primary objective of this study is to estimate the difference in means between GSK3858279 60 mg SC and placebo and GSK3858279 360 mg SC and placebo, in change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS, in adult participants with DPNP, where persistent use of prohibited pain therapy and study treatment discontinuations due to lack of efficacy or AEs are considered a negative outcome, in the absence of other study treatment discontinuations and regardless of all other use of prohibited pain therapy and use of allowed rescue medication. A negative change from baseline is evidence of improvement in pain.

The primary efficacy analysis will be characterized using Bayesian posterior probabilities for various criteria of interest (e.g. posterior probability that the true treatment difference from placebo is less than -0.6/-0.7/-0.8), and inferences will be made by comparing these posterior probabilities to a threshold of interest e.g. 70%.

9.2. Multiplicity Adjustment

For strong control of the probability of at least one treatment arm meeting the criteria of interest under no treatment effect, a hierarchical closed testing procedure will be used with 360 mg weekly evaluated first in the hierarchy.

9.3. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure) Note that screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not randomized) are excluded from the enrolled analysis set as they did not enter the study	• Study Population
Randomized	• All participants who were randomly assigned to study intervention in the study • The screened, enrolled and randomized populations must be nested, i.e. the enrolled population must be a subset of the screened population, the randomized population must be a subset of the enrolled population	• Study Population
Safety	• All participants who received at least one dose of study intervention • Participants will be analyzed according to the study intervention they actually received	• Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
Full Analysis Set (FAS)	• All randomized participants who received at least one dose of study intervention • Data will be reported according to the randomized study intervention	• Efficacy • Biomarkers • PROs
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (non-quantifiable [NQ] values will be considered as non-missing values) • Participants will be analyzed according to the study intervention they actually received	• PK

9.4. Statistical analyses

9.4.1. General considerations/definitions

The primary study analysis and reporting will be conducted when the planned target sample size of approximately 240 randomized participants have completed their Week 12 (or Early Withdrawal) study visit. An end-of-study analysis will take place when a target sample size of approximately 240 randomized participants have completed the study (including the off-treatment follow-up period). Recruitment may continue to include additional participants and may be increased by approximately 15% if regional recruitment targets have not been met. The double-blind will be maintained for these additional participants ongoing in the study at the time of the primary analysis and these participants will be analyzed and reported separately.

Unless otherwise stated, baseline will be defined as the latest assessment prior to first dose of study intervention.

The number of participants with each intercurrent event will be summarized by treatment group.

For all analyses, treatment effects will be presented as GSK3858279 60 mg SC weekly vs. placebo and GSK3858279 360 mg SC weekly vs. placebo.

Summary statistics for each treatment arm, time point, and efficacy endpoint will be presented.

For the cases that repeated measurement model is employed to analyze the data, an unstructured correlation matrix will be considered to account for multi-collinearity of repeated measurements data.

Non-informative priors will be used for the Bayesian analyses.

For the primary estimand, persistent use of prohibited pain therapy or treatment discontinuations due to lack of efficacy or AEs are handled with a composite strategy and data post-ICE will be imputed using multiple imputation based on baseline pain scores. For other treatment discontinuations, data that is set to missing under the hypothetical strategy will be assumed to be missing at random (MAR). Any other missing data for the primary estimand will also be assumed to be MAR.

For the first additional estimand, all data that is set to missing due to intercurrent events under the hypothetical strategy will be assumed to be MAR. Any other missing data will also be assumed to be MAR.

For the second additional estimand, missing data following study withdrawal will be imputed using multiple imputation based on off-treatment data under an extended MAR assumption conditioning on treatment status.

9.4.2. Primary endpoint(s)/estimand(s) analysis

Details of the estimands are described in Section 3.1.

The primary efficacy endpoint is the change from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS. The change from baseline will be calculated for each participant using the mean of the 7 daily assessments of average daily pain up to the Week 12 visit date as the Week 12 assessment, and the mean of the 7 daily assessments up to but not including the date of the first dose of study treatment as the baseline assessment. Since the diary will be completed in the evening, assessment on the date of the first dose of study treatment will include time post-treatment and therefore will not be included in the baseline assessment. The change from baseline in the weekly average of average daily pain intensity at each of the other study weeks will be derived similarly.

A Bayesian repeated measurement linear mixed model will be fitted to the change from baseline response including region, baseline assessment, week (categorical) and treatment as fixed effects as well as interactions for baseline-by-week and treatment-by-week. The difference from placebo at Week 12 from this model will be summarized as Mean and 95% equal-tail credible interval of the posterior distribution. Simple summary statistics (Mean, SD, Min, Max, Median) will also be presented for the primary endpoint by treatment group.

9.4.3. Secondary endpoint(s)/estimand(s) analysis

9.4.3.1. Safety analysis

The strategy for handling ICEs is described in Section 3.2.

No formal statistical testing will be performed on safety data. Safety data from the treatment period and the off-treatment follow-up will be summarized together.

AEs will be coded using the MedDRA coding dictionary and summarized by preferred term and treatment. Separate summaries will be provided for all AEs, drug-related AEs, SAEs, AESIs and AEs leading to permanent discontinuation of study intervention or withdrawal from the study.

Laboratory data, immunogenicity data, ECG and vital signs will be presented in tabular and/or graphical format and summarized descriptively according to GSK standards at each time point. No imputations will be performed for the reporting of safety.

9.4.3.2. Efficacy analysis

Details of the estimands for secondary efficacy endpoints are described in Section 3.1.

The change from baseline in Short-Form McGill Pain Questionnaire total score will be analyzed using a Bayesian repeated measures mixed model including region, baseline assessment, week (categorical) and treatment as fixed effects as well as interactions for baseline-by-week and treatment-by-week. The difference from placebo at each time point from this model will be summarized as Mean and 95% equal-tail credible interval of the posterior distribution.

The Bayesian repeated measures model used for the analysis of the primary endpoint will also be used to estimate the change from baseline in the weekly average of average daily pain intensity over time. The difference from placebo at each time point from this model will be summarized as Mean and 95% equal-tail credible interval of the posterior distribution.

The occurrence of ≥30% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS, will be analyzed using a Bayesian logistic model including region, baseline assessment and treatment as fixed effects and a binary variable (with 1 if ≥30% reduction from baseline and 0 otherwise) as response.

The odds ratio and 95% credible interval of the posterior distribution will be presented. To analyze the occurrence of ≥50% reduction from baseline in the weekly average of average daily pain intensity at Week 12, assessed on the NRS, the same approach will be used.

9.4.3.3. Pharmacokinetic (PK)

PK (Cmax, tmax, Ctau, Cavg and AUC(0-tau)) will be predicted using a model-based analysis. Details of the planned analyses will be provided in the SAP. Any deviations from the planned analyses will be described in an SAP addendum or justified in the final Clinical Study Report.

PK, TE, demographic and efficacy data may be integrated with other ongoing or completed studies to inform the dose-exposure-response relationships in pain.

9.4.4. Tertiary endpoints

Planned analyses of tertiary/exploratory endpoints will be described in the SAP.

9.5. Interim analysis

Prior to the primary study analysis, one interim analysis is planned.

An interim analysis for overall study futility data is planned when approximately 30 participants in each arm (approximately 90 total) qualify for a Week 12 efficacy assessment, either by attending the Week 12 visit or through data imputation strategy. Additional data (including safety and PK/TE) may also be reviewed. Interim NRS pain data will be used to build a predictive distribution of end-of-study Week 12 NRS pain, to enable decisions on study futility. The potential outcome of this interim is either continue or stop the study. The non-binding futility rule will be prospectively specified in the interim analysis charter.

An iDRC will be appointed for this study to review the interim analysis data in an unblinded manner (see Section 10.1.6). Specific details regarding all interim analyses will be outlined in the iDRC charter, along with the outline of how the iDRC will ensure data integrity and appropriate quality control of data prior to making decisions and an outline of the committee membership.

Additional administrative interim may occur, e.g. in order to inform internal decision-making or support regulatory interactions. No change to the study is planned as a result of these additional interim analyses. Full details of all interim analyses including the timing and reason for the interim analysis will be prospectively outlined in the iDRC Charter.

9.6. Sample size determination

Approximately 240 participants will first be stratified based on region (Japan, China or the rest of the world) and an average of the average daily pain score at baseline (<7 or ≥7) and then randomized in a 1:1:1 ratio to GSK3858279 60 mg SC weekly, GSK3858279 360 mg SC weekly and placebo SC weekly within each stratum. The recruitment may continue beyond this by approximately 15% to ensure regional requirements are met. The probability of achieving various criteria of interest given various sample sizes was assessed, conditional on different true values for the treatment difference. The results are summarized in Table 8, and are not conditional on the planned interim analysis. Based on these results, a sample size of 80 participants per arm is considered sufficient.

For these calculations, the population standard deviation for the change from baseline is assumed to be 2.2 for each treatment arm. [Rauck, 2013], reported a standard deviation of 2.2 for change in NRS Pain through Week 16. Similarly, [Campbell, 2012], reported a standard deviation of 2.1 for change in NRS Pain at Week 16.

The same standard deviation (i.e. 2.1) was reported in an unpublished clinical trial by Laurenza and his team [Laurenza, 2013].

Table 8 Probability of meeting various criteria of interest, conditional on different true treatment differences, standard deviations and sample sizes.

			Probability of meeting criterion given true treatment difference (Δ)					
Criterion of Interest	N per arm	Assumed SD	Δ = -1.2	Δ = -1	Δ = -0.8	Δ = -0.6	Δ = 0	Observed difference vs. placebo required
Posterior probability (true difference from placebo <-0.6) >70%	70	2.2	86%	71%	51%	30%	2%	-0.795
		2.7	79%	64%	47%	30%	3%	-0.839
	80	2.2	89%	73%	52%	30%	1%	-0.782
		2.7	81%	66%	48%	30%	3%	-0.823
	90	2.2	90%	76%	53%	30%	<1%	-0.772
		2.7	83%	68%	49%	30%	2%	-0.811
	100	2.2	92%	78%	55%	30%	<1%	-0.763
		2.7	85%	70%	50%	30%	2%	-0.800
Posterior probability (true difference from placebo <-0.7) >70%	70	2.2	79%	61%	40%	21%	<1%	-0.895
		2.7	72%	55%	38%	23%	2%	-0.939
	80	2.2	82%	63%	41%	21%	<1%	-0.882
		2.7	74%	57%	39%	22%	2%	-0.924
	90	2.2	84%	65%	41%	20%	<1%	-0.872
		2.7	76%	59%	39%	22%	1%	-0.911
	100	2.2	86%	67%	42%	20%	<1%	-0.863
		2.7	78%	60%	40%	21%	1%	-0.900

			Probability of meeting criterion given true treatment difference (Δ)					
Criterion of Interest	N per arm	Assumed SD	Δ = -1.2	Δ = -1	Δ = -0.8	Δ = -0.6	Δ = 0	Observed difference vs. placebo required
Posterior probability (true difference from placebo <-0.8) >70%	70	2.2	71%	51%	30%	14%	<1%	-0.995
		2.7	64%	47%	30%	17%	1%	-1.040
	80	2.2	73%	52%	30%	14%	<1%	-0.982
		2.7	66%	48%	30%	16%	<1%	-1.024
	90	2.2	76%	53%	30%	13%	<1%	-0.972
		2.7	68%	49%	30%	15%	<1%	-1.011
	100	2.2	78%	55%	30%	12%	<1%	-0.963
		2.7	70%	50%	30%	15%	<1%	-1.000

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 the following:
  - 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 GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, IDFU, and/or 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 (CTIS will be used in EU as per the requirements).
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

- The Investigator will be responsible for the following, as applicable:
  - 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/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

- The Investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study centre.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- By default, collected samples for the study will be stored for a maximum of 15 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- 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 reconsented 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.

- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any 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.
- In case of unexpected pregnancy, participant must be informed that personal information such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.
- If female partners of male participants become pregnant during the study, consent will need to be obtained or notification given as per local regulation to the partner before collecting their Personal Information such as last menstrual period and/or year of birth or the PI such as date of birth and/or sex of their baby as part of safety follow-up.

10.1.4. Recruitment strategy

Feedback from patients with DPNP on the proposed study design was solicited and the study design amended accordingly. Prior to selecting a site for inclusion in the study, data will be gathered to understand the numbers of participants that they may be able to enrol from their own patients and networks. Sponsor will develop posters and flyer pads, a dear patient letter and a media kit that may be used in local outreach efforts. These items will provide basic information and site contact information and are designed to assist with recruitment.

In addition, the sponsor will develop several items designed to help the potential participant understand the study including for example, a SoA table to represent the visit tests and procedures, an informed consent flow chart to help site staff walk patients through the ICF, a video and a brochure. Recruitment will be monitored throughout the study and mitigation plans put in place if needed.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the Investigator. 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.
- GSK will ensure protection of the personal data of the Investigator and site staff which is collected within the framework of and for the purpose of the study.

- 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 that their data will 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**.**
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- GSK, third parties working on behalf of GSK, and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

A Safety Review Team (SRT) is in place for each GSK product. It comprises a global cross-functional team responsible for the ongoing assessment of benefit/risk for a product. The SRT contribute to the continual assessment of incoming efficacy and safety information.

An iDRC will be appointed for this study to review interim analysis data in an unblinded manner for the assessment of futility. No study personnel with direct contact with sites or site staff will be involved in the iDRC. Full details of the data to be reviewed, the frequency of review and members of the committee is included in the iDRC charter.

An IDMC will be implemented in this study. The overall responsibility of the IDMC is to protect the ethical and safety interests of participants recruited into this study while protecting as far as possible the scientific validity of the data. The IDMC will include physicians with relevant clinical expertise and a statistician, none of whom is affiliated with the sponsor. The IDMC will review unblinded data regularly and on an as needed basis. The initial early review, frequency of further reviews and the unblinded data, is detailed in the IDMC charter.

10.1.7. Dissemination of clinical study data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the Investigator with the full summary of the study results, including a summary of trial results understandable to laypersons.
- The Investigator is encouraged to share the layperson summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and Investigator signatory will be made public.
- GSK will provide the Investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care.
- This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be pre-defined in the QTL plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These pre-defined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor 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).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for a minimum period of 15 years from the issue of the final CSR/equivalent summary, or in accordance with Applicable Law, whichever is longer. 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. In the event of conflict between this Protocol and fully executed clinical study agreement, the protocol shall prevail with respect to record retention.

10.1.9. Source documents

- For this study there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- 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 eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgment.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor will perform monitoring to confirm that data entered into the eCRF 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.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. endpoint adjudication committee; expert

reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the Investigator sites prior to transfer. These documents will be used by the third-party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

First Act of Recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.
- IDMC recommendation to terminate the study.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or temporarily 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 temporary suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

The tests detailed in Table 9 will be performed by the central laboratory apart from urine pregnancy and dipstick urinalysis tests, and T-SPOT TB test (with prior Sponsor's approval) if applicable.

NOTE:

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- For participants from China sites, COVID-19 test will be performed by a 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.

Investigators must document their review of each laboratory safety report.

The addresses of the clinical laboratories in charge of human biological sample testing are provided in a separate document ('List of clinical laboratories and key vendors') and stored in TMF at the time of the protocol finalization.

Table 9 Protocol-required safety laboratory tests

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="4">Hematology[1]</td><td>Platelet Count</td><td rowspan="4" colspan="2">RBC Indices:
Mean Corpuscular Volume (MCV)
Mean Corpuscular Hemoglobin (MCH)
%Reticulocytes</td><td rowspan="4">White Blood Cell (WBC) Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>Red Blood Cell (RBC) Count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td rowspan="5">Clinical Chemistry[2]</td><td>Calcium</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Bicarbonate</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose (non-fasting)</td><td>Creatine Phosphokinase (CPK)</td><td>Alkaline Phosphatase</td><td>Albumin</td></tr>
<tr><td>Blood Urea Nitrogen (BUN)</td><td>BUN/creatinine ratio</td><td>Gamma Glutamyl Transpeptidase (GGT)</td><td>Creatinine</td></tr>
<tr><td colspan="4">Estimated Creatinine Clearance/ glomerular filtration rate (CKD-EPI[3])</td></tr>
<tr><td>Other labs</td><td colspan="2">Lipid Panel, fasting (LDL [direct], HDL, total cholesterol, triglycerides)</td><td>HbA1c</td><td>QuantiFERON TB Gold Plus Test (or, if unavailable, T-SPOT TB with prior Sponsor’s approval)</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="4">• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick performed locally
• Urine sample must be sent to the central laboratory for samples on Day 1 and Week 12. For all other visit the urine sample may be sent to the central laboratory for further testing based on Investigator assessment, if required</td></tr>
<tr><td colspan="4">• Urine Protein Creatinine Ration (UPCR) and Urine Albumin Creatinine Ration (UACR) at Day 1 and Week 12</td></tr>
<tr><td>Pregnancy testing</td><td colspan="4">• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for WOCBP)[4]</td></tr>
</table>

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone (FSH) (as needed in women of non-childbearing potential only) • Urine Drug Screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, marijuana (THC) and its metabolites, and benzodiazepines • COVID-PCR • Serology: HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B virus DNA (HBV DNA), hepatitis C virus antibody, and hepatitis C RNA. For participants from sites in Japan only: hepatitis B surface antibody (HBsAb) and hepatitis B virus DNA (HBV DNA).

NOTES:
1. Hematological abnormality stopping criteria: White Blood Cell Count (WBC) <2.0×10^9/L; Platelets count <100×10^9/L; Hemoglobin <8 g/dL.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6. All events of ALT ≥3× ULN and total bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
3. Chronic Kidney Disease Epidemiology Collaboration equation will be used for calculating and reporting eGFR. For participants from sites in Japan, the Japanese coefficient (0.813) modified CKD-EPI will be used for calculating and reporting eGFR. Renal function stopping criteria: the eGFR decreased >25% compared to baseline, confirmed by a repeat test.
4. Serum pregnancy test required at screening, thereafter local urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

AE definition
An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e. not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- 'Lack of efficacy' or 'failure of expected pharmacological action' per se will not be reported as an AE or SAE.

  Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination).
- 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. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. **Results in death**

b. **Is life-threatening**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect in the offspring of a study participant**

f. **Abnormal pregnancy outcomes** (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)

g. **Other situations**

Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as an SAE.

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

– Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of cardiovascular events

Cardiovascular events (CV) definition
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Definition of treatment-emergent AE (TEAE)

TEAE definition
A TEAE is an event that emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.5. Recording, assessment and follow-up of AE, SAE, AESIs and pregnancies

10.3.5.1. 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 reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is not acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as an AE/SAE.

10.3.5.2. Assessment of intensity

The Investigator will make an assessment of intensity for each AE, AESI, and SAE reported during the study and assign it to one of the following categories:

- **Mild:**
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:**
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:**
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.5.3. Assessment of causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.

The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. 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 their 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.

10.3.5.4. Assessment of outcomes

The Investigator will assess the outcome of all serious and non-serious unsolicited AEs recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

10.3.5.5. Follow-up of AEs, SAEs, AESIs, pregnancies or any other events of interest

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, SAE or AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally submitted documents. The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE/AESI/pregnancy or any other event of interest, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 8.5.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until they are resolved or until the participant is lost to follow-up.

Follow-up during the study:

AEs/SAEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until they are resolved.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

Follow-up of pregnancies:

Pregnant participants or pregnant female partners of male participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the AEs Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the Investigator must report any SAE occurring as a result of a post study pregnancy, that is considered by the Investigator to be reasonably related to the study intervention, to GSK as described in Section 10.3.6.

10.3.5.6. Updating of SAE, AESI and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator. The updated report should be sent to the study contact for reporting SAEs (refer to Section 8.5.8).

10.3.6. Reporting of SAEs, AESIs and pregnancies

SAE reporting to GSK via an electronic data collection tool:

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours of awareness.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, non-serious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous Individual Case Safety Reports (ICSRs).

- Contacts for SAE reporting can be found in Section 8.5.8.

SAE reporting to GSK via paper data collection tool:

- Secure email transmission of the scanned SAE paper data collection tool is the preferred method to transmit this information to the Medical Monitor.
- In rare circumstances and in the absence of email, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.5.8.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Women of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche.
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Notes: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods (for the purpose of this study) include:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

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

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

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women of Non-childbearing Potential (WNCBP)

Women in the following categories are considered WNCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

a. Documented hysterectomy.

b. Documented bilateral salpingectomy.

c. Documented bilateral oophorectomy.

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

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

2. Postmenopausal female.

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   – A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

   – Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Male Contraceptive Requirement

A male participant with a partner who is a WOCBP is required to use a condom during sexual intercourse throughout the study and for 16 weeks after the last dose of study medication.

10.4.2. Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine Device (IUD)
Intrauterine hormone-releasing System (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview
Highly effective methods[b] that are user dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence 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 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 amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Genetics

Use/analysis of DNA:

Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis after the participant agrees and signs the optional genetic ICF.

DNA samples will be used for research related to GSK3858279 or DPNP and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to GSK3858279 or study interventions of this drug class, and pain. Genetic research may consist of the analysis of candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3858279 or study interventions of this class. The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on GSK3858279 (or study interventions of this class) or DPNP continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

10.6. Appendix 6: Liver safety: suggested actions and follow-up assessments

Phase 2 Liver chemistry stopping criteria and required follow-up assessments:

<table>
<tr><th colspan="3">Liver chemistry stopping criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥5× ULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥3× ULN persists for >4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥3× ULN and total bilirubin ≥2× ULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥3× ULN and INR >1.5</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥3× ULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥3× ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required actions, monitoring and follow-up assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow-Up assessments</th></tr>
<tr><td>• Immediately discontinue study intervention; report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform follow-up assessments as described in the follow-up assessment column
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)</td><td colspan="2">• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, as soon as possible, and at least 7 days after last dose[5]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), glutamate dehydrogenase (GLDH), and serum albumin
• Fractionate bilirubin, if total bilirubin ≥2× ULN
• Obtain complete blood count with differential to assess eosinophilia</td></tr>
</table>

Liver chemistry stopping criteria	
MONITORING: **If ALT ≥3× ULN AND total bilirubin ≥2× ULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2× ULN and INR >1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total 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 **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention since **not allowed per protocol;** continue participant in the study for any protocol-specified follow-up assessments	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications • Record alcohol use on the liver event alcohol intake form **If ALT ≥3× ULN AND total bilirubin ≥2× ULN or INR >1.5** obtain the following in addition to the assessments listed above: • 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 assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use very unlikely in the preceding week (e.g. where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete Liver Imaging Form • Liver biopsy may be considered and discussed with local specialist if available: o In participants when serology raises the possibility of autoimmune hepatitis (AIH)

Liver chemistry stopping criteria	
	○ In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In participants with acute or chronic atypical presentation • If liver biopsy conducted complete Liver Biopsy Form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for participant if ALT ≥3× ULN **and total** bilirubin ≥2× ULN. 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 ≥3× ULN **and** total bilirubin ≥2× ULN (>35% direct bilirubin) or ALT ≥3× ULN **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 participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A Immunoglobulin M (IgM) 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); hepatitis E IgM antibody.
5. 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 in the eCRF. 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 provided in the Central Laboratory Manual.

Phase 2 Liver chemistry increased monitoring criteria with continued study intervention:

Liver chemistry increased monitoring criteria and actions with continued study intervention	
Criteria	**Actions**
ALT ≥3x ULN and ≤5x ULN **and** total bilirubin <2x ULN or INR ≤1.5**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilize or return to within baseline • If at any time participant meets liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3× ULN and bilirubin <2× ULN and INR ≤1.5, monitor participants twice monthly until liver chemistry tests resolve or return to within baseline

10.7. Appendix 7: Important study assessment details & study-specific equipment

10.7.1. Douleur Neuropathique 4 (DN4) questionnaire

The DN4 is a physician administered questionnaire that was developed and validated for identifying participants with neuropathic pain [Spallone, 2012]. The DN4 score is calculated by counting the number of positive responses to each of the 10 items on the questionnaire, which include burning, painful cold, electric shocks, tingling, pins and needles, numbness, itching hypoesthesia to touch, hypoesthesia to prick and brushing. A diagnosis of neuropathic pain is made by a score of ≥4.

10.8. Appendix 8: Country-specific requirements

France specific requirement:

This appendix includes all applicable requirements of French Public Health Code/specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the «Selection of study population and withdrawal criteria»

A subject will be eligible for inclusion in this study if he/she is either affiliated to or beneficiary of a social security category (French Public Health Code L.1124-1).

It is the Investigator's responsibility to ensure and to document (in source documents/ subject notes) that the subject is affiliated to or beneficiary of a social security category.

Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the ICF. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.

2. Concerning the «Study governance considerations»

In section "Regulatory and ethical considerations, including the informed consent process" of study protocol

a. Concerning **the process for informing the subject**, the following text is added:

   French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject written consent. It also contains a reference to the single scientific and ethical regulatory authorization.

b. Concerning **the management of the Patient Informed Consent Forms**, the following text is added:

   French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

   The first page of the Patient Informed Consent Form is given to the Investigator. The copy is kept by the patient.

- **Notification to the Hospital Director**

  In accordance with Article R.1123-69 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in his/her establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the Investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- **Information to the Hospital Pharmacist**

  In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his/her establishment. The Pharmacist is supplied with a copy of the protocol (which allows him/her to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB), the name of the

Investigator(s), the number of sites involved in his/her establishment and the estimated time schedule of the trial.

- **Ethnic origin**

  In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **Testing of biological samples**

  In accordance with the French Public Health Code article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

3. Concerning the «Data Management» the following text is added:

Within the framework of this clinical trial, data regarding the identity of the Investigators and/or co-Investigators and/or the Pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subject status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow-up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

4. Concerning «Data privacy»

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to him/her, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

5. Investigational Medicinal Product accountability, reconciliation, and destruction

In specific situations where institutional practices dictate that the site disposes of and/or destroys IMP prior to allowing the "monitor" to verify and document IMP accountability, the following applies:

*"During the conduct of the study, Investigational Medicinal Product (IMP) will be destroyed by the Institution prior to a GSK "**monitor**" conducting final IMP accountability. Institution agrees that such destruction will comply with Institution's Investigational Medicinal Product accountability procedures and will provide GSK with IMP accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006)".*

Japan specific requirement:

For evidence of an active or past hepatitis B infection participants from sites in Japan are required to test for hepatitis B surface antibody (HBsAb) in addition to hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Participants from sites in Japan are not eligible if positive for HBsAb AND consequently positive for HBV DNA.

For participants who are HBsAb positive (and negative for HBV DNA), hepatitis B reactivation monitoring will be needed throughout the study if vaccination history could not be confirmed.

In addition to the hepatitis B monitoring timepoints in the schedule of assessments, monitoring will also be tested at Week 16 (Visit 18) and Week 20 (Visit 19) in participants from sites in Japan.

Chronic Kidney Disease Epidemiology Collaboration equation will be used for calculating and reporting eGFR. For participants from sites in Japan, the Japanese coefficient (0.813) modified CKD-EPI will be used for calculating and reporting eGFR.

South Korea specific requirement:

Participants from South Korea are required to be aged at least 19 years or greater for entry into the study.

10.9. Appendix 9: Protocol amendment history

Amendment 1 (24 July 2023)

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the safety monitoring of participants and the scientific value of the study.

Overall rationale for Amendment 1:

In response to regulatory feedback, the following changes were made:

1. Increase in safety laboratory and pregnancy testing during the treatment period.
2. Establishment of an Independent Data Monitoring Committee (IDMC).
3. Update to individual participant stopping criteria.
4. Update to eligibility criteria based on individual participants stopping criteria.
5. Introduction of contraceptive requirements for male participants and collection of information from pregnant female partners of participants.
6. Update to intercurrent event handling strategy for primary estimand.

In addition, the following minor changes were implemented:

Updated accurate pain reporting training schedule, ECG assessment schedule, provision of limited NSAID use, secondary objective of change from baseline in key laboratory parameter updated and moved to tertiary.

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

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Section 1.3 Schedule of Activities.	Added: Urine pregnancy testing frequency increased from monthly to weekly during the treatment period.	Added following regulatory agency request.
Section 1.3 Schedule of Activities.	Added: Hematology, clinical chemistry and urinalysis frequency increased to testing at least every 2 weeks during the treatment period.	Added following regualtory agency request
3.1 Efficacy Estimands	Update to ICE strategy for treatment discontinuations and persistent prohibited pain therapy, renumber additional estimands.	Updated primary estimand per regulatory agency feedback.
4.1 Overall Design	Added: Establishment of an IDMC Further details throughout protocol in relevant sections.	Added following regulatory agency request.
5.1 Inclusion criteria	Added: Inclusion criterion 10: Male participant contraceptive requirements added.	Added following a regulatory agency request
5.2 Exclusion criteria	Added: Exclusion criterion 16: White blood cell count, hemoglobin and platelet count cut-off values added.	Updated to accommodate updated individual participant stopping criteria requested by a regulatory agency
7. Discontinuation of study intervention and participant discontinuation/withdrawal	Added: Renal function, hematological abnormality, and ECG parameters individual participant stopping criteria.	Added following a regulatory agency request.

Section # and title	Description of change	Brief rationale
8.5.6 Pregnancy	Added: Details of monitoring for the reporting of pregnancy in female partners of male participants.	Added following a regulatory agency feedback

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