TITLE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo Controlled, Single Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive.

Protocol Number: 213960 / Amendment 06

Compound Number or Name: GSK3888130B

Brief Title: A FTIH study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive.

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

EudraCT: 2021-002063-22

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Approval Date: 21 Mar 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date of Issue**	**Document Identifier**
Amendment 6	*21 Mar 2023*	TMF-15719887
Amendment 5	*25 January 2023*	TMF-15650507
Amendment 4	*03 Nov 2022*	TMF-15099564
Amendment 3	*05 August 2022*	TMF-14605174
Amendment 2	*10 February 2022*	TMF-14432742
Amendment 1	*27 September 2021*	TMF-14006150
Original Protocol (00)	*19 August 2021*	TMF-12912890

Amendment 06; 21 Mar 2023

Identified in the Table below are substantial changes made to the Study Protocol since the previous submitted version.

Section # and title	**Description of change**	**Brief rationale**
Section 1.1 Synopsis	An additional Follow-up phone call added CCI days after the last study visit.	In line with MHRA condition for approval of Protocol Amendment 5.
Section 1.1 Synopsis	Duration of study extended from CC I weeks to CC I weeks.	In line with MHRA condition for approval of Protocol Amendment 5.
Section 1.3.1 Screening, Admission and Follow-Up	Extra column added for Follow up phone call CCI days post last study visit which includes Concomitant Medication Review, AE Review and SAE Review.	In line with MHRA condition for approval of Protocol Amendment 5.
Section 4.1 Overall Design	An additional Follow-up phone call added CCI days after the last study visit.	In line with MHRA condition for approval of Protocol Amendment 5.
Section 4.1 Overall Design	Duration of study extended from CCI weeks to CCI weeks.	In line with MHRA condition for approval of Protocol Amendment 5.
Section 6.8 Concomitant Therapy	The following text was amended to include the word ‘final’ in bold: ‘Participants must abstain from taking prescription or non-prescription drugs (including NSAIDs, vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the	In line with MHRA condition for approval of Protocol Amendment 5.

Section # and title	Description of change	Brief rationale
	start of study intervention until completion of the **final** follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.'	
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	The following text was amended to include the word 'final' (below in bold). • All SAEs will be collected from the signing the inform consent form until the **final** follow-up visit at the time points specified in the SoA (Section 1.3). • All SARs to study procedure/GSK products will be reported from the signing of the informed consent form (ICF) until the **final** follow-up visit at time points specified in the SoA (Section 1.3). • All AEs will be collected from the start of intervention until the **final** follow-up visit at the time points specified in the SoA (Section 1.3).	In line with MHRA condition for approval for Protocol Amendment 5.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo Controlled, Single Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive.

Brief Title: A FTIH study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GSK3888130B in Healthy Participants aged 18-55 inclusive.

Rationale:

This is a first time in human (FTIH) study designed to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile of single ascending doses (SAD) of GSK3888130B.

CCI [redacted] CCI [redacted] CCI [redacted]

This study aims to provide sufficient confidence in the safety and tolerability of the molecule and will provide preliminary information relating to the PK and PD profile of GSK3888130B following intravenous (IV) or subcutaneous (SC) injection routes of delivery, to support future clinical development.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of single IV and SC doses of GSK3888130B in healthy participants.	• Occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs). • Occurrence of clinically significant changes in laboratory values ($CD4^+$ T cell counts, hematology, chemistry, urinalysis and virology), vital signs and 12lead electrocardiogram (ECG) readings.
Secondary	
• To characterise the serum PK profile of single IV or single SC	• Serum concentrations of GSK3888130B and derived PK parameters as data permit, including: area under the concentration-time curve [AUC], maximum concentration

Objectives	Endpoints
doses of GSK3888130B in healthy participants.	[Cmax], time to Cmax [Tmax], half-life [t½], clearance [CL].
• To evaluate the immunogenicity of single doses of GSK3888130B in healthy participants.	• Incidence of Anti-Drug Antibodies (ADAs) against GSK3888130B.
• To characterise the effects of GSK3888130B on target engagement (TE).	• Change from baseline CCI [redacted]) over time.
• To characterise the effect of single doses of GSK3888130B on PD biomarker Bcl-2.	• Change from baseline in T cell Bcl-2, measured in blood over time.

Overall Design:

This is a single centre, randomised, double-blind, placebo controlled, dose escalation study comprising of seven planned SAD cohorts, designed to assess safety, tolerability, PK and PD of GSK3888130B over a range of dose levels (from CCI [redacted] mg to CCI [redacted] mg) in healthy participants.

Brief Summary:

The purpose of this study is to evaluate safety, tolerability, PK and PD of GSK3888130B in healthy participants.

Participants will attend a screening visit within 28 days of study intervention. In subjects who require an influenza vaccination and/or SARS-CoV-2 vaccination or booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1 to confirm eligibility. Holter monitoring, viral serology (HIV, hepatitis B and hepatitis C), Mycobacterium tuberculosis (TB) screening, CCI [redacted] (CCI [redacted]) does not need to be repeated for extended screening windows or rescreens if within 3 months of initial screening.

Participants will be admitted to the clinical unit on Day -1 before administration of study intervention on Day 1. For cohorts where treatment administration is by IV injection, participants will remain in the unit until completion of all assessments on Day CCI [redacted] For cohorts where treatment administration is by SC injection, participants will remain in the unit until completion of all assessments on Day CCI [redacted] This period may be amended at the discretion of the principal investigator (or designee) and the GSK Dose Escalation Committee (DEC) as PK and safety data evolves.

All participants will then be required to attend the clinic for up to 9 outpatient visits over the course of CCI days after dosing for safety assessment and sample collection and will receive two follow-up telephone calls; the first will be CCI days post last study visit and the second CCI days after their last study visit. If required, additional follow-up visits may be scheduled.

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Number of Participants:

A sufficient number of participants will be screened to ensure a minimum number of participants are eligible to be randomised to receive either GSK3888130B or placebo in a 3:2 ratio in cohorts 1 and 2 or 3:1 ratio in all other SAD cohorts.

The study will aim to recruit 54 participants into seven SAD cohorts; five participants in cohorts 1 and 2 and eight participants in all other cohorts, CCI . Additional participants/cohorts may be enrolled to allow for replacement of withdrawals and/or evaluation of additional dose levels or expansion of a cohort at a particular dose level.

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

The total number of participants randomised into the study will be capped at 90 participants (across all SAD cohorts).

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

Intervention Groups and Duration:

As this is the first administration of GSK3888130B in humans, sentinel dosing will be utilised for each increasing dose level (if the selected dose level is below or equivalent to the previous dose level, sentinel dosing may still be applied).

Sentinel dosing will be implemented in each cohort, so that one participant is dosed with GSK3888130B and one participant is dosed with placebo followed by review of post-dose safety data before additional participants in each cohort are dosed.

The duration of post-dose safety data required for IV and SC cohorts is described below.

For cohorts where treatment administration is by IV injection, the remaining participants in these cohort will only be dosed after review of at least CCI hours safety & tolerability data (i.e. AE/SAEs, laboratory values, vital signs and 12-lead ECGs) from the sentinel participants by the Principal Investigator (PI) or appropriately qualified delegate, in consultation with the Medical Monitor or delegate if unavailable, and it has been deemed safe to do so.

For cohorts where treatment administration is by SC injection, the remaining participants in these cohorts will only be dosed after review of at least CCI days safety & tolerability data (i.e. AE/SAEs, laboratory values, vital signs and 12-lead ECGs) from the sentinel participants by the Principal Investigator (PI) or appropriately qualified delegate, in consultation with the Medical Monitor or delegate if unavailable, and it has been deemed safe to do so.

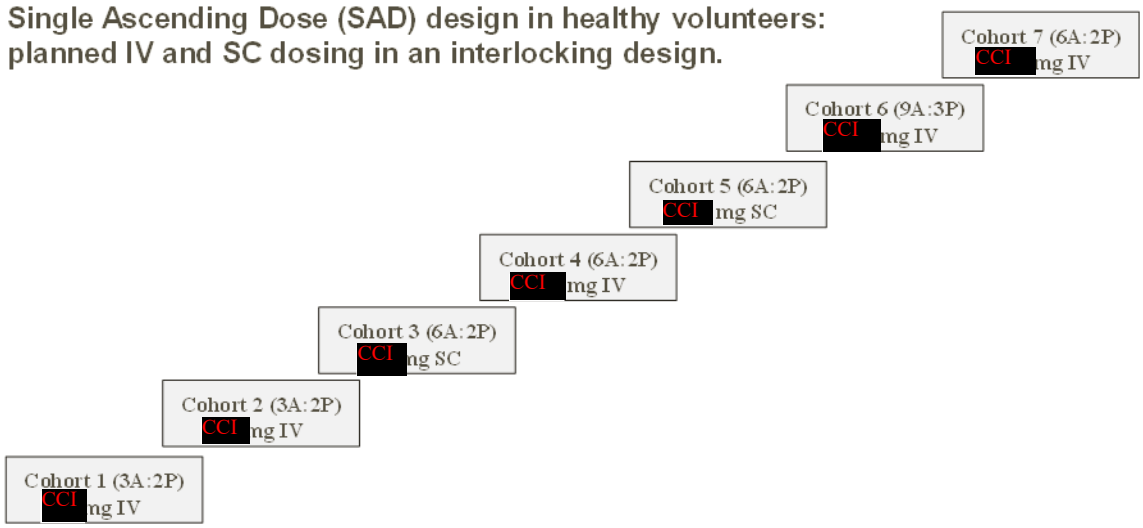
Doses between cohorts are planned to escalate in a sequential fashion contingent on the safety, tolerability (including absolute $CD4^+$ T cell counts) and pharmacokinetic profile, up to and including Day CCI from a minimum of 2 participants dosed with GSK3888130B in cohorts 1 and 2 or a minimum of 4 participants dosed with GSK3888130B in all other SAD cohorts. The decision to proceed to the next dose level of GSK3888130B will be made by the GSK Dose Escalation Committee (DEC).

The total duration of the study for each participant will be approximately CCI weeks.

While every effort will be made to identify participants CCI to assess the impact of GSK3888130B on the CCI [redacted]

Data Monitoring/ Other Committee: A GSK Dose Escalation Committee (DEC) will be used for this study.

1.2. Schema



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1.3. Schedule of Activities (SoA)

1.3.1. Screening, Admission and Follow-Up

Procedure	Screening (up to 28 days before Day 1)[1]	Day -1	E.D	Follow-up ([CCI] days post last study visit)	Follow-up ([CCI] days post last study visit)	Notes E.D = early discontinuation/withdrawal 1. In participants who require an influenza vaccination and/or SARS-CoV-2 booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1.
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demography	X					
Full physical examination including height and weight	X					

Procedure	Screening (up to 28 days before Day 1)[1]	Day -1	E.D	Follow-up ([CCI] days post last study visit)	Follow-up ([CCI] days post last study visit)	Notes E.D = early discontinuation/withdrawal 1. In participants who require an influenza vaccination and/or SARS-CoV-2 booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1.
Medical history (includes substance usage, vaccination history and Family history of premature CV disease)	X					
Current medical conditions	X					
Influenza vaccination	X					If dosing is during influenza season (1st October to 30th April) participants who have not had a seasonal influenza vaccine will be given an MHRA-approved influenza vaccine at least 30 days before dosing

Procedure	Screening (up to 28 days before Day 1)[1]	Day -1	E.D	Follow-up ([redacted] days post last study visit)	Follow-up ([redacted] days post last study visit)	Notes E.D = early discontinuation/withdrawal 1. In participants who require an influenza vaccination and/or SARS-CoV-2 booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1.
Viral serology (HIV, hepatitis B and C)	X					Hepatitis B screening to include surface antigen and core antibody test. Viral serology does not need to be repeated for rescreens if within 3 months of initial screening.
TB screening (QuantiFERON Gold)	X					TB screening does not need to be repeated for rescreens if within 3 months of initial screening.
12-lead ECG	X		X			Performed in triplicate.

Procedure	Screening (up to 28 days before Day 1)[1]	Day -1	E.D	Follow-up (CCI days post last study visit)	Follow-up (CCI days post last study visit)	Notes E.D = early discontinuation/withdrawal 1. In participants who require an influenza vaccination and/or SARS-CoV-2 booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1.
CCI [redacted]						
Concomitant medication review	X	X	X	X	X	
Admission		X				

Procedure	Screening (up to 28 days before Day 1)[1]	Day -1	E.D	Follow-up (CCI days post last study visit)	Follow-up (CCI days post last study visit)	Notes E.D = early discontinuation/withdrawal 1. In participants who require an influenza vaccination and/or SARS-CoV-2 booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1.
Laboratory assessments (include clinical chemistry and haematology panels)	X	X	X			
CD4+ T cell counts	X	X				
Urinalysis (Dipstick ±microscopy)	X	X				If dipstick is positive or participant has urinary symptoms send for microscopy. CCI [redacted].
Vital signs	X	X	X			
Brief Physical exam		X	X			

Procedure	Screening (up to 28 days before Day 1)[1]	Day -1	E.D	Follow-up ([CCI] days post last study visit)	Follow-up ([CCI] days post last study visit)	Notes E.D = early discontinuation/withdrawal 1. In participants who require an influenza vaccination and/or SARS-CoV-2 booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1.
Breath alcohol test, smoking breath test and urine drug screen	X	X				
SARS-CoV-2 Test	<==========>					As per local guidelines.
Confirmation of postmenopausal status in females if required.	X					FSH and oestradiol test.
AE Review			X	X	X	
Blood collection for Immunogenicity testing			X			
SAE Review	X	X	X	X	X	Collected from signing the informed consent form.

Procedure	Screening (up to 28 days before Day 1)[1]	Day -1	E.D	Follow-up (CCI days post last study visit)	Follow-up (CCI days post last study visit)	Notes E.D = early discontinuation/withdrawal 1. In participants who require an influenza vaccination and/or SARS-CoV-2 booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1.
CCI	CCI [redacted]					

1.3.2. Intravenous Dosed Cohorts

Procedure		Intervention Period (Days) for IV cohorts												Notes
CCI														
Randomization	X													
Urinalysis (Dipstick ±microscopy)		X		X	X	X	X	X	X	X	X	X	X	If dipstick is positive or participant has urinary symptoms send for microscopy. CCI .
Study Intervention Administration (IV)	X													
Discharge				X										
SARS-CoV-2 Test		<==========											==========>	As per local guidelines.
Brief Physical Exam				X									X	
Laboratory assessments (include clinical chemistry, and haematology panels)		X		X	X	X	X	X	X	X	X	X	X	
CD4+ T cell counts		X				X		X	X	X	X	X	X	
CCI														
Viral quantification and serology (EBV, CMV and VZV)	X							X					X	Day 1 collection prior to administration of study intervention.
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	Single readings to be recorded pre-dose and at PK timepoints. Performed in triplicate if suspected clinically significant findings.
CCI														

Procedure		Intervention Period (Days) for IV cohorts												Notes
	CCI													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Day 1 vitals to be taken pre-dose and end of IV infusion and at CCI CCI from start of IV dosing on Day 1.
Blood collection for Pharmacokinetics	X	X	X		X	X	X	X	X	X		X	X	Day 1 PK samples to be collected prior to, midpoint and end of IV infusion, and at CCI post-start of IV dosing.
Blood collection for Target Engagement (TE) biomarkers	X	X	X		X	X	X	X	X	X		X	X	Day 1 TE samples to be collected prior to and at CCI post-start of IV dosing.
Blood collection for Immunogenicity	X							X		X		X	X	Day 1 collection prior to administration of study intervention
CCI	X		X		X	X		X		X			X	Day 1 collection prior to administration of study intervention
Blood collection for cellular biomarkers	X		X		X	X		X		X			X	Day 1 collection prior to administration of study intervention
CCI	X					X				X				Day 1 collection prior to administration of study intervention
AE Review	☐==========												☐	
SAE Review	☐==========												☐	
Concomitant medication review	☐==========												☐	

Procedure		Intervention Period (Days) for IV cohorts	Notes
	CCI		
CCI			
CCI			

1.3.3. SC Dosed Cohorts

Procedure	Intervention Period [Days] for SC cohorts CCI	Notes
Randomisation	X	
Urinalysis (Dipstick ±microscopy)	X X X X X X X X X X X X X	If dipstick is positive or participant has urinary symptoms send for microscopy CCI
Study Intervention Administration (SC)	X	
Discharge	X	
SARS-CoV-2 Test	<========== ==========>	As per local guidelines
Brief Physical Exam	X X	
Laboratory assessments (include clinical chemistry, and haematology panels)	X X X X X X X X X X X X X	
CD4+ T cell counts	X X X X X X X X X X X X X	
CCI		
Viral quantification and serology (EBV, CMV and VZV)	X X X	Day 1 collection prior to administration of study intervention.

Procedure	Intervention Period [Days] for SC cohorts														Notes
	CCI														
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Triplicate readings to be recorded pre-dose and at PK timepoints whilst admitted CCI Single readings to be recorded at PK timepoints for outpatient visits. These will be performed in triplicate if suspected clinically significant findings.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Day 1 vitals to be taken pre-dose and at CCI post administration of study intervention.
Blood collection for Pharmacokinetics	X	X	X			X		X	X	X	X	X		X	Day 1 PK samples to be collected prior to and at CCI post administration of study intervention
Blood collection for Target Engagement (TE) Biomarkers	X	X	X			X		X	X	X	X	X		X	Day 1 TE samples collected prior to and at CCI post-administration of study intervention.
Blood collection for Immunogenicity	X									X		X		X	Day 1 collection prior to administration of study intervention
CCI															
Blood collection for Cellular Biomarkers	X		X			X		X		X		X		X	Day 1 collection prior to administration of study intervention
CCI															

Procedure	Intervention Period [Days] for SC cohorts CCI [redacted]	Notes
AE review	☐==========☐	
SAE Review	☐==========☐	
Concomitant medication review	☐==========☐	

CCI [redacted]
CCI [redacted]

Procedure	Intervention Period [Days] for SC cohorts	Notes
CCI	CCI	

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Additional visits may be scheduled as required, based on participants $CD4^+$ T cell counts and other safety data.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment.
- Participants with $CD4^+$ counts $<0.2x10^9$/L at day CCI will be offered further monitoring if, in the opinion of the Investigator (in discussion with the Medical Monitor as necessary), the low $CD4^+$ counts can be reasonable attributable to study participation. Monitoring will initially involve laboratory assessments (including clinical chemistry and haematology panels) and a repeat $CD4^+$ count approximately CCI post day CCI Additional monitoring or onward referral for clinical care will be made at the discretion of the Investigator. Data collected during further monitoring will be reported in the clinical study report.
- 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.
- CCI .

2. INTRODUCTION

GSK3888130B is a humanised monoclonal antibody (mAb; CCI) raised against recombinant human interleukin (IL)-7, being developed for the treatment of Multiple Sclerosis.

2.1. Study Rationale

This is a first time in human (FTIH) study designed to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile of single ascending doses (SAD) of GSK3888130B.

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This study aims to provide sufficient confidence in the safety and tolerability of the molecule and will obtain preliminary information relating to the PK and PD profile of GSK3888130B following intravenous (IV) or subcutaneous (SC) injection routes of delivery to support future clinical development.

2.2. Background

Interleukin (IL)-7 is reported to be a non-redundant cytokine, required for early T cell development as well as T cell homeostasis. It is secreted by stromal cells in the thymus and bone marrow (BM) environment [Mazzucchelli, 2007] and produced by fibroblastic reticular cells (FRC) in T cell zones of lymph nodes (LN) [Link, 2007]. It signals through the heterodimeric IL-7 receptor (IL-7R) complex, which consists of the IL-7Rα chain (Cluster of Differentiation (CD)127) and the common γ-chain (CD132). Signalling of the receptor heterodimer is driven through proximity-mediated activation of Janus kinase (JAK)1 and JAK3 tyrosine kinases leading to recruitment and subsequent signal transducer and activator of transcription (STAT)5 phosphorylation [Kovanen, 2004]. In

addition, IL-7 plays a non-redundant role in upregulating Bcl-2 expression in T cells which enables their survival in the periphery [Karawajew, 2020]

The IL-7R is expressed on naïve and memory $CD4^+$ and $CD8^+$ T cells, T follicular helper cells, B cell subsets and natural killer (NK) cells, but it is notably absent or has very low expression on T regulatory cells [Park, 2004]. Furthermore, IL-7 can support differentiation of human T cells into Th1 and Th17 T cell phenotypes [Lee, 2011; Wan, 2011]. Importantly, homeostasis of regulatory T (Treg) cells appears independent of IL-7, as regulatory T cells characteristically express low numbers of IL-7Rα and instead critically depend on IL-2 for their development and homeostasis [Burchill , 2007; Liu, 2006].

The IL-7 pathway has been implicated in a number of autoimmune diseases with growing evidence supporting a genetic association with Multiple Sclerosis (MS) [International Multiple Sclerosis Genetics Consortium, 2019].

Multiple Sclerosis is characterised by relapses, episodes of acute neurological dysfunction (e.g., loss of vision, weakness, numbness) and disease progression (accumulation of neurological deficits) [Thompson, 2018]. The pathological mechanisms that underly relapse biology (acute inflammation and breakdown of the blood brain barrier leading to demyelination) are well-understood whereas those driving disease progression (ongoing compartmentalised chronic central nervous system (CNS) inflammation) that leads to neurodegeneration have not been well-characterised and have been notoriously difficult to treat [Hauser, 2020].

The pathogenic autoreactive T cells in MS are maintained by a pool of memory T cells, and IL-7 is key for their development, proliferation and activation. IL-7 also enhances effector T cell function including proinflammatory cytokine production. CCI [redacted] CCI [redacted] CCI [redacted] Blockade of IL-7 in the periphery therefore represents an opportunity to target the pathogenic cells at an early point, upstream of current therapies, in addition to targeting their effector function.

Additionally, IL-7 plays a role in the development of ectopic/tertiary lymphoid tissue (tertiary lymphoid organ [TLOs]) involved in local T and B cell activation and associated with accelerated disease progressing in MS patients [Mitsdoerffer, 2016]. In chronic autoimmune diseases, TLOs are involved in local T and B cell activation and CCI [redacted] Specifically, IL-7 is critical for the development of innate lymphoid cells (ILCs) that lead to TLO formation and for function of follicular helper T (Tfh) that are directly involved in B cell activation. IL-7 blockade would therefore also be expected to lead to decreased B cell activation, decreased autoantibody production and decreased B cell antigen presentation and decreased TLO formation/maintenance, all associated with autoimmunity.

Despite recent advances in the treatment of MS, particularly for Relapsing Remitting MS (RRMS) where relapse frequency can be effectively reduced, a large unmet need remains

for treatments that can further slow disease progression and delay or avoid disability [Kappos, 2020]. Most patients with RRMS will transition to secondary progressive MS (SPMS) despite available treatments [Ziemssen, 2020]. For patients with Primary Progressive MS (PPMS), whose disease tends to be identified later in life, treatment is currently limited to the anti-CD20 depleting antibody Ocrevus (ocrelizumab). It is expected that additional therapies will come onto the market, but the need remains to target other disease mechanisms and to develop treatments that offer improved efficacy. The blockade of IL-7 signalling has the potential to benefit patients with both relapsing and progressive forms of the disease by blockade of both memory T cell activation and development of TLOs.

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A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK3888130B is provided in the GSK Investigator's Brochure (IB) [RPS-CLIN-014183].

2.3. Benefit/Risk Assessment

The risk assessment of GSK3888130B is based on the pre-clinical studies conducted to date. Summaries of findings from these pre-clinical studies can be found in the IB. Details of these risks and the proposed strategy to mitigate/monitor these risks are detailed in Section 2.3.1.

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CCI [redacted].

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK3888130B		
Dose selection	The first dose level (Cohort 1) of GSK3888130B is anticipated to have clinically insignificant biological activity, with the rationale for dose selection explained in Section 4.3. There is a risk that the first dose level may have greater pharmacological activity than predicted. If this is the case, then the risks outlined in this risk assessment may be increased. [Note: Cohort 1 has completed study participation and so this risk has been discharged. It is retained here as a record of benefit/risk considerations.]	Monitoring: Participants undergo inpatient monitoring following IMP administration. Sentinel dosing is utilised for all cohorts. Dose modification: Dose escalation decisions are based review of safety, tolerability and PK data. Available TE data will also be explored during dose escalation decisions. Dosing schedule may be modified within defined exposure limits.
Infection / lymphopenia	GSK3888130B potently blocks IL-7 and shows the expected impact on human T cells (inhibiting signalling, activation, cytokine production and proliferation of both $CD4^+$ and $CD8^+$ T cells). This may impact T-cell differentiation and function, increasing the risk for infection. Lymphopenia is one of the most prominent markers of moderate/severe coronavirus disease (COVID-19), with lower lymphocyte counts closely correlated with disease severity [Jamilloux, 2020; Zheng, 2020]. Constitutive, global IL-7 deficient mice have pan-lymphocytopenia, with arrested development of B and T cell subsets, thymic hypoplasia, peripheral lymph nodes (hypocellular or absent), Peyer's patches (greatly diminished or absent) and splenic hypoplasia with greatly diminished B and T cell regions and rare or absent marginal zone (MZ) B cells.	***Reactivation/new infections:*** Exclusion: participants with recent or recurrent infections. Monitoring: Baseline, midpoint and end of study serology and viral quantification of EBV, CMV and VZV. Temporary Halt Criteria: CD4+ T cell counts below 0.2×109/L sustained for at least 7 days in 1 participant will result in review by the GSK DEC before further participants are dosed.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	[redacted] CCI [redacted] CCI [redacted]. Pre-clinical experience with healthy cynomolgus monkeys, as well as internal experience with a monoclonal antibody to the IL-7R (GSK2618960) in two Phase 1 HV studies (NCT01808482 and NCT022931610) [Ellis, 2019], indicate that after single doses of anti-IL-7R mAb there were minimal changes on T cell subsets and absolute lymphocyte counts respectively, which were also transient. An excess of infections was not reported in these studies; only nasopharyngitis was observed in 17% and 50% of participants on anti-IL-7R mAb for studies I7R116702 and 200902, respectively. Baseline serology (EBV, HIV, HepB, HepC, HSV, CMV, VZV) was stored for analysis and comparison if symptoms of viral infection occurred (Study I7R116702), and serology analysed (EBV and CMV) only if participants had alanine amino transferase (ALT) >3xULN (Study 200902). There were no reports of viral infection, therefore virology samples were not analysed. Across both studies, no deaths, SAEs or other significant AEs were reported. No AEs led to study withdrawal. In a 12-week repeat dose study (different regimens), with an anti-IL-7R mAb [Herold, 2019], there was a significant decline over the dosing period in $CD4^+$ and $CD8^+$ effector and central memory T cells and $CD4^+$ naive cells, but there were fewer effects on $CD8^+$ naive T cells. Only a small decline in these cells was noted after the first dose of each regimen. All dosing regimens had receptor occupancy >90%. Serum was collected for EBV and cytomegalovirus (CMV) IgG antibodies and viral deoxyribonucleic acid (DNA) at baseline, on day 85 and at the end of follow-up. Four participants seroconverted from negative EBV IgG before treatment to positive IgG antibody. Two of these participants had EBV symptoms. One participant who was negative at baseline for CMV viral DNA but positive for IgG antibody, had detectable viral DNA on day 85 (asymptomatic), returning to negativity by day 127. Recombinant IL-7 cytokine was currently being trialled (InterLeukin-7 [CYT107] To Improve Clinical Outcomes in Lymphopenic Patients with COVID-19 Infection UK Cohort [ILIAD-7-UK]; NCT04379076) to improve clinical outcomes in lymphopenic patients with SARS-CoV-2 infection. The study was terminated in April 2022 due to poor accrual. There are no publicly available results from this study.	***During the ongoing SARS-CoV-2 infection risk:*** Inclusion: participants must complete a two-dose SARS-CoV-2 vaccination schedule and adhere to travel restrictions. Exclusion: participants with recent SARS-CoV-2 positive contacts. Temporary Halt Criteria: 1. CD4+ T cell counts below 0.2×109/L sustained for at least 7 days in 1 participant will result in review by the GSK DEC before further participants are dosed. 2. SARS-CoV-2 infection risk data are evolving. SARS-CoV-2 infection data in the UK and specifically local area data in the vicinity of the Phase 1 unit where the study will be conducted will be monitored. In the event of an increase in SARS-CoV-2 infection rates, with resultant increase in moderate to severe COVID-19, that cannot be managed through two-dose vaccination regimens available at the time of the study (e.g. new variants), the study will be temporarily halted. Participant counselling: See Appendix 6

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	As social contact returns to pre-pandemic norms there is likely to be a resurgence in influenza activity in winter 2022 to 2023 to levels similar to or higher than before the pandemic [Gov.UK. National flu immunisation programme, 2022] and may remain elevated in subsequent years. It is unknown whether blockade of IL-7 pathways may increase the risk of contracting, or severity of, influenza infection.	***Influenza:*** All participants must have received an influenza vaccination at least 30 days prior to dosing, if dosing falls on or between 1st October and 30th April.
CCI [redacted]		
CCI [redacted]		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]	CCI [redacted]
Immunogenicity and / or hypersensitivity	A mAb raised against the IL-7Rα (GSK2618960) experienced a high incidence of anti-drug antibodies (ADA), both in cynomolgus monkey studies and in humans. This is likely due to receptor mediated activity.	Exclusion: Any participant with a current or past history of clinically significant allergic reactions (anaphylaxis, urticaria) will be excluded. Monitoring:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]. CCI [redacted]	• A validated ADA assay (screening, confirmation, and titration methods) will be used in this study. • Participants will be monitored for occurrence of hypersensitivity reactions and ADA titers. Temporary halt criteria: Clinically significant [National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5, National cancer institute - common terminology criteria for adverse events [NCI-CTCAE]) grade 3 or greater] infusion reactions occurring in 1 participant.
Malignancy	As with other immunomodulating agents, GSK3888130B could increase the possibility of immunosuppression resulting in an increased risk of malignancy. Genetic evidence indicates an association between the IL-7R locus and basal cell carcinoma with evidence that an IL-7R missense variant (Thr244Ile) is driving this association. The direction of this mutation is in the opposite direction as that seen in MS where knowledge about the IL-7/IL-7R biology is consistent with activating T cells. Blockade of this biology by GSK3888130B and any consequential risk is unknown. The IL-7R locus is amplified in a number of epithelial solid tumours (5-10%; NSCLC, oesophageal, bladder, cervical) and diverse tumour types (<10%). The functional significance of these amplifications is uncertain as they do not appear to result in increased IL-7R mRNA expression levels.	Exclusion: Participants with a history of cancer, including malignant and non-malignant skin cancer. Counselling: Participants will be counselled to follow usual precautions to avoid excessive sun exposure due to a genetic association with basal cell carcinoma.
Reproductive toxicity	Animal reproductive toxicity studies have not yet been carried out with GSK3888130B. However, there is a theoretical risk that GSK3888130B could affect the development of T and B cells in a developing fetus.	Inclusion: • Only male participants and female participants of non-childbearing potential.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Male participants will be required to refrain from intercourse or use a condom, avoid semen exposure to a women of child bearing potential (WOCBP), and refrain from donating sperm for CCI days.
Injection site reactions	Injection site reactions have been reported for other mAbs and appear to occur more frequently with proteins carrying foreign sequences, such as murine or chimeric mAbs. The reported incidence typically ranges from 1-5%. Serious hypersensitivity reactions are rare.	Exclusion: Any participant with a current or past history of clinically significant allergic reactions (anaphylaxis, urticaria) will be excluded. Monitoring: Participants will be closely monitored for injection site reactions.
CCI		
CCI		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		CCI [redacted]
CCI [redacted]		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI	[redacted]	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI	[redacted]	

2.3.2. Benefit Assessment

The proposed study will be conducted in healthy participants. There will be no medical benefit to the study participants.

Participants in this study will be contributing to the process of developing a new therapy in areas of unmet need including the treatment of disease progression in Multiple Sclerosis.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK3888130B at the doses to be administered are considered minimal and justified.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of single IV and SC doses of GSK3888130B in healthy participants.	• Occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs). • Occurrence of clinically significant changes in laboratory values ($CD4^+$ T cell counts, haematology, chemistry, urinalysis and virology), vital signs and 12-lead electrocardiogram (ECG) readings.
Secondary	
• To characterise the serum PK profile of single IV or single SC doses of GSK3888130B in healthy participants.	• Serum concentrations of GSK3888130B and derived PK parameters as data permit, including: area under the concentration-time curve [AUC], maximum concentration [Cmax], time to Cmax [Tmax], half-life [$t_{½}$], clearance [CL].
• To evaluate the immunogenicity of single doses of GSK3888130B in healthy participants.	• Incidence of Anti-Drug Antibodies (ADAs) against GSK3888130B.
• To characterise the effects of GSK3888130B on target engagement (TE).	• Change from baseline in CCI [redacted]) over time.

Objectives	Endpoints
• To characterise the effect of single doses of GSK3888130B on PD biomarker Bcl-2.	• Change from baseline in T cell Bcl-2, measured in blood over time.

CCI

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a single centre, randomised, double-blind, placebo controlled, dose escalation study comprised of seven planned SAD cohorts, designed to assess safety, tolerability, PK and PD of GSK3888130B over a range of dose levels (from CCI mg to CCI mg) in healthy participants.

CCI [redacted].

While every effort will be made to identify participants CCI to assess the impact of GSK3888130B on the CCI [redacted].

All participants in the study will attend a screening visit within 28 days prior to administration of study intervention (Day 1). In subjects who require an influenza vaccination and/or SARS-CoV-2 vaccination or booster, the screening window may be increased to 60 days. This extended screening window applies only to those participants, and if their initial screening assessments are conducted more than 28 days prior to Day 1, screening assessments will be repeated within 28 days of Day 1 to confirm eligibility. Holter monitoring, viral serology (HIV, hepatitis B and hepatitis C), Mycobacterium tuberculosis (TB) screening, CCI [redacted] (CCI [redacted]) does not need to be repeated for extended screening windows or rescreens if within 3 months of initial screening.

Participants who meet the entry criteria and provide informed consent will be randomised to receive either GSK3888130B or placebo. Safety assessments will be conducted throughout the study duration and blood samples collected for PK, immunogenicity and biomarker evaluation (TE and pharmacodynamic markers).

Participants will be admitted to the clinical unit on Day -1 for final eligibility checks before administration of study intervention on Day 1. Administration of treatment intervention will be by IV infusion or SC injection, investigated in separate cohorts. A detailed listing of the timing of assessments and study procedures can be found in Section 1.3 (Schedule of Activities [SoA] Table).

As this is the first administration of GSK3888130B in humans, sentinel dosing will be utilised for each increasing dose level (if the selected dose level is below or equivalent to the previous dose level, sentinel dosing may still be applied). Participants will be randomised to receive either GSK3888130B or placebo in a 3:2 ratio in cohorts 1 and 2 or in a 3:1 ratio in all other SAD cohorts.

Sentinel dosing will be implemented in each cohort, so that one participant is dosed with GSK3888130B and one participant is dosed with placebo followed by review of post-dose safety data before additional participants in each cohort are dosed.

- The duration of post-dose safety data required for IV and SC cohorts is described below.

For cohorts where treatment administration is by IV injection:

- The remaining participants in these cohorts will only be dosed after review of at least CCI safety & tolerability data (i.e. AE/SAEs, laboratory values, vital signs and 12-lead ECGs) from the sentinel participants by the Principal Investigator (PI) or appropriately qualified delegate, in consultation with the Medical Monitor or delegate if unavailable, and it has been deemed safe to do so.
- Participants will remain in the unit until completion of all assessments on Day CCI This period may be amended at the discretion of the Principal Investigator (or designee) and GSK DEC as safety and PK data evolves.

For cohorts where treatment administration is by SC injection:

- The remaining participants in these cohorts will only be dosed after review of at least CCI safety & tolerability data (i.e. AE/SAEs, laboratory values, vital signs and 12-lead ECGs) from the sentinel participants by the Principal Investigator (PI) or appropriately qualified delegate, in consultation with the Medical Monitor or delegate if unavailable, and it has been deemed safe to do so.
- Participants will remain in the unit until completion of all assessments on Day CCI This period may be amended at the discretion of the Principal Investigator (or designee) and the GSK DEC as safety and PK data evolves.

CCI

All subjects will then be required to attend the clinic for up to outpatient visits over the course of days after dosing for safety assessment and sample collection and will receive two follow-up telephone calls; the first will be days post last study visit and the second will be days post last study visit. If required, additional follow-up visits may be scheduled.

The total duration of the study for each participant will be approximately weeks.

Doses between cohorts are planned to escalate in a sequential fashion contingent on the safety, tolerability and pharmacokinetic profile from a minimum of 2 participants dosed with GSK3888130B in cohorts 1 and 2 or a minimum of 4 participants dosed with GSK3888130B in all other SAD cohorts. The decision to proceed to the next dose level of GSK3888130B will be made by the GSK DEC following a review of the safety, tolerability (including absolute $CD4^+$ T cell counts) and PK data up to and including Day for both IV and SC dosed cohorts. Available TE data (total IL-7 levels) will also be explored. Further details on the GSK DEC are provided in Section 10.1.5.

4.2. Scientific Rationale for Study Design

This study will be the first administration of GSK3888130B in humans and has therefore been designed in accordance with regulatory guidance for the conduct of First Time in Human (FTIH) studies, with data obtained from preclinical assessments of GSK3888130B contributing to the number and timing of safety assessments and monitoring during the study.

This study aims to evaluate safety, tolerability, PK and PD of GSK3888130B in healthy participants with the inclusion of a placebo control to allow for evaluation of safety and tolerability attributable to treatment, versus those independent of treatment.

Data from healthy participants will provide preliminary data following single dosing, in healthy participants who are not on any concomitant medications, as to the safety and tolerability of GSK3888130B and enable evaluation of potential lymphopenia, risk of infection and risk of reoccurring infections following suppression of memory T cell

responses prior to study in patients with autoimmune disease, who may already be predisposed to infection risks and/or less able to fight-off infections due to an altered immune response.

The inclusion of a placebo control will also act as biological control to account for biological variation (not attributable to GSK3888130B) in PD assessments being taken to provide confidence in TE and inhibition of downstream biological signalling.

As this is a FTIH study, a sentinel dosing approach will be employed for any dose level not previously administered to humans (i.e. each increasing dose level). This will permit immediate assessment of the safety and tolerability of GSK3888130B in a single participant before the remaining participants receive study treatment. Any escalation of doses between cohorts, including definition of the next dose, will be made by the GSK DEC based upon the review of all available safety, tolerability and PK data from the previous dose level(s). In addition, available TE data (total IL-7 levels) will be explored. The duration of inpatient admission and requirement for safety data is based on the predicted PK time course (Cmax). The duration of this period may be amended at the discretion of the Principal Investigator (or designee) and GSK DEC as safety and PK data evolves.

The study includes both IV and SC administration in separate cohorts to evaluate pharmacokinetics for the two routes. For SC administration, CCI [redacted]. The two SC dose levels will provide information on GSK3888130B CCI [redacted], which might be dose-dependent. The IV route of administration was selected for the initial dosed cohorts to enable monitoring of early safety signals during infusion. SC cohorts are interspersed with IV cohorts to minimise the number of subjects who are exposed to GSK3888130B. The dose escalations have been planned to ensure that exposure increments remain consistent between ascending dose levels/cohorts based on PK exposure predicted from pre-clinical data (see Section 4.3.2).

To ensure unbiased outcomes, a double-blind approach will be used, with the participants, Investigator and Clinical Unit staff all blind to treatment allocation.

CCI [redacted]

CCI [redacted]

As GSK3888130B potently neutralises IL-7 and is therefore anticipated to impact T cell development, differentiation and function (including memory T cell responses), GSK3888130B has the potential to increase the risk of infection.

Previous clinical experience with an anti-IL-7R mAb antagonist GSK2618960 in two Phase 1 studies (NCT01808482 and NCT022931610) in 24 healthy participants, reported no viral infections [Ellis, 2019] and CCI [redacted]

In a Phase 2b, 12-week repeat-dose escalation study (NCT02038764) evaluating IL-7R blockade with RN168 (a humanised IgG1 mAb which binds to IL-7RA (CD127)), in 37 subjects with type 1 diabetes, four participants seroconverted from negative Epstein-Barr Virus (EBV) IgG before treatment to positive IgG antibody response following dosing. Two of these participants had symptomatic EBV infection [Herold, 2019]. In this repeat dose study, between 90% and 100% IL-7R occupancy and near-complete inhibition of pSTAT5 (IL-7R downstream signaling) was observed at all dose levels and regimens tested.

Prevalence of viral infections in the community are generally considered to be of low-risk in the UK due to high childhood vaccination uptake (with the exception of the recent SARS-CoV-2 pandemic). Therefore, in the absence of viral infections in healthy volunteer studies with an anti-IL-7R GSK21618960, preclinical toxicity study with GSK3888130B and risk mitigation plans within this study (detailed in Section 2.3.1), the risk to healthy volunteers from a single dose of GSK3888130B is considered to be very low. In addition, baseline, midpoint, and end of study viral samples will be drawn and analysed for EBV, CMV and VZV infection in order to characterize the infection risk (including asymptomatic infection) and determine trends to inform future clinical development.

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARs-CoV-2) vaccination and UK Government policies have seen the risk of severe Coronavirus 19 (COVID-19) disease reduced in the general population in the UK. However, it is noted that the greatest impact of IL-7R inhibition has been shown to be on the central and effector memory T cell response/cell number [Herold, 2019]. While these cell populations drive the autoimmune response in disease, they are also important in mounting a T cell mediated memory

response to infections and inhibition of IL-7 may reduce this response. Evidence suggests that the current approved SARS-CoV-2 vaccines are protective largely due to the B-cell antibody response, as efficacy correlates with antibody titres and their neutralising capacity [Earle, 2021]. Therefore, participants will be required to have been fully vaccinated for SARS-CoV2 vaccines (two-dose regimen) 30 days prior to dosing, as efficacy of these vaccines are reported to give substantial protection against hospitalisation from current SARS-CoV-2 strains.

As social contact returns to pre-pandemic norms there is likely to be a resurgence in influenza activity in winter 2022 to 2023 to levels similar to or higher than before the pandemic [Gov.UK. National flu immunisation programme, 2022]. Therefore, all participants recruited into the study to be dosed within the influenza season (1st October to the 30th April) will be required to be vaccinated with an approved seasonal influenza vaccine.

CCI [redacted] 12-lead ECGs will be routinely performed in both IV and SC cohorts to provide contemporaneous safety analysis and data for the primary outcome.

4.2.1. Participant Input into Design

There has been no participant input into this trial design.

4.3. Justification for Dose

4.3.1. Human dose prediction for GSK3888130B

CCI [redacted].

The drug concentration and total IL-7 in blood from monkey studies were fitted with a two-compartment PK model that is linked to a target-mediated drug-disposition PD model. The model was extrapolated to human, by scaling PK parameters using allometry and assuming CCI CCI [redacted]. The extrapolated model was then used to predict the dose-response relationships for human PK, the associated exposure safety margin in relation to the NOAEL in the monkey, CCI [redacted]

The PK-PD data of CCI [redacted] in monkey were modelled using a turnover model, where the drug reduced production of CCI [redacted] This model, combined with the PK model that was scaled from monkey to human by allometry, was used to predict the dose-response relationship of CCI [redacted] reduction in human.

These PK-PD models were further translated from blood to tissue. However, this translation has not been validated by any tissue data. The CCI [redacted] predicted that monthly dosing of approximately CCI CCI [redacted]

CCI for Copaxone® (at its therapeutic dose) and the IL-7 receptor antagonist RN168 at doses investigated for type-1 diabetes. In absence of any disease biomarker, the therapeutic meaning of the PK-PD predictions is highly uncertain.

4.3.2. Dose escalation plan for GSK3888130B

GSK3888130B is considered a low-risk molecule for several reasons. First, it belongs to a drug class (monoclonal antibodies; mAbs) which is acknowledged to have low risk of off-target toxicity. Second, inhibition of the IL-7 pathway has been previously studied. IL-7 receptor (IL-7R) blockade has been investigated in healthy volunteers [Ellis, 2019] and patients with Type 1 diabetes [Herold, 2019]. Third, the molecule has similar *in vitro* IL-7 binding affinity for monkey and human, making the pharmacology and safety findings in the monkey highly relevant to the human.

PK-PD modelling was conducted using pooled data from two PK/PD studies and the 4-week toxicity study (all in cynomolgus monkeys) to describe PK, TE (CCI and pathway pharmacology (CCI) in order to support the planning of dose escalation in the FTIH trial.

At the no observed adverse effect level (NOAEL) found in the 4-week toxicology study in monkeys (the top dose studied), CCI was demonstrated in a Phase 2b, 12-week repeat-dose escalation study (NCT02038764) evaluating IL-7R blockade with RN168 (anti-IL-7R mAb) [Herold, 2019] and with the therapeutic dose for Copaxone® [CopaxonePrescribingInformation, 2009; Ruggieri, 2006]. Modelling and simulation data predict that a CCI mg dose of GSK3888130B CCI will give a reduction CCI

It is anticipated that the CCI mg starting dose will result in CCI in blood; this low biological effect is considerably below the level of CCI suppression previously observed in humans with RN168 and Copaxone®. The starting dose of CCI mg is deemed appropriate for healthy volunteers given the low risk for off-target toxicity, the existing knowledge of the target pathway in human, and the high pharmacology and safety relevance of the pre-clinical species (outlined above in this Section). The starting dose of CCI mg is further supported by PK-PD modelling and simulation which suggest adequate safety margins in relation to the NOAEL CCI found in the 4-week toxicology study in monkeys (see Section 4.3.3).

4.3.3. Predicted plasma exposure, safety margins, target engagement CCI and pathway pharmacology CCI

Planned Dose [mg]	Dosing Route*	Exposure		Exposure Ratio Monkey: Human$		Peak reduction in blood (%)	
		AUC (µg/mL*h)	CMAX (µg/mL)	AUC	CMAX	CCI	CCI
CCI							

Planned Dose [mg]	Dosing Route*	Exposure		Exposure Ratio Monkey: Human[$]		Peak reduction in blood (%)	
		AUC (µg/mL*h)	CMAX (µg/mL)	AUC	CMAX	CCI	CCI
CCI	CCI	CCI		CCI			CCI
[$]Ratios based on total exposure at NOAEL of CCI mg/kg/wk IV in 4-wk monkey study: AUC CCI µg/mL*h and Cmax CCI µg/mL							
AUC=AUC from time 0 extrapolated to infinity. Cmax = maximum concentration							

Dose escalation will be at up to half-log increments in exposure, accounting for the anticipated exposure difference between subcutaneous and intravenous administrations.

It is not possible to determine the therapeutic dose of GSK3888130B prior to studies in patient populations, as the relationship between pharmacology and clinical outcomes is unknown. Given this uncertainty, the study is design to explore a range of doses to explore pharmacological response and the top dose will, within practicality of drug administration, maximise the safety cover for future patient trials where repeat-dosing. In this single-dose study, the planned top dose of CCI mg is based on NOAEL from the 4-week toxicology study in monkeys, and provides CCI predicted safety margins for AUC and Cmax, respectively. Guided by emerging data, the actual top dose will generate the anticipated mean AUC and Cmax with at least CCI safety margin in relation to the exposure at the NOAEL identified in the monkey.

CCI

CCI

[redacted]

4.4. End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all relevant parts of the study including the final follow-up telephone call.

5. STUDY POPULATION

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

CCI

CCI

[redacted]

CCI [redacted]

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 informed consent form (ICF) and in this protocol.

CCI [redacted]

5.2. Exclusion Criteria

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

Medical Conditions

1. Prior medical history of anaphylaxis or severe adverse reactions to vaccines.
2. Immunodeficiency or autoimmunity assessed by medical history.
3. A history of recurrent infections.
4. Treatment of a chronic infection within 3 months prior to the first dose of study drug, including both serious local infection (e.g. cellulitis, abscess) or systemic infection (e.g. pneumonia, Tuberculosis, hepatitis B, Shingles).
5. Any acute infection (including upper respiratory tract infections and urinary tract infections) which has not fully resolved within four weeks of dosing.
6. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor, poses a safety risk with regards to participation in the trial.
7. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
8. Participants with a history of renal disease or renal abnormalities.
9. A clinically significant abnormality in the 12-lead ECG performed at screening including:
    - Heart rate <45 or >100 bpm (male) or <50 or >100 bpm (female)
    - PR interval <120 or >220 msec

- QRS duration <70 or >120 msec
- QTcF interval >450 msec (QT interval corrected for heart rate according to Fridericia's formula)
- Evidence of previous myocardial infarction (does not include ST segment changes associated with re-polarization).
- Conduction abnormality (including but not specific to left or right complete bundle branch block, atrioventricular block [2nd degree or higher], Wolf-Parkinson-Wright syndrome).
- Sinus Pauses >3 seconds.
- Non-sustained or sustained ventricular tachycardia (>3 consecutive ventricular ectopic beats).
- Any significant arrhythmia which, in the opinion of the Investigator or the GSK Medical monitor, that will interfere with the safety for the individual participant.

10. CCI [redacted]
11. History of malignancy, including malignant or non-malignant skin cancer.
12. Participants with known SARS-CoV-2 positive contacts in the past 14 days.
13. Prior moderate/severe SARS-CoV-2 infection requiring oxygen supplementation or admission to hospital.

CCI [redacted]

CCI [redacted].

Prior/Concomitant Therapy

20. Antibiotics or antiviral therapy within 30 days of dosing.
21. Receipt of live vaccination within 30 days of dosing or plan to receive live vaccination during the study.
22. Use of prescription drugs or non-prescription drugs, including non-steroidal anti inflammatory drug (NSAIDs), within 7 days prior to dosing, if in the opinion of the Investigator (in consultation with the GSK Medical Monitor if required) the medication will interfere with the study procedures or compromise participant safety. Participants must not currently take any of the following: oral or systemic steroids or any other immune modulators (the washout period will be determined on a case by case basis, in consultation with the GSK Medical Monitor). Paracetamol, at doses of ≤4 grams/day, is permitted for use any time during the study.

CCI [redacted]

Prior/Concurrent Clinical Study Experience

24. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day of the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
25. Exposure to more than 4 new chemical entities within 12 months prior to dosing.

Diagnostic assessments

26. A positive diagnostic Mycobacterium tuberculosis (MTB) test at screening (defined as a positive QuantiFERON Gold test).

    NOTE: In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once and if their second test is negative, they will be eligible. In the event a second test is also indeterminate, the participant is not eligible.
27. A positive pre-study hepatitis B surface antigen, hepatitis B core antibody or positive hepatitis C antibody result at screening.

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

    NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
29. A positive test for HIV antibody at screening.
30. A positive drug/alcohol test at screening or Day -1.

Other Exclusions

31. CCI [redacted].
32. Current smoker or user of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) during or within 30 days prior to study participation.
33. CCI [redacted].
34. An average weekly intake of >14 units of alcohol. One unit is equivalent to 8g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
35. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
36. The participant does not agree to adhere to UK government guidance on international travel during the study period. Participants must ensure that any travel does not impair their ability to attend scheduled visits.

CCI [redacted]

5.3. Lifestyle Considerations

5.3.1. Alcohol, and Tobacco

- During dosing (Day 1) session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Use of tobacco products will not be allowed from screening until after the final study visit on Day CCI [redacted]

5.3.2. Activity

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

5.3.3. SARS-CoV-2 related restrictions

- Participants will be required to adhere to any national, local and site-specific guidance regarding COVID-19, including any self-isolation guidance.

5.3.4. Other consideration

- Participants should follow usual precautions to avoid excessive sun exposure.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered in the study due to not meeting eligibility requirements. Unused participants that meet eligibility criteria are not considered screen failures and may undergo repeated rescreening to confirm eligibility requirements if randomization into study planned outside of initial screening window.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Individuals who failed initial screening but passed rescreening may be admitted into the study based upon clinical judgement and after consultation with the GSK Medical Monitor.

Holter monitoring, viral serology (HIV, hepatitis B and hepatitis C) and TB screening does not need to be repeated for rescreens if within 3 months of initial screening.

If a participant fails any of the laboratory criteria, the test may be repeated once within the screening period without this constituting a rescreen. If the participant fails the laboratory criteria for a second time, they will be considered a screen failure.

5.5. Criteria for Temporarily Delaying Enrolment/Randomization/Administration of Study Intervention Administration

- SARS-CoV-2 outbreak leading to a rapid rise in case numbers and hospitalisations for which the approved two-dose SARS-CoV-2 vaccines appear to have lower/unknown efficacy, based upon clinical judgement and consultation with the GSK Medical Monitor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered.

	Study Intervention		CCI	
ARM Name	GSK3888130B	Placebo	CCI	CCI
Intervention Name	GSK3888130B Injection	Placebo	CCI	CCI
Type	Drug	Drug	CCI	CCI
CCI			CCI	
Unit Dose Strength(s)	CCI mg/mL		0.9%	CCI
Dosage Level(s)	IV: CCI mg SC: CCI mg		Volume to match volume of	CCI

	Study Intervention		CCI	
		active dose administered		
Route of Administration	IV or SC injection	IV or SC injection	CCI	
Use	experimental	placebo	CCI	
IMP and AMP	IMP	IMP	CCI	
Sourcing	Provided centrally by the Sponsor	Locally sourced by the site	CCI	
CCI	CCI	CCI	CCI	CCI

For the IV cohorts GSK3888130B is planned to be infused over an approximate duration of CCI. GSK3888130B can be diluted in saline (0.9% sodium chloride) prior to administration.

For the SC cohorts: the appropriate volume of GSK3888130B will be injected using a syringe at no more than CCI per injection. Up to CCI injections per dose may be needed.

The same volume of saline (used as placebo) will be infused (IV) or injected (SC) in the same manner as the corresponding GSK3888130B administrations in that cohort.

Infusion durations may vary by cohort due to the wide range of dose concentrations planned to be administered. Where possible volumes and infusion rates will be kept constant. Infusion durations maybe modified based on emerging safety and PK data.

Full instructions for dilution of study intervention to dose concentrations to be administered will be provided in the Pharmacy Manual.

CCI [redacted]

6.2. Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorised site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions will either be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.
- CCI [redacted].

6.3. Measures to Minimize Bias: Randomization and Blinding

On Day 1 of each cohort, participants will be assigned a unique randomisation number in ascending numerical order. The randomisation number encodes the participant's assignment to either GSK3888130B or placebo, according to the randomisation schedules generated prior to the study by the Statistics Department at GSK, using validated internal software. Once assigned, randomisation numbers must not be reassigned to any other participant in the study.

The unblinded pharmacist will receive a copy of the randomisation schedules from the GSK randomisation co-ordinator to enable dispensing of study medication.

The PI or delegated responsible person will assign the randomisation numbers as described above and the randomisation number will be entered in the case report form (CRF).

To prevent accidental unblinding of participants, the investigators and study site will not review participant-level data concerning PK and PD parameters. Participant-level CCI [redacted] will be reviewed by the Medical Monitor. The investigators and study site will only be informed if the CCI [redacted] have met or are approaching the temporary halt criteria, or for other reasons related to participant safety. The transmission of this information will be recorded in the investigator site file.

For the purposes of producing summaries of PK data for review prior to each dose escalation, Clinical Pharmacology Modelling and Simulation (CPMS) will extract blood concentration time data, with scrambled subject IDs from the GSK SMS2000 system. Thus, the subject number stated in the PK dataset will not match the true subject number presented with the safety data. This is to ensure that the review team is blinded with respect to linking PK and safety data.

For the purposes of providing summary data (CCI [redacted]) to the DEC for review prior to each dose escalation, the study Statistics and Programming team will be unblinded. However, no individual subject number identifiers will be included in the data presented to the DEC, to ensure all other members remain blinded.

6.3.1. Unblinding

- In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind.
- The date and reason for the unblinding must be fully documented in the investigator site file.
- A participant may continue in the study if the participant's treatment code is unblinded by the Investigator or treating physician. If the participant discontinues the date and primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- Members of the DEC may be unblinded if individual data needs to be reviewed as part of the interim analysis.
- Procedures for unblinding will be documented in the SRM.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule, but mean exposure is not predicted to exceed AUC(0-∞) of CCI µg/mL*h or Cmax of CCI µg/mL, which are CCI of the exposure observed at NOAEL in the 4-week monkey toxicity study. The planned top dose for this study of CCI mg has sufficient safety cover i.e., CCI predicted safety margins for AUC and Cmax respectively based on the corresponding values at NOAEL from the 4-week toxicology study in the monkeys [GSK Document number 2020N457447_00].

The decision to proceed to the next dose level of GSK3888130B (either an increase, repeat at the same level [dose expansion] or a decrease) will be made by the GSK DEC following a review of the safety, tolerability (including absolute $CD4^+$ T cell counts) and PK data, obtained in at least two GSK3888130B-treated participants in cohorts 1 and 2 and at least four GSK3888130B-treated participants in all other SAD cohorts, up to and including DayCCI for both IV and SC dosed cohorts at the prior dose level. Available TE (total IL-7 levels) data will also be explored.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, PK and PD findings at a given dose level or to add cohorts to evaluate up to two additional dose levels below the planned top dose CCI mg. The study procedures for these additional participant(s)/cohort(s) will be the same as those described for other study participants/cohorts.

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

There is no continued access to study intervention after the end of this study.

6.7. Treatment of Overdose

For this study, any dose of GSK3888130B greater than the dose to be administered in the study in each cohort (protocol planned doses or doses defined as part of dose escalation decisions) will be considered an overdose.

CCI [redacted]

GSK does not recommend specific treatment for an overdose. The Investigator (or physician in charge of the participant at the time) will use clinical judgment to treat any overdose.

In the event of an overdose, the Investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until serum concentration of study intervention falls to below that observed in the highest dose cohort and lymphocyte differentials are >LLN. Duration and frequency of monitoring will be at least that described in the SoA.
- Obtain additional serum sample(s) for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

6.8. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

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

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

Participants must abstain from taking prescription or non-prescription drugs (including NSAIDs, vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the final follow-up visit, unless,

in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Participants must not currently take any of the following: oral or systemic steroids or any other immune modulators (the washout period will be determined on a case by case basis, in consultation with the GSK medical monitor).

Live vaccination is not permitted within 30 days of dosing or during the study. All other vaccinations (including a two-dose SARS-CoV-2 vaccination and seasonal influenza vaccination as per eligibility requirements) will be completed at least 30 days prior to dosing.

Participants who have not received a MHRA-approved seasonal influenza vaccination will be required to receive vaccination as part of screening if dosing in between 1st October and 30th April. Information on influenza vaccination will be included within the ICF and participants will be provided with the product's Patient Information Sheet prior to vaccination. The period for which influenza vaccination is required for study enrolment will be kept under review and may be changed based on emerging data. Any changes to the vaccination period will be approved by the DEC and will not constitute a protocol deviation or amendment. The influenza vaccination is not considered an Investigational Medicinal Product within this study.

No participants who have a medical history of severe adverse reaction to vaccines will be offered or advised to undergo vaccination to meet the eligibility requirements of this study.

Paracetamol, at doses of ≤4 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

This is a single-dose study. In rare instances, a participant may not be able to complete the IV infusion or SC injection(s). In such circumstances, if the study intervention is permanently discontinued, the participant will be encouraged to remain in the study for the planned duration, or minimally to complete safety and PK assessments up to Day CCI The duration for which a participant will be encouraged to remain in the study will be at the discretion of the Investigator in discussion with the Medical Monitor. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

CCI

[redacted]

7.2. Study Stopping Criteria

7.2.1. Liver Chemistry Criteria

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

- Any participant meeting the liver chemistry criteria (ALT ≥3x ULN) will have enhanced monitoring as detailed in Section 10.5. The participant should continue in the study, given this is a single dose study.
- Liver events characterized by an ALT ≥3x ULN but not meeting SAE criteria, if reasonably attributable to GSK3888130B, will result in review by the GSK DEC before further participants are dosed.

7.2.2. QTc Criteria

QTc study stopping criteria, and individual participant increased monitoring criteria, have been designed to assure participant safety. The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. Use of Fridericia's formula (QTcF) is preferred in this study. The formula may not be changed or substituted once the participant has been enrolled; for example, if a participant is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual participant as well. Safety ECGs and other non-protocol specified ECGs are an exception.

Participants that meet either of the bulleted criterion below, additional monitoring will be undertaken until the QTc value is no longer clinically significant. The frequency of this monitoring and the decision as to when the QTc value is no longer clinically significant will be at the discretion of the Investigator. The participant should continue in the study, given this is a single dose study.

- QTcF >500 msec.
- Change from baseline: QTc >60 msec.

If a single ECG demonstrates a prolonged QTc interval, then a further two ECG readings should be obtained over a brief recording period (e.g., 5-10 minute) and the averaged QTc interval used to determine whether the participant meets the criteria to trigger further monitoring.

If a participant meets any of the criteria above, this will result in review by the GSK DEC before further participants are dosed.

7.2.3. SARS-CoV-2 Related Stopping Criteria

- Participants who report symptoms suggestive of SARS-CoV-2 while in the research unit should be isolated in the unit or at home and tested for SARS-CoV-2 infection using an approved molecular test according to local site procedures.

- Participants testing positive for SARS-CoV-2 will be actively followed up, with early referral as per standard of care if there is evidence of deterioration.

- Withdrawal of participants from the study will be at the discretion of the Principal Investigator or designee but should first be discussed and agreed with the GSK Medical Monitor.

- Further study related procedures for the participant, except those required for participant safety and well-being, should be paused until the discussion is complete.

- Participants who test positive for SARS-CoV-2 infection during the course of the study may be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator.

7.2.4. Pharmacokinetic Dose Adjustment / Stopping Criteria

All available PK data from previous dose levels will be rapidly evaluated to estimate and predict the systemic exposure (Cmax and AUC(0-∞)) to the next dose level.

The PK stopping criteria will be mean exposure exceeding or predicted to exceed AUC(0-∞) of [redacted] µg/mL*h or Cmax of [redacted] µg/mL, which are [redacted] of the exposure observed at NOAEL in the 4-week monkey toxicity study.

If the PK stopping criteria is met, then dose escalation will be stopped or dose adjustment will be planned, as appropriate.

7.2.5. Safety Dose Adjustment / Stopping Criteria

The GSK DEC will temporarily halt the study based on of the following:

- $CD4^+$ T cell counts below 0.2×10^9/L are considered clinically relevant (BHIVA Guidelines Subcommittee, National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5, NCI-CTCAE) grade 3 or greater) and if sustained for at least 7 days in one participant, this will result in review by the GSK DEC before further participants are dosed.
- CCI [redacted] this will result in review by the GSK DEC before further participants are dosed. NOTE: CCI [redacted] which, in the opinion of the Investigator, can be reasonably attributed to GSK3888130B.
- CCI [redacted] are considered clinically relevant (National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5, NCI-CTCAE) grade 3 or greater). If the CCI [redacted] in the opinion of the Investigator, can be reasonably attributed to GSK3888130B then this will result in review by the GSK DEC before further participants are dosed.
- Clinically significant [National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5, NCI-CTCAE) grade 3 or greater] infusion reactions occurring in one participant.
- As a result of review of safety data at the end of each cohort.
- If one or more participants from any dose level experiences a Serious Adverse Event (SAE) which has a reasonable possibility of relation to GSK3888130B, no further participants will be dosed until a full safety review of the data has taken place.
- If two or more participants in the same cohort experience a 'severe' non-serious adverse reactions which has a reasonable possibility of relation to GSK3888130B, no further participants will be dosed until a full safety review of the data has taken place. 'Severe' non-serious adverse reactions can be either within or not within the same system organ class.

In the event of reaching the stopping criteria, the dose escalation will stop, and no further participants will be dosed. If after consultation the Sponsor deems that dosing can resume at that level or higher the Sponsor will submit an application for a substantial amendment to the Regulatory Agency to present the data and approve a revision to the protocol.

The above criteria will apply even if measured PK parameters are below the pre-specified PK stopping criteria. Every effort will be made to take a blood sample for PK analysis at the time of any of the above events.

7.3. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4. Lost to Follow Up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Safety/Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not be expected to exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Not applicable for this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

8.2.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

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

8.2.3. Electrocardiograms

- Triplicate and single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- If triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.
- Use of Fridericia's formula (QTcF) is preferred in this study. The formula may not be changed or substituted once the participant has been enrolled. Safety ECGs and other non-protocol specified ECGs are an exception.

8.2.4. CCI [redacted]

- CCI [redacted].
- CCI [redacted] will be captured as outlined in the SoA [Section 1.3].

8.2.5. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with abnormal values (above or below the normal range) during participation in the study should be repeated until the values return to normal or baseline or are not considered clinically significant by the Investigator or Medical Monitor.
    - 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.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.6. Injection site Reactions

Symptoms and signs of an infusion reaction include tenderness, warmth, redness at the site of injection or along the vein, and/or itching. More severe reactions may additionally include pain at the site of injection, blistering or skin damage.

Management may consist of discontinuing the infusion (if possible), hot or cold compresses, and analgesia. Treatment will be at the discretion of the Investigator and may include referral for specialist input if there is significant skin injury or symptomatic extravasation.

8.2.7. Hypersensitivity Reactions

As GSK3888130B is a humanised monoclonal antibody, it is considered unlikely that acute allergic reactions will occur in response to exposure; however, all participants should be monitored carefully for evidence of allergic response.

Participants should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, vomiting, or other symptoms that may represent a hypersensitivity reaction to study intervention. It is important to recognize early signs of a hypersensitivity reaction and prevent progression to a severe reaction. In the case of a mild reaction during dosing, study intervention administration may be reinitiated (with appropriate pre-medication) at the discretion of the Investigator.

In the event of a suspected severe acute hypersensitivity reaction or anaphylaxis, sites should manage this at the discretion of the Investigator in accordance with relevant local or national guidelines.

8.2.8. Immunosuppression and Infections

Participants with signs and symptoms suggestive of infection should be treated as clinically indicated according to medical best practice. Blood, sputum, urine, and/or stool cultures will be obtained as appropriate for detection and diagnosis of infection. Blood samples for determination of viral serology ± measurement of viral load (CMV, EBV, VZV) as well as measurement of immunoglobulins, will be taken if the participant demonstrates clinical symptoms consistent with viral reactivation. Serology samples for these viruses will routinely be taken at baseline, midpoint and at end of study as per SoA.

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

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

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

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7.2).

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.

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

- All SAEs will be collected from the signing the inform consent form until the final follow-up visit at the time points specified in the SoA (Section 1.3).
- All SARs to study procedure/GSK products will be reported from the signing of the informed consent form (ICF) until the final follow-up visit at time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the final follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until [redacted] days after the single dose of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female partner of a male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participant's pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.4. Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of GSK3888130B as specified in the SoA (Section 1.3).

- The timing of PK samples may be altered and/or extra samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak serum concentrations) to ensure appropriate monitoring.
- Instructions for the collection, processing and handling of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of GSK3888130B serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these samples.
- Intervention concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Genetics and Pharmacogenomics (PGx)

Genetics are not evaluated in this study.

CCI

CCI

[redacted]

CCI [redacted]

8.7. Biomarkers

8.7.1. Target Engagement Biomarkers

Serum samples will be collected to characterise the effects of GSK3888130B on TE. CCI [redacted] Samples will be collected according to the schedule described in the SoA and as detailed in the SRM.

8.7.2. Blood Biomarkers

Serum samples will be collected to investigate the effect of single doses of GSK3888130B on PD biomarkers.CCI [redacted]. CCI [redacted]. Samples will be collected according to the schedule described in the SoA and as detailed in the SRM.

CCI [redacted]

8.7.4. Cellular Biomarkers

Blood samples will be collected to characterise the effects of GSK3888130B on blood immune cell numbers and phenotypes. Biomarkers may include, but are not limited to, T cell Bcl-2 expression, CCI [redacted]. Samples will be collected according to the schedule described in the SoA and as detailed in the SRM.

CCI [redacted]

CCI [redacted]

8.8. Immunogenicity Assessments

Antibodies to GSK3888130B will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to GSK3888130B and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to GSK3888130B and/or further characterize the immunogenicity of GSK3888130B.

The detection and characterization of antibodies to GSK3888130B will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for GSK3888130B serum concentration to enable interpretation of the antibody data.

Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention.

8.9. Health Economics

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of this study is to assess the safety and tolerability of single IV and SC doses of GSK3888130B in healthy participants. No formal hypotheses are being tested in this study.

9.2. Sample Size Determination

Approximately 54 participants will be recruited to seven single ascending dose cohorts. Five participants will be randomized to either GSK3888130B or placebo in 3:2 ratio in cohorts 1 and 2. Eight participants will be randomized to either GSK3888130B or placebo in 3:1 ratio in all other cohorts, CCI [redacted]

No formal statistical techniques were used to calculate the sample size for this study; it has been determined to allow preliminary assessment of safety, tolerability, PK and PD. However, as a key secondary endpoint, considerations has been given to the ratio to baseline of the PD biomarker Bcl-2. It is assumed that this endpoint is $\log_e$ normally distributed. Based on 6 participants from the highest GSK3888130B dosed cohort and 14 placebo participants pooled across all cohorts, the probability of different true inhibition (GSK3888130B vs. placebo) thresholds of interest is given in the Table below. A non-informative prior distribution and a maximum between participant SD ($\log_e$ scale) of 0.3 is assumed for both GSK3888130B and placebo arms.

True Inhibition thresholds	Probability of Meeting Thresholds Given the Following True Inhibitions
CCI [redacted]	CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted].

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

9.3. Analysis Sets

For the purpose of analysis, following analysis sets are defined:

Analysis Set	Description
Screened	All participants who signed the ICF and are screened for eligibility.
Enrolled	All participants in the Screened analysis set who are entered into the study.
Safety	All participants who received study intervention.
Pharmacokinetic	All participants in the Safety analysis set and who had received an active study intervention and had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).
PD	All participants in the Safety analysis set who had at least 1 post-baseline PD assessment.
CCI	[redacted]

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to first participant first visit (FPFV) and it will include a more technical and detailed description of the statistical analyses described in this Section. This Section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The main statistical analyses will be carried out in the Bayesian framework. Non informative priors will be used for all modelling parameters.

The following summaries of the posterior distribution will be reported: posterior median, 95% equal tailed credible interval, posterior probabilities of the true treatment effect being greater/lower than pre-specified thresholds.

9.4.2. Baseline Definition

The baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 (or Day -1 where applicable) assessments are assumed to be taken prior to dose and used as baseline.

If baseline data is missing, no derivation will be performed, and baseline will be set to missing.

9.4.3. Primary Endpoint(s)

No formal statistical testing will be performed on safety data.

All safety data evaluations will be based on the "Safety" analysis set.

Clinical interpretation will be based upon review of displays of adverse events, laboratory values, vital signs and 12-Lead ECG readings. The principal consideration in this evaluation will be the investigator-reported relationships of adverse events to investigational product.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standard.

9.4.4. Secondary Endpoint(s)

9.4.4.1. Pharmacokinetic parameters

The pharmacokinetic (PK) analyses will be based on the "Pharmacokinetic" analysis set.

Individual serum concentration-time data will be graphically displayed and summary statistics will be produced by time point. Serum GSK3888130B concentration-time data will be analysed by non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study. From the serum concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: area under the concentration-time curve [AUC], maximum concentration [Cmax], time to Cmax [Tmax], half-life [t½], clearance [CL] .

Descriptive statistics (n, arithmetic mean, standard deviation (SD), 95% CI, minimum, median and maximum,) will be calculated for all pharmacokinetic parameters. In addition, for $\log_e$-transformed variables geometric mean, 95% confidence interval (CI), standard deviation on the $\log_e$ scale and $\%CV_b$ will be provided. Full details of planned secondary analysis will be specified in the SAP.

CCI [redacted].

9.4.4.2. Pharmacodynamic and Target Engagement endpoint(s)

The analyses will be based on the "PD" analysis set.

The pharmacodynamic biomarker, T Cell Bcl-2 will be analysed using a Bayesian repeated measures model, including study treatment, visit, study treatment-by-visit interactions and baseline. Non informative priors will be used for all model parameters. An inverse Wishart prior will be used for the within-subject unstructured covariance matrix. Other options may be investigated to determine an appropriate covariance structure in case of issues. If data permits, then a dose response model will be fitted. Full details of planned analysis will be specified in the SAP.

CCI [redacted] will also be analysed as specified above.

CCI [redacted]

9.4.4.3. Other Safety Analyses

The analyses will be based on "Safety" analysis set.

Immunogenicity data will be summarized as the number and percentage of participants with confirmed positive anti-GSK3888130B antibodies and where applicable the titres will be listed.

CCI [redacted]

9.5. Interim Analyses

Prior to each dose escalation, the DEC will review data from a minimum of 2 participants dosed with GSK3888130B (Cohorts 1 and 2) or a minimum of 4 participants dosed with GSK3888130B (all other SAD cohorts). Safety, tolerability (including absolute $CD4^+$ T cell counts) and PK data up to and including Day CCI will be reviewed. Available TE data will also be explored. Further details are described in Section 4.1, Section 6.5 and Section 10.1.5.

In addition, interim analyses will be performed once a minimum of four participants dosed with GSK3888130B in cohort 4 have completed up to and including the Day CCI visit. At this point, in addition to the Sponsor study statistics and programming team members, the study CPMS team (as required) will be unblinded to cohorts 1 to 4 only, in order to provide required outputs to the team. As for the preparation of outputs for the previous dose escalations, the randomisation schedules and unblinded datasets will be stored on internal restricted drives such that the remaining study team members will not be unblinded, unless there is a specific requirement to review individual participants (Section 6.3.1). Safety, tolerability (including absolute $CD4^+$ T cell counts), PK, immunogenicity, TE (total IL-7 assay measurements) and PD (T cell Bcl-2 if feasible) data will be reviewed by the GSK DEC to inform on internal decision-making activities.

Additional interim analyses may be performed during the course of the study to inform internal decision-making activities. No changes to the conduct of the study will be implemented as a result of these analyses.

The SAP will describe the planned interim analyses in greater detail.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:

    i. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

    ii. Applicable ICH Good Clinical Practice (GCP) Guidelines

    iii. Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

- The Investigator will be responsible for the following:

    iv. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC

    v. Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures

    vi. 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 to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant.

- Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3888130B or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3888130B approved for medical use or approved for payment coverage.

The ICF contains a separate Section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate 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.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

A GSK Dose Escalation Committee (DEC) will be in place for this study.

10.1.5.1. Dose Escalation Committee

- The GSK DEC will consist of, at a minimum, the Principal Investigator (or appropriate designee), GSK Medical Monitor, GSK Clinical Sciences representative, CPMS representative, GSK Statistician, GSK Data Quality representative and a GSK Global Safety representative. Additional internal GSK representatives may be consulted and included in the dose escalation decision making, as deemed necessary by the GSK DEC.
- Participant safety will be continuously monitored by the GSK DEC, which includes safety signal detection at any time during the study.
- The GSK DEC will make the decision to proceed to the next dose level of GSK3888130B following review of safety, tolerability (including absolute $CD4^+$ T cell counts), and PK data up to and including Day[redacted] for both IV and SC dosed cohorts as described in Section 4.1 and Section 6.5. Available TE data (total IL-7 levels) will also be explored.
- Safety, PK and PD stopping criteria will be strictly applied. Details of stopping and temporary halt criteria can be found in Section 7.2.
- A Dose Escalation Charter will be written outlining in detail how the study team will ensure data integrity used in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions, as well as outlining the responsibilities of the investigators and site staff for reporting safety data, participation during dose escalation meetings, and confirmation that the data used for dose escalation are accurate and complete.
- If a stopping criterion is met, dose escalation will stop, and no further participants will be dosed at that dose level or any higher level. If after consultation, the Sponsor deems that dosing can resume at that level or higher the Sponsor will submit an application for a substantial amendment to the Regulatory Agency to present the data and approve a revision to the protocol.
- Case unblinding may be performed for above reviews if necessary. The data may be reviewed in an unblinded fashion by the unblinded members of the DEC should a safety concern arise during the blinded review. These unblinded members will be defined within the Dose Escalation Charter.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical Tables, Figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the eCRF instructions.
- Quality tolerance limits (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 and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk

Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- 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 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

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

10.1.10. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	$CD4^+$ T cell Count	CCI [redacted]		
Clinical Chemistry[1]	Urea/BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase[2]	
	CCI [redacted]	CCI [redacted]		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal, or if any other trace is detected)			

Laboratory Assessments	**Parameters**
	• CCI [redacted] described in SRM
Viral quantification and serology	• EBV, CMV and VZV. • SARS-CoV-2 (serology only)
Other Screening Tests	i. Follicle-stimulating hormone and oestradiol (as needed in women of non-childbearing potential only) ii. Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) iii. Serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B core antibody and hepatitis C virus antibody and hepatitis C RNA) iv. Mycobacterium tuberculosis QuantiFERON Gold v. SARS-CoV-2 testing (performed as per site local procedures) vi. Smoking breath test

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5. All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.

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 conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** o In general, hospitalisation 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 hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. o Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• **Results in persistent or significant disability/incapacity** o The term disability means a substantial disruption of a person's ability to conduct normal life functions. o This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may

interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Other situations:**
  - Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
  - Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

1. The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
2. 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.
3. The site will enter the SAE data into the electronic system as soon as it becomes available.
4. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
5. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next Section) or to the medical monitor by telephone.
6. Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

a) Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.

b) In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

c) Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

d) Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

- Postmenopausal female

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

a. A high follicle-stimulating hormone (FSH) level and low oestradiol 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 measurement in line with local thresholds is required.

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

- Male Participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for CCI days after the single dose of study intervention:

- Refrain from donating sperm

Plus either:

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

OR

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

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

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

Phase 1 Liver Chemistry Stopping Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN

If ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, report to GSK as an SAE[1,2].</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>1. Immediately discontinue study intervention
2. Report the event to GSK within 24 hours
3. Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
4. Perform liver event follow up assessments as described in the Follow Up Assessment column.

Do not restart or rechallenge participant with study intervention

5. Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING)

MONITORING:

If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5

6. Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, total bilirubin and INR)</td><td>• Viral hepatitis serology[3]
  • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample(s) for pharmacokinetic (PK) analysis as required, after the most recent dose[4]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant medications on the concomitant medications report form including</td></tr>
</table>

Liver Chemistry Stopping Criteria	
and perform liver event follow up assessments within **24 hours** 7. Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline 8. A specialist or hepatology consultation is recommended **If ALT≥3xULN AND total bilirubin <2xULN and INR ≤1.5:** 9. Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** 10. Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	acetaminophen, herbal remedies, recreational drugs, and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT≥3xULN AND total bilirubin ≥ 2xULN 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. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialists if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected drug induced liver injury (DILI) progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable**, record the absence/presence of detectable urinary bilirubin on dipstick**, which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported **to GSK** as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants

3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody

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. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

10.6. Appendix 6: SARS-CoV-2 Risk Mitigation Participant Counselling

The risk to participants from SARS-CoV-2 is an evolving situation and dependent on factors such as public health measures, vaccination rates and the effectiveness of vaccination against novel variants. As such, it is impossible to predict how the risk to participants may change over the course of this study. The approach to risk mitigation is informed by UK Government guidance and is broadly described below. Any changes to the advice given to participants will be approved by the Principal Investigator and Medical Monitor, with approval from Competent Authority and ethics committee as required.

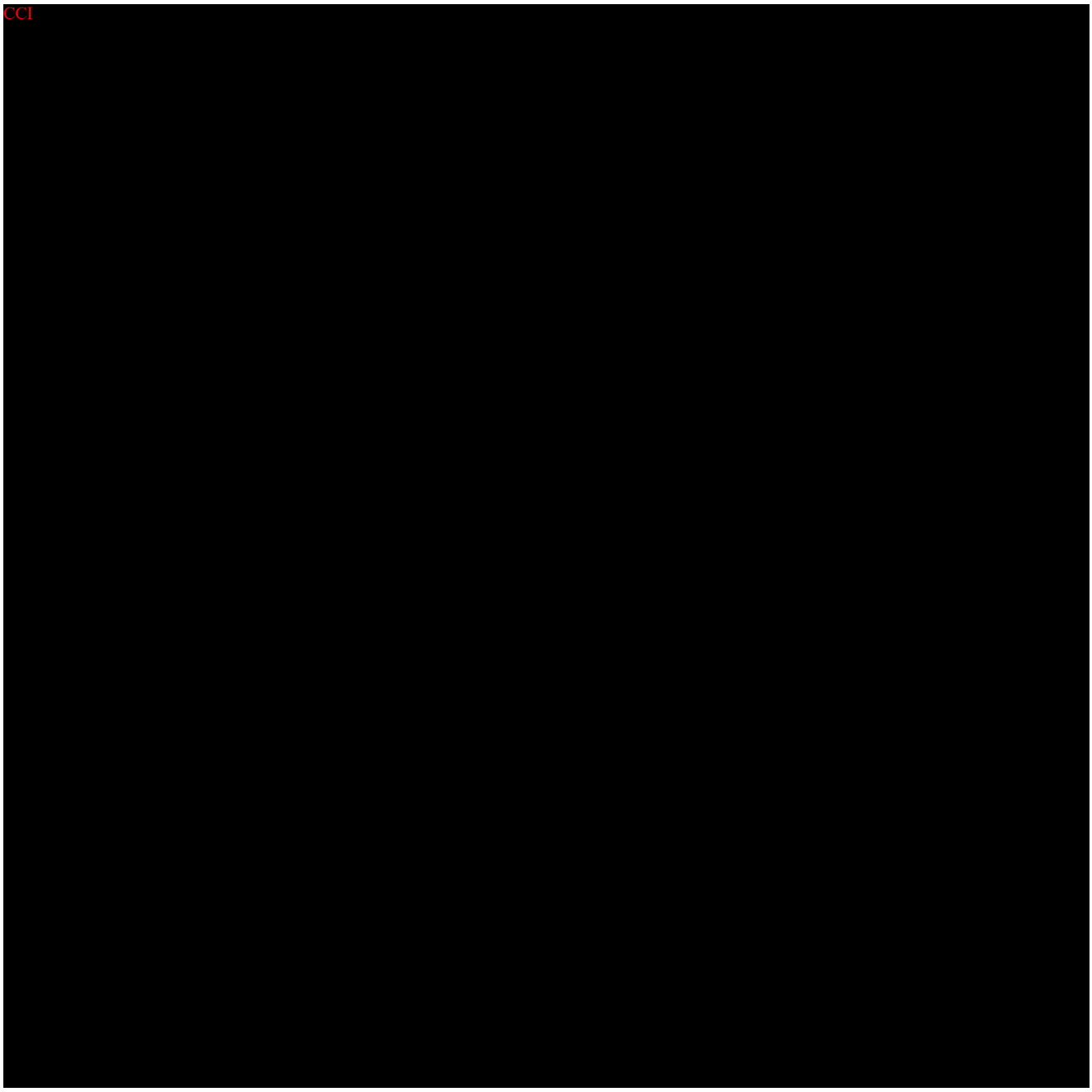
All study participants:

- Given that the extent of immunosuppression caused by GSK3888130B is unknown, there is the potential that prior vaccination may not provide the same level of protection against infection. Furthermore, it is unknown to what extent GSK3888130B might impair the level of protection provided by vaccines (either to a new pathogen, SARS-CoV-2 variant or as a booster) given after exposure to GSK3888130B and before pharmacodynamic markers return to baseline.
- All participants will be counselled that prior vaccination may not be as effective against circulating infections. The risk of infection is considered low based on prior experience, pre-clinical data and because immunosuppression is expected to be minimal in this single dose study. However, all participants should be vigilant of any new or prolonged symptoms which are suggestive of infection.
- In view of the uncertainty of vaccination and potential variants to SARS-CoV-2, participants must agree to adhere to UK government guidance on international travel during the study period.
- Participants who become eligible for booster vaccinations to SARS-CoV-2 are permitted to receive these during the course of the study in accordance with national or local policy. The sole exception to this would be where participants are offered a live vaccine to SARS-CoV-2 (none currently available in the UK), in view of the risk of activate infection. Participants will be counselled that any booster vaccination may provide less protection due to immunosuppression.
- All participants will be instructed to follow the Public Health England guidance on how to stop the spread of SARS-CoV-2 infection (How to stop the spread of coronavirus (COVID-19) - GOV.UK (www.gov.uk)).
- In the event a participant experiences any signs/symptoms of SARS-CoV-2 infection or other potential infectious disease from the start of study until completed follow-up, they will be instructed to call the phase 1 unit as a matter of urgency for further advice/telephone assessment in the first instance. Early referral to the hospital setting will be considered if a participant is experiencing mild COVID-19 symptoms which is progressing. Hospital referral will be made urgently in the event a participant has moderate/severe disease. Participants who become symptomatic after completion of follow-up should seek medical care through standard pathways (e.g., Accident & Emergency, General Practice).

CD4+ T cell counts <$0.2x10^9$/L (from detection to resolution)

- Additional study visits and blood tests may be performed at the discretion of the Investigator until $CD4^+$ T cell counts return to levels >$0.2x10^9$/L
- Advised to follow the Public Health England Guidance for people previously considered clinically extremely vulnerable from COVID-19 - GOV.UK (www.gov.uk):
    - Follow advice you may receive from your doctor
    - Take care to avoid routine coughs, colds, and other respiratory viruses
    - Follow Public Health England guidance for Living safely with respiratory infections, including COVID-19 - GOV.UK (www.gov.uk).

CCI



10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
AIH	Autoimmune Hepatitis
ALT	Alanine Amino Transferase
AMP	Auxiliary Medicinal Product
CCI	[redacted]
AST	Aspartate Amino Transferase
AUC	Area Under the Curve
CCI	[redacted]
BHIVA	British HIV Association
BM	Bone Marrow
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA	Competent Authority
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organisations of Medical Sciences
Cl	Clearance
Cmax	Maximum Concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CONSORT	Consolidated Standards Of Reporting Trials
COVID-19	Coronavirus Disease
CPMS	Clinical Pharmacology Modelling and Simulation
CRF	Case Report Form
CRLF	Cytokine Receptor Like Factor
CSR	Clinical Study Report
CV	Cardiovascular
DEC	Dose Escalation Committee
DEP	Dose Escalation Plan
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
DTH	Delayed Type Hypersensitivity
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

ED	Early Withdrawal
FPFV	First Participant First Visit
FRC	Fibroblastic Reticular Cells
FSH	Follicle Stimulating Hormone
FTIH	First Time In Huma
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hr	Hour
HRT	Hormone Replacement Therapy
HV	Healthy Volunteer
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
CCI	[redacted]
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
ILC	Innate Lymphoid Cells
ILH	Immediate Local Hypersensitivity
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
IV	Intravenous
JAK	Janus kinase
kg	kilogram
CCI	[redacted]
LLN	Lower Limit of Normal
m^2	metres squared
mAb	Monoclonal Antibody
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Cell Volume
mL	millilitre
mm	millimetre
MMR	Measles Mumps Rubella
MS	Multiple Sclerosis
MSDS	Material Safety data sheet
msec	millisecond
MTB	Mycobacterium Tuberculosis

MZ	Marginal Zone
CCI	[redacted]
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NK	Natural Killer
NOAEL	No Observed Adverse Effect Level
NSAID	Non-Steroidal Anti Inflammatory Drug
NSCLC	Non-small cell lung carcinoma
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
CCI	[redacted]
PPMS	Primary Progressive Multiple Sclerosis
CCI	[redacted]
QTcF	QT Interval corrected for heart rate according to Fridericia's formula
QTL	Quality Tolerance Limit
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RRMS	Relapsing Remitting Multiple Sclerosis
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SD	Standard Deviation
SGOT	Serum Glutamic Oxalacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SoA	Schedule of Activities
SPMS	Secondary Progressive Multiple Sclerosis
SRM	Study Reference Manual
STAT	Signal Transducer and Activator of Transcription
SUSAR	Suspected Unexpected Serious Adverse Event
T1/2	Half life
T1D	Type 1 Diabetes
TB	Tuberculosis
TE	Target Engagement
CCI	[redacted]
TLO	Tertiary Lymphoid Organ
Tmax	Time to maximum concentration

CCI [redacted]	[redacted]
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VZV	Varicella Zoster Virus
WBC	White Blood Cell
WOCBP	Women Of Child Bearing Potential
WONCBP	Women Of Non Child Bearing Potential
µg	microgram

Trademark Information

Trademarks of the GSK group of companies
None

Trademarks not owned by the GSK group of companies
Copaxone
ProImmune REVEAL

10.9. Appendix 9: Protocol Amendment History

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

Amendment 05: 25 Jan 2023

Identified in the Table below are substantial changes made to the Study Protocol since the previous submitted version.

Section # and title	Description of change	Brief rationale
Section 2.3.1 Risk Assessment: Reproductive toxicity	CCI [redacted]	CCI [redacted]
Section 5.1 Inclusion criteria: Sex and Contraceptive/Barrier Requirements	CCI [redacted]	CCI [redacted]
Section 8.3.5 Pregnancy	Duration for which details of pregnancies in female partners of male participants will be collected CCI [redacted].	Period of data collection CCI [redacted]
Section 10.4.1: Appendix 4: Contraceptive and Barrier Guidance	CCI [redacted].	CCI [redacted]
Section 1.3.2: Schedule of Activities Intravenous Dosed Cohorts	Included Day 1 into AE & SAE Review	Corrected table formatting to include Day 1 in AE & SAE review to correspond with text in Section 8.3.1. • All AEs will be collected from the start of intervention until the follow-up visit. • All SAEs will be collected from the signing the inform consent form until the follow-up visit.
Section 1.3.2: Schedule of Activities Intravenous Dosed Cohorts	Included Day 1 into Concomitant medication review	Corrected table formatting to include Day 1 in concomitant medication review to correspond with text in Section 6.8. • Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or

Section # and title	Description of change	Brief rationale
		herbal supplements) that the participant receives during the study must be recorded.

Amendment 4 03 Nov 2022

Identified in the Table below are substantial changes made to the Study Protocol since the previous submitted version.

Section # and title	Description of change	Brief rationale
Section 1.3 Schedule of Activities	Additional CCI [redacted].	Updated to CCI [redacted]
Section 3 Objectives and Endpoints	Additional exploratory objective and related endpoints added.	CCI [redacted] CCI [redacted].
Section 2.3 Benefit/ Risk Assessment: Renal,	CCI [redacted].	CCI [redacted].
Section 2.3 Benefit/ Risk Assessment: haemotological	Minor change to existing text.	Grammatical correction.
Section 2.3 Benefit/ Risk Assessment: CCI [redacted]	The statement 'there have been no CCI [redacted] has been corrected to 'there have been no CCI [redacted] CCI [redacted]	Location correction of adverse event.

Section # and title	Description of change	Brief rationale
Section 2.3 Benefit/ Risk Assessment: [redacted]	[redacted] was moved to the appropriate section [redacted]).	Location correction of adverse event.
Section 8.7 Biomarkers	Addition of Section 8.7.3 [redacted].	Included to provide instruction for collection and storage of [redacted] for assessment of [redacted].

Amendment 3 [05 August 2022]

Identified in the Table below are substantial changes made to the Study Protocol since the previous submitted version.

In addition, minor typographical errors and inconsistencies have been corrected and minor formatting changes have been made.

Section # and title	Description of change	Brief rationale
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities	[redacted]. Updated number of participants and recruitment cap included. Recruitment statement added. Description of procedures, samples to be taken, change in Schedule of Activities updated to include Day[redacted] activities for IV cohorts and to specify [redacted]	[redacted]
Section 2.1 Study Rationale Section 2.2 Background	[redacted]. [redacted]	[redacted]

Section # and title	**Description of change**	**Brief rationale**
Section 2.3 Benefit/ Risk Assessment	Updated GSK3888130B risks relating to dose selection, infection/lymphopenia, immunogenicity and malignancy. CCI [redacted].	CCI [redacted].
Section 3 Objectives and Endpoints	CCI [redacted].	Additional tertiary/exploratory/other objectives and endpoints included.
Section 4. Study Design	CCI [redacted]. Description of procedures, samples to be taken, change in Schedule of Activities updated to include Day CCI activities for IV cohorts and to specify CCI [redacted]. Scientific rationale and CCI [redacted].	CCI [redacted]

Section # and title	**Description of change**	**Brief rationale**
Section 5. Study Population	Additional inclusion and exclusion criteria added on CCI [redacted]	To specify requirements for CCI [redacted]
Section 6. Study Intervention	Inclusion of CCI [redacted] CCI [redacted]	Update to include details of challenge agents for the CCI [redacted]
Section 8. Study Assessments	CCI [redacted] CCI [redacted]	CCI [redacted]
Section 9. Statistical Considerations	Increased the participants and included a justification	Updated to reflect CCI [redacted]

Amendment 2 [10 February 2022]

Identified in the Table below are substantial changes made to the Study Protocol since the previous submitted version.

In addition, non-substantial clarifications have been made to Section 1.3.2 and Section 1.3.3 to formalise the pre-dose PK sampling in the schedule of activities. In addition, minor typographical errors and inconsistencies have been corrected and minor formatting changes have been made.

Section	Current text	Proposed text	Rationale for change
Section 2.3.1 Risk Assessment		CCI [redacted] **against GSK3888130B; a humanized monoclonal antibody.** **We do not know whether this finding might also occur in humans. Risk mitigation will be implemented in this study to further characterize this risk.** **Mitigation strategy:** **<u>Exclusion:</u> Participants must be overtly healthy to participate in this study and will be excluded if they have abnormal blood tests or a medical history of autoimmunity.** **<u>Monitoring</u>:** • **Participants will be closely monitored for signs of** CCI [redacted] **including regular**	New risk added to Risk Assessment Table based on pre-clinical finding of CCI [redacted].

Section	Current text	Proposed text	Rationale for change
		CCI [redacted]. • **A validated ADA assay (screening, confirmation, and titration methods) will be used in this study.**	
Section 7.2.5 Safety Dose Adjustment / Stopping Criteria		CCI [redacted] **are considered clinically relevant (National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5, NCI-CTCAE) grade 3 or greater).** CCI [redacted] **, in the opinion of the Investigator, can be reasonably attributed to GSK3888130B then this will result in review by the GSK DEC before further participants are dosed.**	New stopping criterion added based on CCI [redacted]
Section 9.5 Interim Analysis	Safety, tolerability (including absolute $CD4^+$ T cell counts), PK, CCI [redacted]) and PD (T cell Bcl-2) data will be reviewed by the GSK DEC to inform on internal decision-making activities.	Safety, tolerability (including absolute $CD4^+$ T cell counts), PK, CCI [redacted], CCI [redacted] and PD (T cell Bcl-2) data will be reviewed by the GSK DEC to inform on internal decision-making activities.	CCI [redacted]
Section 10.2 Appendix 2: Clinical Laboratory Tests		Table 1 Protocol-Required Safety Laboratory Tests: CCI [redacted] CCI [redacted]	CCI [redacted] added to laboratory assessment Table. Update

Section	Current text	Proposed text	Rationale for change
			made to increase monitoring for [redacted]

Amendment 1 [27 September 2021]

Identified in the Table below are substantial changes made to the Study Protocol since the previous submitted version. Deleted text is formatted in ~~strikethrough~~ and added text is formatted in **bold**.

Section	Current text	Proposed text	Rationale for change
Section 1.1. Synopsis	To characterise the effects of GSK3888130B on target engagement.	To characterise the effects of GSK3888130B on target engagement **(TE)**.	Abbreviation for target engagement added, abbreviation used throughout the protocol
Section 1.1 Synopsis & Section 1.3 Schedule of Assessments & Section 4.1 Overall design	All participants will then be required to attend the clinic for up to [redacted] outpatient visits over the course of [redacted] days after dosing for safety assessment and sample collection, and will receive a follow-up telephone call [redacted] days post last study visit. If required, additional follow-up visits may be scheduled.	All participants will then be required to attend the clinic for up to [redacted] outpatient visits over the course of [redacted] days after dosing for safety assessment and sample collection, and will receive a follow-up telephone call [redacted] days post last study visit. If required, additional follow-up visits may be scheduled.	Extended the follow-up phone call to [redacted] days to cover [redacted] Updates made throughout the protocol where applicable.
1.1. Synopsis & Section 4.1 Overall design	The total duration of the study for each participant will be approximately [redacted] weeks.	The total duration of the study for each participant will be approximately [redacted] weeks.	Revised total duration to reflect the change in timing of follow-up telephone call
Section 1.3.1 Screening, admission and follow-up	Applicable to IV cohorts [redacted] hr ~~baseline~~ reading required prior to dosing.	Applicable to IV cohorts [redacted] hr reading **during screening period is** required prior to dosing.	Revised to clarify that this will be used for screening participants, and not for baseline
Section 1.3.2 Intravenous dosed cohorts	Recording to be started [redacted] pre-dose.	Recording to be started [redacted] pre-dose.	[redacted] revised to increase duration of baseline data collection.
Section 2.3.1. Risk assessment		**Potential risk: Dose selection**	New risk added to Risk Assessment

Section	Current text	Proposed text	Rationale for change
		Rational for risk: The first dose level (Cohort 1) of GSK3888130B is anticipated to have clinically insignificant biological activity, with the rationale for dose selection explained in Section 4.3. There is a risk that the first dose level may have greater pharmacological activity than predicted. If this is the case, then the risks outlined in this risk assessment may be increased. **Mitigation strategy:** **Monitoring: Participants undergo inpatient monitoring following IMP administration.** **Sentinel dosing is utilised for all cohorts.** **Dose modification: Dose escalation decisions are based on review of safety, tolerability and PK data. Available TE data will also be explored during dose escalation decisions.** **Dosing schedule may be modified within defined exposure limits.**	Table to clarify that the first dose of IMP (Cohort 1) may have pharmacological activity.
Section 2.3.1. Risk assessment	Male participants will be required to refrain from intercourse or use a condom, avoid semen exposure to a women of child bearing potential (WOCBP), and refrain from donating sperm for[redacted] days.	Male participants will be required to refrain from intercourse or use a condom, avoid semen exposure to a women of child bearing potential (WOCBP), and refrain from donating sperm for [redacted] days.	Contraception requirements [redacted]
Section 4.2 Scientific rational for study design	The study includes both IV and SC administration in separate cohorts to evaluate pharmacokinetics for the two routes. For SC administration, a lower and	The study includes both IV and SC administration in separate cohorts to evaluate pharmacokinetics for the two routes. For SC administration, a lower and a	Revised to clarify the rationale for interspersing SC dosing cohorts

Section	Current text	Proposed text	Rationale for change
	a higher dose level is selected as per feasible drug administration within the proposed dose range with the higher SC dose limited by the volume of administration. The IV route of administration was selected for the initial dosed cohorts to enable monitoring of early safety signals during infusion. The dose escalations have been planned to ensure that exposure increments remain consistent between ascending dose levels/cohorts based on PK exposure predicted from pre-clinical data.	higher dose level is selected as per feasible drug administration within the proposed dose range with the higher SC dose limited by the volume of administration. CCI [redacted] The IV route of administration was selected for the initial dosed cohorts to enable monitoring of early safety signals during infusion. **SC cohorts are interspersed with IV cohorts to minimise the number of subjects who are exposed to GSK3888130B**. The dose escalations have been planned to ensure that exposure increments remain consistent between ascending dose levels/cohorts based on PK exposure predicted from pre-clinical data **(see Section 4.3.2)**.	with IV dosing cohorts
Section 4.1 Overall design Section 4.2 Scientific rational for study design, Section 6.5 Dose modification & Section 10.1.5 Committees and structure	Available TE data will also be explored.	Available TE data **(total IL-7 levels)** will also be explored.	Clarity provided to define what TE data may be available for review (total IL-7 levels).

Section	Current text	Proposed text	Rationale for change
Section 4.3.1 Human dose prediction	The model was extrapolated to human, by scaling PK parameters using allometry and CCI [redacted] The extrapolated model was then used to predict the dose-response relationships for human PK, the associated exposure safety margin in relation to the NOAEL in the monkey, and the suppression of CCI [redacted] in human blood.	The model was extrapolated to human, by scaling PK parameters using allometry and CCI [redacted]. The extrapolated model was then used to predict the dose-response relationships for human PK, the associated exposure safety margin in relation to the NOAEL in the monkey, and the suppression of CCI [redacted] in human blood.	Updated to provide additional information on antibody CCI [redacted] used to support dose prediction between IV and SC cohorts
Section 4.3.2 Dose escalation plan	It is anticipated that the CC[redacted] mg starting dose will result in suppression ~~of~~CCI [redacted]. ~~This~~ low biological effect is considerably below the level of Bcl-2 suppression previously observed in humans with RN168 and Copaxone. The starting dose of CC[redacted] mg is supported by PK-PD modelling and simulation which suggest adequate safety margins in relation to the NOAEL CCI [redacted] found in the 4-week toxicology study in monkeys (see Table below).	It is anticipated that the CC[redacted] mg starting dose will result in CCI [redacted] previously observed in humans with RN168 and Copaxone. **The starting dose of CC[redacted] mg is deemed appropriate for healthy volunteers given the low risk for off-target toxicity, the existing knowledge of the target pathway in human, and the high pharmacology and safety relevance of the pre-clinical species (outlined above in this Section).** The starting dose of CC[redacted] mg is **further** supported by PK-PD modelling and simulation which suggest adequate safety margins in relation to the NOAEL (CCI [redacted]) found in the 4-week toxicology study in monkeys (see Table below).	Updated to clarify the rationale to support the starting dose

Section	Current text	Proposed text	Rationale for change
Section 4.3.3 Predicted plasma exposure, safety margins, target engagement (IL-7 reduction) and pathway pharmacology (Bcl-2 reduction)	[$]Ratios based on total exposure at NOAEL of CCI mg/kg/wk IV in 4-wk monkey study: AUC CCI µg/mL*h and Cmax CCI µg/mL	[$]Ratios based on total exposure at NOAEL of CCI mg/kg/wk IV in 4-wk monkey study: AUC CCI µg/mL*h and Cmax CCI µg/mL **AUC=AUC from time 0 extrapolated to infinity. Cmax = maximum concentration**	Definition added in footnote for AUC and Cmax
Section 5.1 Inclusion criteria & Section 10.4 Contraceptive and barrier guidance	Male participants are eligible to participate if they agree to the following during the study intervention period and for CCI days after the single dose of study intervention: ○ Refrain from donating ~~fresh unwashed semen~~	Male participants are eligible to participate if they agree to the following during the study intervention period and for CCI days after the single dose of study intervention: ○ Refrain from donating **sperm** Sperm donation not permitted to eliminate risks due to potential exposure of IMP	Contraception requirements extended to CCI [redacted] Sperm donation not permitted to eliminate risks due to potential exposure of IMP
Section 7.2.5 Safety dose adjustment / stopping criteria	• If one or more participants from any dose level experiences a Serious Adverse Event (SAE) which has a reasonable possibility of relation to GSK3888130B, no further participants will be dosed until a full safety review of the data has taken place.	• If one or more participants from any dose level experiences a Serious Adverse Event (SAE) which has a reasonable possibility of relation to GSK3888130B, no further participants will be dosed until a full safety review of the data has taken place. • **If two or more participants in the same cohort experience a 'severe' non-serious adverse reactions which has a reasonable possibility of relation to GSK3888130B, no further participants will be dosed until a full**	Additional stopping criteria added per EMA guidance for First-in-Man trials.

Section	Current text	Proposed text	Rationale for change
		safety review of the data has taken place. 'Severe' non-serious adverse reactions can be either within or not within the same system organ class.	

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