TITLE PAGE

Protocol Title: A 52-week, phase 3, multicentre, randomised, double blind, efficacy and safety study, comparing GSK3196165 with placebo and with tofacitinib in combination with conventional synthetic DMARDs, in participants with moderately to severely active rheumatoid arthritis who have an inadequate response to conventional synthetic DMARDs or biologic DMARDs.

Protocol Number: 201791 / Amendment 02

Compound Number: GSK3196165

Compound Name: Otilimab

Study Phase: Phase 3

Short Title: Efficacy and safety of GSK3196165 versus placebo and tofacitinib in participants with moderately to severely active rheumatoid arthritis who have an inadequate response to conventional synthetic/biologic DMARDs.

Study Name: contRAst-2

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND: 121958

EudraCT: 2019-000867-26

Approval Date: 21-JAN-2020

SPONSOR SIGNATORY:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	21-JAN-2020	2018N385740_02
Amendment 1	22-MAY-2019	2018N385740_01
Original Protocol	06-MAR-2019	2018N385740_00

Amendment 2: 21-JAN-2020

Overall Rationale for the Amendment: (1) To detail revised risks, entry and stopping criteria following the update to comparator drug (tofacitinib) label; (2) To introduce new medical device safety reporting wording, required in advance of roll out of pre-filled syringes to this study. (3) Other minor corrections and clarifications.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis	Addition of time points to safety and tolerability endpoint & update to Number of Participants section, to clarify key Asian country subgroup.	To reflect the updates in body of protocol (detailed below).
Section 1.3 Schedule of Activities (SoA)	Updated SoAs: remove fasting requirement for lipid test; clarify ECG requirement; refer to SAE section for reporting times at screening; and add urine pregnancy test at safety f/u.	Clarifications and reflect updates in body of protocol.
Section 2.3.1 Risk Assessment	Injection site reaction mitigation strategy - recommend to rotate sites.	Clarification.
	Tofacitinib risks and mitigation strategy updated.	Recent safety update for tofacitinib label.
	Handling and usage risks associated with the prefilled syringe devices.	Addition to align with introduction of prefilled syringes.
Section 3 Objectives and Endpoints	Addition of time points to safety and tolerability endpoint.	Clarification.
Section 5 Study Population	Addition of reference to EULAR recommendations for vaccination.	Provide guidance for countries where no local guidelines exist.
Section 5.1 Inclusion Criteria	Clarification of inclusion criteria 7, permitting prior bDMARD exposure.	Clarification.
Section 5.2 Exclusion Criteria	Updates to exclusion criteria 12 and 13.	Due to recent safety update for Tofacitinib label.
	Exclusion 12: Reduce myocardial infarction exclusion to 3 months.	3 months is considered to be appropriate to stabilise ischemic heart disease.
	Change to exclusion criteria 24 to remove exclusion of participants with prior *non-JAKi* tsDMARD treatment.	Not necessary to exclude prior *non-JAKi* tsDMARD treatment.
Section 5.4 Screen Failures	Update to clarify implications of a positive repeat TB test.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 6.1.1 Medical Devices	Description of pre-filled syringes (medical devices) used in the study.	To comply with new regulatory requirements.
Section 6.5.1 Permitted Therapies, Table 2	Permit PRN use of NSAIDs and weak opioids except 24hr before assessment visits, and permit PRN use of strong opioids after week 12, except 24hr before assessment visits.	Clarification to make clear how PRN use is managed.
	Addition of Hyaluronic acid and associated restrictions.	To clarify and align with clinical practice.
Section 6.5.2 Prohibited Therapies, Table 3	Removal of marijuana from prohibited list and update to vaccination recommendations wording.	To clarify and align with clinical practice.
	Update of tsDMARD restrictions and clarify duration of exclusion.	Clarification and reflect changes to exclusion 24.
Section 7.1.2 Other Stopping Criteria	Updates to permanent stopping criteria including discontinuation due to VTE, PE and DVT.	Recent safety update for Tofacitinib per local label.
	Permit permanent discontinuation due to a significant medical event, at discretion of investigator.	Clarification.
Section 7.1.3.3 Haematologic Abnormalities	Clarification of local confirmatory test requirement.	Clarification.
Section 7.1.3.5 Renal Abnormalities	Addition of reassessment renal test	Risk mitigation
Section 8.2.7.2 Tuberculosis Testing	Addition of unscheduled TB testing if participant has been in contact with someone who has untreated active TB	To mitigate risk further
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Clarification that SAE collection is from beginning of study intervention (except in China, or if related to study participation).	Clarification of safety reporting requirements.
Section 8.3.8 Medical Device Deficiencies	Added sections covering the reporting and follow-up of medical device deficiencies.	To comply with new regulatory requirements.
Section 8.4 Treatment of Overdose	Clarify definition, require documentation to be handled by unblinded CRA.	Clarification.
Section 9.2 Sample Size Determination	Update to more clearly explain that key Asian country subgroup may continue to be recruited after study target reached.	Clarification.
Section 9.6 Interim Analyses	Interim analysis wording updated to describe how the key Asian country subgroup will be analysed.	Clarification.
Section 10.1.8 Data Quality Assurance	Addition of eCOA quality wording.	Clarification
Section 10.2: Clinical Laboratory Tests	Removal of fasting requirement for lipid tests.	Not considered necessary, so remove fasting requirement to minimise unnecessary inconvenience to participants.

Section # and Name	Description of Change	Brief Rationale
	Permit final assessment visit values of hsCRP & ESR to be provided to site.	These are baseline for LTE and are not individually unblinding.
Section 10.3: Adverse Events: definitions and procedures for Recording, Evaluation, Follow-up and Reporting	Explain that this section is for AEs and SAEs which are not related to medical devices, and reference to Appendix 9 for medical device incidents.	To enable addition of medical device incidents appendix.
Section 10.9: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and procedures for Recording, evaluating, Follow-up and reporting	Addition of medical device adverse effects reporting appendix.	To comply with new regulatory requirements.
All sections	Other minor, grammatical and typographical corrections to improve readability.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A 52-week, phase 3, multicentre, randomised, double blind, efficacy and safety study, comparing GSK3196165 with placebo and with tofacitinib in combination with conventional synthetic DMARDs, in participants with moderately to severely active rheumatoid arthritis who have an inadequate response to conventional synthetic DMARDs or biologic DMARDs.

Short Title: Efficacy and safety of GSK3196165 versus placebo and tofacitinib in participants with moderately to severely active rheumatoid arthritis who have an inadequate response to conventional synthetic/biologic DMARDs.

Rationale: The aim of this study is to determine the efficacy and safety of GSK3196165, in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to csDMARDs or biologic DMARDs (bDMARDs). Two doses of GSK3196165 (90 mg subcutaneous [SC] weekly and 150 mg SC weekly) will be compared with placebo (to Week 12) and with tofacitinib (5 mg twice daily [BID]), an inhibitor of Janus Kinase (JAK) that is approved for the treatment of adults with moderately to severely active RA who have had an inadequate response to cs/bDMARDs.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of GSK3196165 at doses of 90 mg and 150 mg weekly versus placebo for the treatment of participants with moderately to severely active RA who are on a stable background of csDMARDs and who have had an inadequate response to csDMARDs or bDMARDs.	• Proportion of participants achieving ACR20 at Week 12
Secondary	
To compare: • Efficacy of GSK3196165 at doses of 90 mg and 150 mg weekly versus tofacitinib for the treatment of participants with moderately to severely active RA who are on a stable background of csDMARDs and who have had an inadequate response to csDMARDs or bDMARDs	**Major Secondary Efficacy Endpoints** Week 12 versus placebo: • Proportion of participants achieving CDAI total score ≤10 (CDAI LDA). • Change from baseline in HAQ-DI. Non-inferiority versus tofacitinib at Week 12: • Proportion of participants achieving ACR20.

Objectives	Endpoints
	Other Secondary Efficacy Endpoints Week 12 (vs. placebo and vs. tofacitinib), Week 24 and Week 52 (vs. tofacitinib): Proportion of participants achieving: • CDAI total score ≤10 (CDAI LDA). • CDAI total score ≤2.8 (CDAI Remission). • ACR20/50/70. • DAS28-CRP ≤3.2 and DAS28(ESR) ≤3.2 (DAS28 LDA). • DAS28-CRP <2.6 and DAS28(ESR) <2.6 (DAS28 Remission). • A good/moderate EULAR response. • ACR/EULAR Remission. • No radiographic progression defined as a change from baseline in van der Heijde mTSS score of ≤0.5. Change from baseline in: • CDAI total score. • DAS28-CRP/DAS28-ESR. • van der Heijde mTSS.
• Effect of GSK3196165 on Patient Reported Outcomes (PROs) versus placebo and the active comparator tofacitinib	Change from baseline at Week 12 (vs. placebo and vs. tofacitinib), Week 24 and Week 52 (vs. tofacitinib) in: • HAQ-DI. • Arthritis pain VAS. • SF-36 physical and mental component scores, and domain scores. • FACIT-Fatigue.
• Safety and tolerability of GSK3196165 versus placebo and the active comparator tofacitinib	• Incidence of AEs, SAEs and AESIs. • Change from baseline in key laboratory parameters at Weeks 12, 24 and 52. • Proportion of participants with NCI-CTCAE ≥Grade 3 haematological/clinical chemistry abnormalities.
• To determine the immunogenic potential of GSK3196165	**Safety Biomarker Endpoints** • GM-CSF autoantibody concentrations. • Anti-GSK3196165 antibodies.

csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; bDMARDs = biologic disease-modifying antirheumatic drugs; ACR2050/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; CDAI = clinical disease activity index; HAQ-DI = health assessment questionnaire disability index; VAS = visual analogue scale; LDA = low disease activity; DAS28 = disease activity score including 28 different joints; CRP = C-reactive protein; EULAR = European league against rheumatism; ESR = erythrocyte sedimentation rate; mTSS = modified total sharp score; AEs = adverse events; SAEs = serious adverse events; AESIs = adverse events of special interest; NCI-CTCAE = National Cancer Institute-common terminology criteria for adverse events; SF-36 = short form-36; FACIT = functional assessment of chronic illness therapy; RA = rheumatoid arthritis; GM-CSF = granulocyte-macrophage colony stimulating factor.

Overall Design: This is a double-blind, parallel group, multicentre, placebo and active comparator-controlled study of the efficacy and safety of GSK3196165 in participants with moderately to severely active RA who have had an inadequate response to cs/bDMARDs. The study consists of a screening phase of up to 6 weeks, a 52-week treatment phase and an 8-week safety follow-up visit. Upon successful screening, participants will be randomised to one of six intervention arms. Participants who complete this study may be eligible to participate in a long-term extension study to further evaluate the efficacy and safety of GSK3196165.

Disclosure Statement: This is a parallel group treatment study with 6 arms that is participant, investigator and outcomes assessor blinded.

Number of Participants: Approximately 3000-3600 participants will be screened to achieve between 1500 and 1800 randomly assigned to study intervention. Approximately 1500 evaluable participants are expected to be included in the primary analysis, of whom approximately 1350 are expected to complete the Week 12 visit. When the approximate target of 1500 participants is reached, recruitment may continue up to a maximum of 1800 participants to ensure sufficient numbers in the key Asian country subgroup.

The sample size calculation is provided in Section 9.2.

Intervention Groups and Duration:

Participants will be randomised in a ratio of 6:6:3:1:1:1 to GSK3196165 150 mg SC weekly, GSK3196165 90 mg SC weekly, tofacitinib capsules 5 mg BID or placebo (3 arms) respectively, all in combination with csDMARD(s). At Week 12, the 3 placebo arms will switch from placebo to active intervention (either GSK3196165 150 mg SC weekly, GSK3196165 90 mg SC weekly, or tofacitinib capsules 5 mg BID). Randomisation will be stratified by previously failed medication (csDMARD only, 1 bDMARD or >1 bDMARD).

A separate randomisation cohort in addition to the main randomisation may be utilised for the key Asian country subgroup, in order to allow separate analyses for these countries if required.

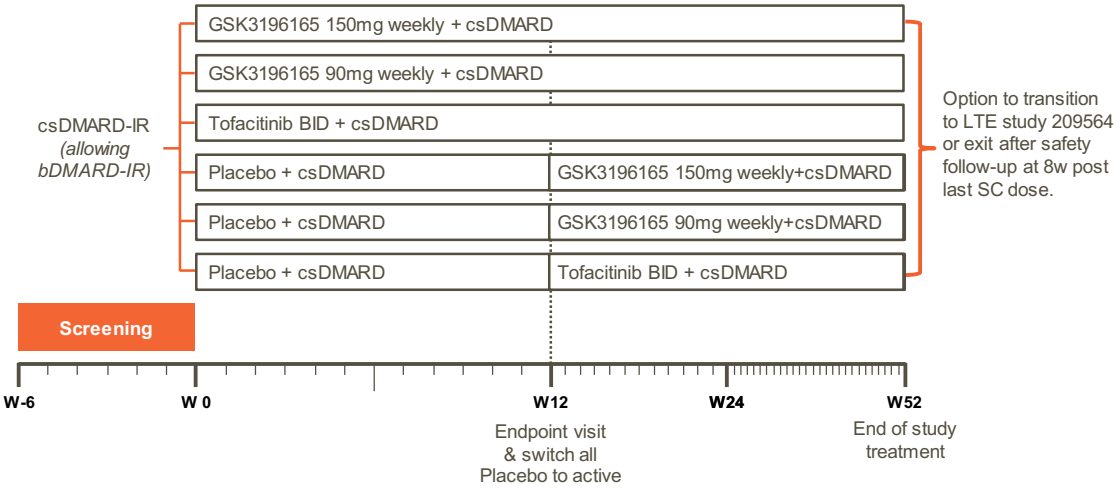
The total treatment period is 52 weeks, with an 8-week safety follow-up period after the last SC dose of study intervention for those participants who do not continue into the long term-extension study.

Independent Data Monitoring Committee: Yes.

Major Adverse Cardiac Event/Gastrointestinal Perforation Adjudication Committee: Yes.

Pulmonary Adjudication Committee: Yes.

1.2. Schema



1.3. Schedule of Activities (SoA)

See Section 8 for further details of study procedures listed in the SoA.

Order of Assessments:

- PROs should be completed first, before any other assessments, procedures or consultations, to avoid influencing participants' perception.
- Where possible, joint counts should follow PRO completion. PhGA should then take place, followed by other assessments (including safety), ECGs, vital signs and blood draws, before dosing.
- PK sampling and blood draws must always take place before dosing.

Study SC Dosing and Visit Schedule:

- Study SC injection should be administered weekly, on the same day each week.
- A window of ±2 days is acceptable for the SC injection (minimum gap of 5 days between each dose, for no more than 2 consecutive doses). Participants should return to their 7 day dosing schedule as soon as possible thereafter. See Section 6.1 for further information.
- Where possible, assessment visits should be scheduled to coincide with the weekly administration of study SC injection, **the injection will then be performed at the site, after completion of PK sampling**.
- The study SC injection must be performed at site on Weeks 0, 1, 12 and 13, after completion of study assessments, and participants must be monitored for 1 hour post dose.

SoA – Screening Period

	Participant Screening Task List (after informed consent, all screening assessments must be completed within the 42 days prior to Randomisation) Day -42 to Day -1 ↓	**Screening assessment notes**
	Informed Consent and optional Genetics consent	1) ECGs should be performed before vital signs and blood draws. 2) Joint assessments should be performed by an independent assessor. Where possible the same assessor should perform all joint assessments for an individual participant. 3) Will be read centrally & imaging CRO will assess presence or absence of erosion(s). 4) Unless performed within previous 12 weeks. 5) For women of child-bearing potential. 6) Fasting is not required, but 6hr fasting status at time of blood draw must be noted on requisition form. 7) See Section 8.3.1 for the time period of SAE collection, which varies between countries. See Section 5.4 for screen failures and rescreening.
	Inclusion/exclusion criteria	
	Participant Demographics	
	Medical, disease and therapy history	
	Review of asthma/COPD/pulmonary disease history	
	Concomitant Medication Review	
Assessments	Triplicate 12-lead ECG[1]	
	Vital signs	
	Full Physical Exam	
	Dyspnoea & Cough assessment, Lung Auscultation, Pulse Oximetry	
	TB evaluation	
	SAE assessment[7]	
	Swollen (66) & Tender (68) joint count[2]	
	Hands and feet X-ray[3]	
	Chest X-ray (posteroanterior)[4]	
Labs	Haematology, Chemistry, Urinalysis (dip stick)	
	HIV, TB, Hepatitis B & Hepatitis C screen	
	hsCRP	
	Serum pregnancy test[5]	
	Lipid profile[6]	

SoA – Treatment Period

		Study intervention GSK3196165 vs tofacitinib vs placebo (W0-11)								Study intervention GSK3196165 vs Tofacitinib (W12-52)											
	Week	0	1	2	3	4	5-7	8	9-11	12	13	14-15	16	17-23	24	25-35	36	37-47	48	49-51	52
	Assessment visit Day / **Study activities**[1]	**Baseline** Day 1	Day 8 (±2d)	Day 15 (±2d)	Day 22 (±2d)	Day 29 (±2d)		Day 57 (±2d)		**Primary endpoint** Day 85 (±3d)	Day 92 (±3d)		Day 113 (±5d)		Day 169 (±7d)		Day 253 (±7d)		Day 337 (±7d)		**End of treatment** Day 365 (± 7d)
	Randomisation	X																			
PROs[1]	Arthritis pain VAS, PtGA, HAQ-DI	X	X	X		X		X		X	X		X		X		X				X
PROs[1]	CCI [redacted]																				
PROs[1]	FACIT-Fatigue, SF-36, CCI [redacted]	X				X				X			X		X		X				X
Assessments	12-lead ECG[2] (S=single, T=triplicate)									S											T
Assessments	Vital signs	X		X		X		X		X	X		X		X		X				X
Assessments	Brief Physical Exam	X		X						X	X		X		X		X				X
Assessments	Dyspnoea & Cough assessment, Lung Auscultation, Pulse Oximetry	X	X	X		X		X		X	X		X		X		X				X
Assessments	Pulmonary function tests (FEV_1, FVC)	X[17]																			
Assessments	Swollen (66) & Tender (68) joint count[3]	X	X	X		X		X		X	X		X		X		X				X
Assessments	Physician Global Assessment[4]	X	X	X		X		X		X	X		X		X		X				X
Assessments	Hands and Feet X-ray[5]									X					X						X
Assessments	Chest x-ray (posteroanterior)																		X[6]		
Labs and blood draws	Haematology, Chemistry, Urinalysis	X		X		X		X		X	X		X		X		X		X		X
Labs and blood draws	Lipid profile[7]					X							X								X[7]
Labs and blood draws	Urine pregnancy test[8]	X				X		X		X			X		<------ Every 8 weeks ------>						X
Labs and blood draws	hsCRP, ESR[9]	X	X	X		X		X		X	X		X		X		X				X
Labs and blood draws	RF, ACPA (anti-CCP)	X																			
Labs and blood draws	TB testing																		X		
Labs and blood draws	Pre-dose PK sample (& GMCSF complex)			X		X		X		X			X		X		X				X
Labs and blood draws	Immunogenicity blood sampling	X[10]		X		X				X			X		X		X				X
Labs and blood draws	CCI [redacted]																				
Dose	Dispense: Weekly SC injection[13,14]	X[13]	X[13]	X	<---------- X[14] ---------->					X[13]	X[13]	<---------- X[14] ---------->									
Dose	Dispense: BID oral intervention[15]	X				X		X		X			<---------- Every 4 weeks ---------->								
	SAE/AE review[16]	<---------- X ---------->																			
	Concomitant medication review[16]	<---------- X ---------->																			
	AE/conmed phone call **if no site visit**[16]	Weekly to Week 12								Every two weeks to W36, every four weeks to W52											

Notes

1. PROs should be completed first, before any other assessments, procedures or consultations, to avoid influencing participants' perception.
2. ECGs should be performed before vital signs and blood draws, where possible.
3. Joint assessments should be performed by an independent assessor. Where possible the same assessor should perform all joint assessments for an individual participant.
4. Where possible, the same individual should perform all physician global assessments for an individual participant.
5. Will be centrally read & assessed for presence or absence of erosion(s).
6. Schedule X-ray between Weeks 48-51.
7. Fasting is not required, but 6hr fasting status at time of blood draw must be noted on requisition form.
8. For women of child-bearing potential.
9. ESR measured locally (using kit provided) by unblind site staff.
10. Day 1 sample includes anti-GM-CSF auto-antibody and free GM-CSF analysis.

CCI [redacted]

13. Monitor participants for 1 hour after SC dosing **at site** at Weeks 0, 1, 12 and 13. SC injection must be administered **at site** when dosing on assessment visit days.
14. Dispense weekly for site administration; OR if available, dispense PFS in boxes of 4, every 4 weeks, for home SC dosing.
15. Dispense 2 bottles of oral intervention every 4 weeks.
16. Minimum weekly review to Week 12, then every two weeks to Week 36, then every four weeks to Week 52. *A phone call is acceptable if a site visit is not scheduled.*
17. May be performed before Day 1 if required.

SoA – Safety Follow-up Visit

	Safety follow-up visit procedures (Follow-up visit only for participants who do not transition into LTE study 209564) Week 59 (Day 414 ± 14 days) ↓
Assessments	Vital signs
	Full Physical Exam
	Dyspnoea & Cough assessment, Lung Auscultation, Pulse Oximetry
	Concomitant Medication Review
	SAE/AE review
Labs	Haematology, Chemistry, Urinalysis (dip stick)
	Urine pregnancy test (for women of child bearing potential only)
	Immunogenicity blood sampling

Assessments for Early Withdrawal from Study

Follow the Week 52 procedures* at the time of withdrawal from the study, or within 1 week of withdrawal, and schedule a safety follow-up visit 8 weeks post last dose of SC administered study intervention.

*Note: A hands/feet x-ray should not be performed at early withdrawal if the participant's last dose of study drug was prior to week 8, OR if a hands/feet x-ray has been carried out within 8 weeks of the early withdrawal date, as part of study assessments.

2. INTRODUCTION

GSK3196165 is a novel human monoclonal anti-granulocyte-macrophage colony stimulating factor (GM-CSF) antibody that is being developed for once-weekly treatment of rheumatoid arthritis (RA).

2.1. Study Rationale

The aim of this study is to determine the efficacy and safety of GSK3196165, in combination with conventional synthetic disease-modifying antirheumatic drug(s) (csDMARDs), for the treatment of adults with moderately to severely active RA who have had an inadequate response to csDMARDs or biologic DMARDs (bDMARDs). Two doses of GSK3196165 (90 mg subcutaneous [SC] weekly and 150 mg SC weekly) will be compared with placebo (to Week 12) and with tofacitinib (5 mg twice daily [BID]), an inhibitor of Janus Kinase (JAK) that is approved for the treatment of adults with moderately to severely active RA who have had an inadequate response to cs/bDMARDs.

2.2. Background

RA is a chronic, systemic inflammatory autoimmune disease, characterised by a symmetrical polyarthritis that is associated with substantial disability and morbidity. RA affects approximately 0.5-1.0% of the worldwide population, primarily women, with a peak incidence of onset between 40 and 60 years of age.

A substantial proportion of patients either fail to respond, or have inadequate response, to currently available RA therapies [Gaujoux-Viala, 2014; Nam, 2014]. Therefore, there is still a medical need for more effective treatments for RA with alternative mechanisms of action.

GM-CSF is a pro-inflammatory cytokine that regulates the functions of myeloid lineage cells that are considered to play key roles in the pathology of RA including macrophages and neutrophils [Avci, 2016; Hamilton, 2016; Wicks, 2016]. Increased levels of GM-CSF are found in the synovial fluid from RA patients and its receptor is expressed in synovial tissue [Avci, 2016; Wicks, 2016]. Preclinical studies using various inflammatory arthritis models have shown that GM-CSF removal or neutralisation improved pain, function and joint histologic structure [Cook, 2001; Plater-Zyberk, 2007; Cook, 2013; Cook 2018a] and inhibited matrix metalloproteinase (MMP)-mediated cartilage degradation in experimental arthritis induced by joint instability [Cook, 2012].

GSK3196165 is a high-affinity recombinant human monoclonal antibody (mAb) that binds specifically to human GM-CSF and prevents its interaction with its cell surface receptor [Steidl, 2008]. Clinical studies in patients with RA have then shown that GSK3196165 [Behrens, 2015] and mavrilimumab (an anti-GM-CSF receptor α-subunit antibody) [Burmester, 2017; Burmester, 2018; Cook, 2018b] are able to reduce RA disease activity and pain. A Phase IIb dose-ranging study of GSK3196165 with methotrexate (MTX) treatment, in patients with RA and an inadequate response to MTX, has now been completed.

In the BAROQUE Phase IIb study (201755), treatment with GSK3196165 in combination with MTX demonstrated efficacy in the treatment of active RA. At Week 12 of the study all doses above 22.5 mg resulted in a significant reduction in DAS28(CRP) (Disease Activity Score including 28 different joints) and significantly higher ACR20 (20% improvement in American College of Rheumatology criteria) response rates in comparison with placebo. Substantial improvements in tender and swollen joint counts, a large effect in CDAI (Clinical Disease Activity Index) and rapid improvements in pain were also identified. The overall adverse event (AE) and serious adverse event (SAE) profile was unremarkable. The majority of AEs were of mild or moderate intensity and there were no deaths, malignancies or venous thromboembolisms during the trial. Additional information is provided in the GSK3196165 Investigator's Brochure (IB) [GSK Document Number 2014N190256_02]. It is therefore hypothesised that GSK3196165, in combination with csDMARD(s) may provide clinical benefit to patients with RA.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3196165 may be found in the IB. The risks associated with the active comparator tofacitinib can be found in the approved product label or local prescribing information.

The potential risk assessment and mitigation strategy for the administration of GSK3196165 in this protocol is outlined below.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3196165]		
Infections	Immune-modulating biologic drugs used in RA (such as anti-TNF agents) are associated with an increased risk of serious and opportunistic infections. Similarly, because of the role of GM-CSF in anti-infective immunity, GSK3196165 also has the potential to increase the risk of infection. **Non-clinical Data:** No changes in peripheral blood populations (lymphocytes, neutrophils, monocytes, eosinophils or basophils), phagocytic activity of peripheral blood polymorphonuclear cells (investigational endpoint in the 26 week study), T-cell dependent B-cell primary or secondary response, or circulating cytokine levels (26 week study) were observed. Studies in knock-out mice showed that GM-CSF deficiency (GM-CSF-/-) affects the ability of mice to control infection when infected with M. tuberculosis or pulmonary group B streptococcus [LeVine, 1999]. **Clinical Data:** Based on the mechanism of action of GSK3196165 an increased risk of infection including TB, fungal and opportunistic infections could be expected for anti-GM-CSF treatment, because of the role of GM-CSF in anti-infective immunity. One healthy volunteer (HV) in study MSC-1000 experienced septic shock secondary to pneumonia	**Eligibility Criteria (Section 5.2):** Exclusion of participants with: • Active infections (including localised infections), or a history of recurrent infections or has required interventions to manage acute/chronic infections. • Symptomatic herpes zoster. • Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency. • History of infected joint prosthesis, chronic leg ulcers, permanent in-dwelling catheters, chronic sinusitis, recurrent chest infections or recurrent urinary tract infections. • White blood cell (WBC) count ≤3.0 x 10^9/L • Evidence of untreated latent TB (unless willing to undergo TB therapy or have successfully undergone TB therapy). • Current or previous active TB regardless of treatment. • Previous close contact with a person with active TB and did not receive satisfactory anti-tuberculosis treatment. • Current acute or chronic Hepatitis B and/or Hepatitis C.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	29 days after receiving a single dose of 1.5 mg/kg but recovered after treatment with antibiotics. In Phase II completed studies, no significant infections or opportunistic infections were reported.	• Known infection with human immunodeficiency virus (HIV) or positive test at screening. Assessment of vaccination status (including against influenza and pneumococcus, according to local guidelines) prior to enrolment. **Monitoring:** • Serious and opportunistic infections, TB and TB reactivation are categorised as AESIs. • Monitoring for signs of infection with appropriate diagnostic tests as necessary. • Instructions to participants as to the signs and symptoms of infection, and to contact site personnel should they develop (also contained within the ICF). • TB evaluation at screening and monitoring for TB and TB re-activation throughout the study (Section 8.2.7.4). • Participants diagnosed with latent TB during screening will need to complete a course of at least 6 months of isoniazid (INH) therapy during the study including at least 4 weeks of therapy prior to randomisation (Section 8.2.7.3). **Withdrawal Criteria:** Temporarily discontinue the study intervention for: • Serious infections until the infection has resolved. • Suspected TB reactivation. • WBC count (<2 x 10^9/L) Permanently discontinue the study intervention for:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• New latent or active TB infection • HBV DNA level ≥200 IU/mL or HBV DNA detected at any level with recent increase in hepatic transaminases (see Figure 2 in Section 8.2.8). • HBV DNA positive (any level ≤200 IU/mL) and on repeat testing within 1 week either: HBV DNA positive (any level) OR HBV surface antigen positive OR increase in hepatic transaminases (see Figure 2 in Section 8.2.8).
Pulmonary alveolar proteinosis (PAP)	GM-CSF signalling is required to maintain the normal function of alveolar macrophages. Long-term absence of GM-CSF signalling (e.g., via hereditary GM-CSF deficiency or development of anti-GM-CSF auto-antibodies) is known to cause the extremely rare condition of PAP. PAP is characterised by the accumulation of surfactant lipids and protein in the alveolar spaces, which might lead to persistent dry cough and is also associated with impairment in gas exchange which may lead to an increased risk of pulmonary infection. The exposure duration to GSK3196165 in this study is 12 months. Although the time course of PAP development in humans is unknown, the published literature suggests that the clinical onset of PAP requires prolonged and complete inhibition of GM-CSF [Martinez-Moczygemba, 2008; Suzuki, 2008]. Risk of PAP is anticipated to be low. **Non-clinical Data:**	**Eligibility Criteria (Section 5.2):** Exclusion of participants with: • Any baseline symptomatology that in the investigator's opinion would confound the early detection of PAP based upon clinical features, such as persistent cough (CTC Grade ≥2) or dyspnoea (dyspnoea scale Grade ≥2). **Monitoring:** • Diagnosis of PAP, persistent cough (CTCAE Grade ≥ 2) or persistent dyspnoea (dyspnoea scale Grade ≥ 2) are categorised as AESIs. • Regular chest auscultation and pulse oximetry measurements. • Specific pulmonary assessments throughout the study with referral to a pulmonologist for clinically-significant pulmonary events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Non-adverse minimal to mild foamy alveolar macrophage accumulation were noted in lungs of monkeys in the 13-week SC and 26-week IV toxicology studies but were reversible following an off drug period. Dose levels at which foamy alveolar macrophages were not observed were identified in these studies. **Clinical Data:** No cases of PAP have been reported to date in the clinical development program. Pulmonary function tests have not identified any safety signals.	• Pulmonary Safety Guidance Document containing pulmonary assessment and management algorithms will be provided to the investigator. • A Pulmonary Adjudication Panel consisting of external experts is available for adjudication of cases. **Withdrawal Criteria:** Temporarily discontinue study intervention for: • persistent cough (CTCAE Grade $\geq$ 2) or persistent dyspnoea (dyspnoea scale Grade $\geq$ 2) for 3 consecutive weeks (21 days). Permanently discontinue study intervention for: • Confirmed PAP
Hypersensitivity reactions	There is a potential risk of hypersensitivity reactions, including anaphylaxis, during and following the administration of protein-based products, such as GSK3196165. **Clinical Data:** No serious allergic or acute systemic reactions have been observed to date in the clinical development program.	**Eligibility Criteria (Section 5.2):** Exclusion of participants with: • Significant allergies to humanised monoclonal antibodies. • Clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions • A history of sensitivity to any of the study interventions, or components thereof. **Monitoring:** • Serious hypersensitivity reactions are categorised as AESIs. • Instructions to participants as to the signs and symptoms of an acute hypersensitivity reaction and to seek immediate medical care

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		should they develop (also contained within the ICF) • Hypersensitivity to be managed appropriately per local guidelines/medical judgement • All participants will be monitored for 1 hour after the first two exposures of GSK3196165 (i.e. Weeks 0, 1, 12, and 13). **Withdrawal Criteria:** • Permanently discontinue study intervention for serious hypersensitivity reactions
Injection site reactions	SC injections may be associated with local reactions (e.g., swelling, induration, pain). **Non-clinical Data:** No macroscopic or microscopic changes indicative of local injection site reactions were observed following SC administration in cynomolgus monkeys. **Clinical Data:** Injection site reactions have been reported in completed Phase II studies and were non-serious and of mild to moderate intensity.	**Monitoring:** • Injection site reactions are categorised as AESIs and reported as an AE. • Monitor for injection site reactions throughout study. • Recommended that injection sites are rotated.
Neutropenia	Although there is a perceived theoretical risk that GM-CSF blockade may affect maturation of leukocytes and their precursors, mice lacking GM-CSF do not develop neutropenia or show any major perturbation of hematopoiesis [Stanley, 1994]. **Clinical Data:** Neutropenia has been observed in completed studies of GSK3196165; however, no clinically significant cases have been observed.	**Eligibility Criteria (Section 5.2):** Exclusion of participants with • Significant neutropenia (absolute neutrophil count <1.0 x 10^9/L) at screening. **Monitoring:** • Neutropenia ≥ Grade 3 (<1.0 x 10^9/L) is categorised as an AESI. • Full blood count (with differential) performed at regular intervals throughout the study

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Withdrawal Criteria: Temporarily discontinue study intervention for the following haematological abnormality until resolved (Section 7.1.3.3): • Absolute neutrophil count (ANC) ≤1.0 x 10^9/L Permanently discontinue study intervention for the following haematological abnormality (Section 7.1.2): • ANC <0.5 x 10^9/L
Reproductive toxicity	Published studies performed with GM-CSF -/- mice have indicated that GM-CSF depletion potentially affects fertility, establishment of pregnancy and postpartum development of offspring in the mouse. **Non-clinical Data:** No GSK3196165-related effects on female or male fertility were noted in the SC 13-week repeat dose monkey study at doses up to 100 mg/kg/week (highest dose tested). In addition, no maternal, embryofoetal or effects on fertility were noted in the reproductive toxicology studies using the surrogate rat anti-mouse GM-CSF monoclonal antibody, 22E9. **Clinical Data:** Two pregnancies have been reported during clinical studies with GSK3196165, 1 in a female partner of a HV participant and 1 in an MS participant. Both pregnancies were electively terminated. The effect of GSK3196165 on human pregnancy is unknown.	**Eligibility Criteria (Section 5.1 and Section 5.2):** • WOCBP and males to meet contraceptive requirements. • Negative serum pregnancy test at screening. Exclusion of female participants who are: • Pregnant, lactating, planning to become pregnant or initiating breastfeeding. **Monitoring:** • Females of reproductive potential using hormonal contraceptives, including oral, injections, implants, and patches, are required to use a secondary method of contraception. • Routine urine pregnancy testing of WOCBP throughout the study. • Collection of pregnancy information in females and in female partners of male participants. • Pregnancy to be followed to determine outcome. • Report as AE/SAE any pregnancy complication or elective termination.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Withdrawal criteria: • Permanently discontinue study intervention in event of pregnancy (Section 7.1.2).
Malignancy	Risk of malignancy is increased in RA and the immunomodulatory therapies may also increase the risk. **Non-clinical & Clinical Data:** There are no reports of malignancy in the non-clinical or clinical GSK3196165 program.	**Eligibility Criteria (Section 5.2):** Exclusion of participants with: • Breast cancer within the past 10 years or lymphoma, leukaemia, or any other malignancy within the past 5 years except for cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease, or basal cell or squamous epithelial cancers of the skin that have been resected with no evidence of recurrence or metastatic disease for at least 3 years. • History of any lymphoproliferative disorder, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, or signs and symptoms suggestive of current lymphatic disease.
Immunogenicity	GSK3196165 is a humanised monoclonal antibody that will be delivered by the subcutaneous route and is targeted to bind and neutralise a soluble target, and for these reasons, is considered to be a relatively low risk of inducing adverse immune responses [FDA, 2014]. **Non-clinical Data:** Anti-drug antibodies (ADAs) to GSK3196165 were detected in some monkeys and this was associated with reduced serum levels of GSK3196165; ADA associated toxicity was not observed.	Blood samples will be tested for anti-drug antibodies (ADAs) to GSK3196165 on Day 1 and at select time points throughout the study (including Follow-up). If present, ADA titres and presence of neutralising antibodies will be assessed. In addition to scheduled immunogenicity assessments, “event-driven” testing will be performed in the context of serious hypersensitivity reactions or AEs deemed to be clinically significant in the opinion of the investigator resulting in discontinuation from study intervention.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical Data: In clinical trials to date, there is no evidence that anti-GSK3196165 antibodies affect GSK3196165 serum concentrations.	
Potential drug interaction with CYP450 substrates	Cytokines can produce concentration-dependent inhibition on various CYP isoforms at the transcription level or by alteration of CYP enzyme stability in patients with infection or inflammation and increase the plasma concentrations of specific CYP substrate drugs. Cytokine modulators may reverse the apparent "inhibition" effect of the cytokines on CYP substrates, resulting in a "normalisation" of CYP activities. GSK3196165 is a cytokine modulator, so it has the potential to 'normalise' CYP expression from a suppressed state in patients with a pro-inflammatory disease (RA). **Clinical Data:** In a phase II study for GSK3196165, the ratio of 4β-hydroxycholesterol to cholesterol was monitored as a biomarker predictive of change in CYP3A4 activity. Based on the data, GSK3196165 showed no risk of alteration of CYP450 3A4 enzyme.	• Information will be collected on concomitant warfarin use (e.g. INR results and any information related to warfarin dose). • Participants of reproductive potential using hormonal contraceptives, including oral, injections, implants, and patches are required to use a secondary method of contraception. • Participants receiving a concomitant CYP450 substrate with narrow therapeutic index (e.g. theophylline) should be monitored for signs in changes in drug exposure.
Study Procedures		
Placebo	Due to ethical considerations, placebo control will only be allowed until Week 12, with all placebo participants being switched to one of the 3 active intervention arms (GSK3196165 90 mg, 150 mg or tofacitinib 5 mg BID) at their Week 12 visit. This will	• Participants randomised to the placebo arm will switch at Week 12 to 1 of 3 active intervention arms (Section 4.1, Section 6.3). • Randomisation ratio of 6:6:3:1:1:1 will minimise the number of participants in the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	enable the study to generate controlled data in participants initially randomised to placebo.	placebo arm (Section 1.1, Section 4.1, Section 6.1, Section 6.3). • Although background therapy with csDMARDS is permitted, the participants have already failed these therapies. • Changes in background medication are not permitted unless required for safety and any dose adjustments must be documented. • Participants are permitted to receive a stable dose of ≤10 mg/day oral prednisolone or equivalent and/or a stable dose of NSAID(s).
Blood draws	Venous access in some participants may be problematic and the needles used may cause bruising (ecchymosis) around the access site.	• A maximum of approximately 450 mL of whole blood will be collected over the course of the study • At visits to collect whole blood samples, one or more samples of sufficient volume will be collected and divided into suitable portions for the various analyses such as PD biomarkers. • Whole blood samples for genetic research will only be collected from those consenting to participate in this research • Whole blood samples will be collected by site personnel experienced in phlebotomy.
Chest X-ray	Generally, the amount of radiation during an X-ray is equivalent to between a few days and a few years of exposure to natural radiation from the environment. The risk of cancer from exposure to X-rays is very small.	• Minimal procedures performed at Screening and end of treatment phase (Week 52). • No requirement for screening X-ray if one was performed within the previous 12 weeks. • Exposure to radiation from X-rays is far less than the exposure to natural radiation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
X-rays of the hands/feet	Structural joint damage evaluation by X–rays (van der Heijde modified total Sharp scores mTSS) is an established endpoint that is accepted in the US and EMA regulatory guidelines to demonstrate prevention of joint damage. Tofacitinib prevents structural joint damage and this study aims to establish if structural bone damage does or does not deteriorate after treatment with GSK3196165.	• Minimal procedures performed at Screening and 3 times post-randomisation (Weeks 12, 24 and 52) to assess structural joint damage • Exposure to radiation from X-rays is far less than the exposure to natural radiation. • A repeat X-ray is not required for participants who are re-screened, only if re-screening is within 4 weeks of original screening x-ray. • Positioning devices will be used to minimise the risk of repeat X-ray
Study Medical Devices		
Handling and usage risks associated with the prefilled syringe devices.	A life-threatening serious risk has been identified that is caused by the participant removing the rigid needle shield with their teeth and choking on the small part. This risk is considered improbable and non-intuitive, it has not been observed in human factors studies for this patient group and is not precedented with other GSK products using the same devices. All other anticipated device effects are non-serious and primarily unlikely, improbable, occasional or remote and are due to user error.	Instructions For Use (IFU) on how to correctly handle and use the device is provided.
Other		
Tofacitinib	Serious infections, malignancies and serious cases of thrombosis including pulmonary embolism, deep vein thrombosis and arterial thrombosis have been reported with tofacitinib.	See GSK3196165 above for serious infections, malignancies and laboratory changes. **Eligibility criteria (Section 5.2):** Exclusion of participants with • Any condition or contraindication as addressed in the local product information or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	An interim analysis from a post marketing safety study evaluating tofacitinib 5 and 10 mg twice daily compared to TNF inhibitors in RA patients who were 50 years of age and older and had at least one cardiovascular risk factor showed that tofacitinib in a dose dependent fashion was associated with: 1) higher all-cause mortality and 2) increased risk of VTE and serious infections. Tofacitinib should be used with caution in patients who have known risk factors for VTE, regardless of indication and dosage. There is a higher incidence of serious and fatal infections in patients over 65 years of age. Patients should be monitored for signs of serious infection including active TB even if the initial latent tuberculosis test is negative. Increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been noted in clinical studies with tofacitinib with maximal effects within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. GI perforations have been reported in clinical studies with tofacitinib in RA, although the role of JAK inhibition in these events is not known. Tofacitinib	local clinical practice for tofacitinib that would preclude the participant from participating in this protocol. For all participants, investigators should carefully review potential risk factors related to VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) and review the risk of infection in participants older than 65 years of age. • Evidence of untreated latent TB (unless willing to undergo TB therapy or have successfully undergone TB therapy). • Current or previous active TB regardless of treatment. • Previous close contact with a person with active TB and did not receive satisfactory anti-tuberculosis treatment. • Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. **Monitoring:** As above for GSK3196165 • Laboratory tests to assess potential changes in lymphocytes, neutrophils, haemoglobin, liver enzymes and lipids. Participants should be managed according to clinical guidelines/standard of care for the management of hyperlipidaemia. • TB evaluation at screening and monitoring for TB and TB re-activation throughout the study (Section 8.2.7.4).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	should be used with caution in patients at increased risk of GI perforations.	• Participants diagnosed with latent TB during screening will need to complete a course of at least 6 months of INH therapy during the study including at least 4 weeks of therapy prior to randomisation (Section 8.2.7.3). • Participants with signs and symptoms of VTE should be promptly evaluated. • All potential events of GI perforation will be adjudicated. **Withdrawal:** In addition to the above for GSK3196165: • Temporarily discontinue study intervention in the event of serious or opportunistic infection or sepsis develops. Do not restart until infection has resolved. • Permanently discontinue study intervention in event of venous thromboembolism, including PE and DVT, requiring anticoagulation (Section 7.1.2).

2.3.2. Benefit Assessment

GM-CSF plays a key role in initiation and progression of inflammation in RA and indirectly increases the destruction of the bone and cartilage. GSK3196165 binds human GM-CSF and inhibits GM-CSF mediated responses in vitro. Clinical studies in RA have shown that GSK3196165 [Behrens, 2015] and mavrilimumab (an anti-GM-CSF alpha-subunit receptor antibody) [Burmester, 2017, Burmester, 2018; Cook, 2018b] were able to reduce RA disease activity and pain. In addition, results from BAROQUE showed that all doses of GSK3196165 above 22.5 mg in combination with MTX resulted in a significant reduction in DAS28(CRP), significantly higher ACR20 response rates, substantial improvements in tender and swollen joint counts, a large effect in CDAI and rapid improvements in pain with an acceptable safety profile when compared with placebo. These data support further evaluation of GSK3196165 as a treatment option in RA.

Participants randomised to the active comparator arm, will receive the marketed drug tofacitinib, which is approved globally for the treatment of adults with moderately to severely active RA. Participants randomised to one of the placebo arms, will receive placebo intervention only for 12 weeks, and will switch at Week 12 to receiving either GSK3196165 or active comparator for the remainder of the study.

Furthermore, each participant will benefit from extensive monitoring of their disease activity with numerous assessments throughout the study such as physical examinations, X-rays, ECGs, vital signs, pulse oximetry, respiratory function tests, laboratory tests, and swollen/tender joint assessments among others.

2.3.3. Overall Benefit: Risk Conclusion

Current preclinical and clinical data with GSK3196165 indicates that it binds and inhibits the function of GM-CSF and that this inhibition may have clinical utility in the treatment of inflammatory and autoimmune diseases, such as RA.

The main potential risks are those that may be associated with inhibition of GM-CSF, including infection, pulmonary alveolar proteinosis, neutropenia, malignancy and reproductive toxicity, plus those associated with the administration of a therapeutic monoclonal antibody, including hypersensitivity reactions, injection site reactions and immunogenicity.

In addition to routine pharmacovigilance, the safety review team (SRT) will review blinded safety data approximately every 4 weeks during the period of study conduct and unblinded safety data will be reviewed by the Independent Data Monitoring Committee (IDMC) at scheduled intervals (see Section 10.1.5). Key safety data that meets predefined thresholds will be reviewed by the IDMC allowing ongoing assessment of the overall benefit:risk throughout the study. Full details of safety thresholds will be provided in the IDMC charter.

Taking into account the measures taken to minimise risk to participants randomised in this study, the potential risks identified in association with GSK3196165 are justified by the anticipated benefits that may be afforded to participants with RA.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of GSK3196165 at doses of 90 mg and 150 mg weekly versus placebo for the treatment of participants with moderately to severely active RA who are on a stable background of csDMARDs and who have had an inadequate response to csDMARDs or bDMARDs.	• Proportion of participants achieving ACR20 at Week 12.
Secondary	
To compare: • Efficacy of GSK3196165 at doses of 90 mg and 150 mg weekly versus tofacitinib for the treatment of participants with moderately to severely active RA who are on a stable background of csDMARDs and who have had an inadequate response to csDMARDs or bDMARDs	**Major Secondary Efficacy Endpoints** Week 12 versus placebo: • Proportion of participants achieving CDAI total score ≤10 (CDAI LDA). • Change from baseline in HAQ-DI. Non-inferiority versus tofacitinib at Week 12: • Proportion of participants achieving ACR20. **Other Secondary Efficacy Endpoints** Week 12 (vs. placebo and vs. tofacitinib), Week 24 and Week 52 (vs. tofacitinib): Proportion of participants achieving: • CDAI total score ≤10 (CDAI LDA). • CDAI total score ≤2.8 (CDAI Remission). • ACR20/50/70. • DAS28-CRP ≤3.2 and DAS28(ESR) ≤3.2 (DAS28 LDA). • DAS28-CRP <2.6 and DAS28(ESR) <2.6 (DAS28 Remission). • A good/moderate EULAR response. • ACR/EULAR Remission. • No radiographic progression defined as a change from baseline in van der Heijde mTSS score of ≤0.5. Change from baseline in: • CDAI total score. • DAS28-CRP/DAS28-ESR. • van der Heijde mTSS.
• Effect of GSK3196165 on Patient Reported Outcomes (PROs) versus	Change from baseline at Week 12 (vs. placebo and vs. tofacitinib), Week 24 and Week 52 (vs. tofacitinib) in:

Objectives	Endpoints
placebo and the active comparator tofacitinib	• HAQ-DI. • Arthritis pain VAS. • SF-36 physical and mental component scores, and domain scores. • FACIT-Fatigue.
• Safety and tolerability of GSK3196165 versus placebo and the active comparator tofacitinib	• Incidence of AEs, SAEs and AESIs. • Change from baseline in key laboratory parameters at Weeks 12, 24 and 52. • Proportion of participants with NCI-CTCAE ≥Grade 3 [NCI, 2017] haematological/clinical chemistry abnormalities.
• To determine the immunogenic potential of GSK3196165	**Safety Biomarker Endpoints** • GM-CSF autoantibody concentrations. • Anti-GSK3196165 antibodies.

CCI

[redacted]

csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; bDMARDs = biologic disease-modifying antirheumatic drugs; ACR2050/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; CDAI = clinical disease activity index; HAQ-DI = health assessment questionnaire disability index; VAS = visual analogue scale; LDA = low disease activity; DAS28 = disease activity score including 28 different joints; CRP = C-reactive

protein; EULAR = European league against rheumatism; ESR = erythrocyte sedimentation rate; mTSS = modified total sharp score; AEs = adverse events; SAEs = serious adverse events; AESIs = adverse events of special interest; NCI-CTCAE = National Cancer Institute-common terminology criteria for adverse events; RNA = ribonucleic acid; SF-36 = short form-36; FACIT = functional assessment of chronic illness therapy; RA = rheumatoid arthritis; GM-CSF = granulocyte-macrophage colony stimulating factor [redacted]

4. STUDY DESIGN

4.1. Overall Design

- This is a Phase 3, randomised, multicentre, double-blind, parallel group, placebo and active comparator (tofacitinib) controlled study, with primary objective to assess the efficacy and safety of GSK3196165 in combination with csDMARDs in participants with moderately to severely active RA who have an inadequate response to csDMARDs or bDMARDs.

- This is a 52-week study with the primary endpoint at Week 12 to coincide with the duration of placebo intervention.

- This study includes X-rays of the hands and feet to assess radiographic progression of structural joint damage.

- Upon successful screening, participants will be randomised to one of six intervention arms in a ratio of 6:6:3:1:1:1 to GSK3196165 150 mg SC weekly, GSK3196165 90 mg SC weekly, tofacitinib capsules 5 mg BID or placebo (three arms) respectively, all in combination with csDMARD(s). At Week 12, participants in the three placebo arms will switch from placebo to active intervention (either GSK3196165 150 mg SC weekly, GSK3196165 90 mg SC weekly, or tofacitinib capsules 5 mg BID). Randomisation will be stratified by previously failed medication (csDMARD only, 1 bDMARD or >1 bDMARD).

- To maintain the blind, all participants will receive capsules BID and weekly SC injections. A double dummy approach will be followed with matching placebo capsules to tofacitinib, and either weekly SC dosing of GSK3196165 and placebo to GSK3196165 by an unblinded administrator or by the use of matching pre-filled syringes of GSK3196165 and GSK3196165 placebo.

- Due to ethical considerations, placebo control will only be allowed until Week 12. At their Week 12 visit, participants in the three placebo arms will switch to receiving the active intervention specified for that arm. This will enable placebo participants to receive active intervention from Week 12 onwards and for the study to accrue additional randomised safety data.

- Participants who successfully complete the 52 week treatment period may be eligible to transition into the long-term extension study 209564. Any participant who does not transition into Study 209564 will undergo a safety follow-up visit at 8 weeks post last dose of SC study intervention.

- Participants who transition into the long-term extension study 209564, will be instructed to take their last capsule of oral study intervention **no later than 6pm** on the evening before their Week 52 visit.

4.2. Scientific Rationale for Study Design

This study is a placebo-controlled, tofacitinib-controlled, parallel-dose study of SC doses of GSK3196165 added on to stable dose(s) of csDMARD(s). Participants will be allowed to receive a stable dose of ≤10 mg/day oral prednisolone or equivalent and/or a stable dose of NSAID(s).

The double-blind, placebo-controlled, randomised clinical study is considered the gold standard for the safety and efficacy assessment of a new therapy both by clinicians and regulatory authorities. Control with a comparator, tofacitinib, will also comply with recent guidelines from regulatory authorities and help further establish the safety and efficacy in comparison with an established targeted synthetic disease-modifying antirheumatic drug (tsDMARD). In this study, participants will continue to receive a stable dose of csDMARD(s). Participants are not allowed to receive any additional bDMARDs other than GSK3196165 or any other additional JAK inhibitor other than tofacitinib during the study, to mitigate the potential increased safety risks of administering a combination of bDMARDs, or a combination of a bDMARD and a JAK inhibitor, or a combination of JAK inhibitors.

Efficacy and safety of GSK3196165 will be compared with placebo (until Week 12) and an established active comparator (until Week 52), tofacitinib which is approved globally for the treatment of RA in participants inadequately controlled with csDMARDs, including MTX.

ACR20 is considered an established endpoint which continues to be an acceptable measure to demonstrate reduction in disease activity as recommended in the US regulatory guidelines.

Health Assessment Questionnaire Disability Index (HAQ-DI) is considered an established endpoint to demonstrate improvement in physical function as recommended in the US and EU regulatory guidelines.

The prevention of structural joint damage will be assessed via X-rays using change from baseline in van der Heijde modified total Sharp scores (mTSS), which is the only currently accepted approach by regulatory agencies. Data from the placebo control and comparative data from tofacitinib, which has established efficacy in the prevention of structural damage, will also be analysed to ascertain how the effects with GSK3196165 compare with tofacitinib.

4.3. Justification for Dose

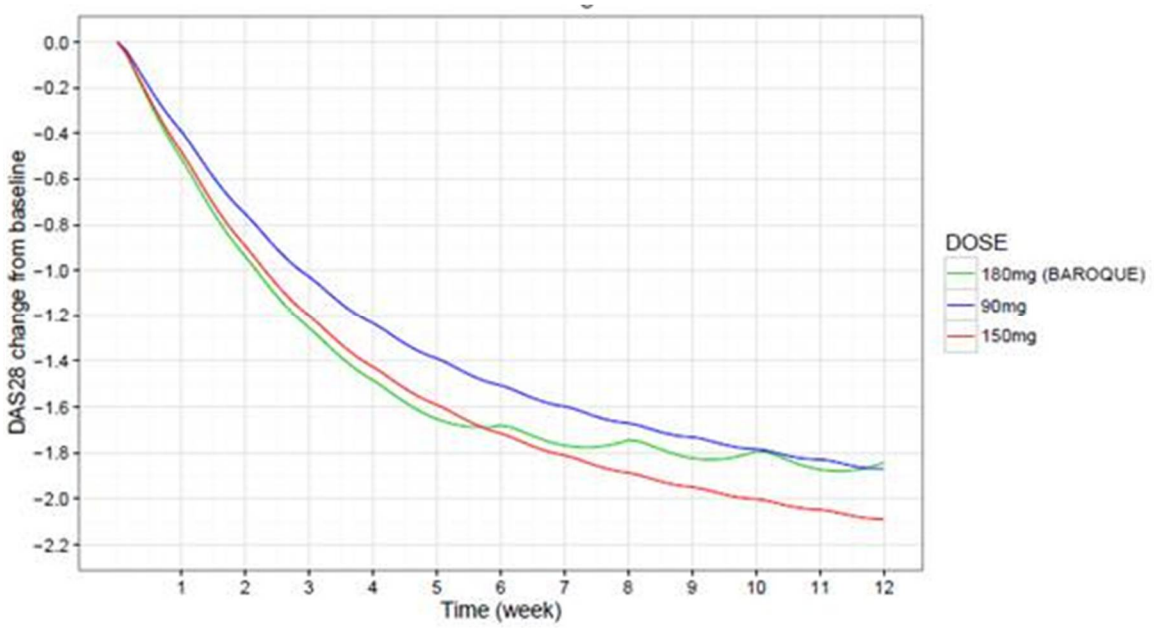
GSK3196165

The GSK3196165 doses for this study have been selected based on pharmacokinetics (PK), efficacy, safety data, exposure-response and dose-response relationships for efficacy endpoints from the phase 2b dose finding BAROQUE (201755) study.

The BAROQUE study showed an acceptable safety profile and clinically meaningful efficacy at the highest dose of 180 mg SC weekly for 5 injections, then every other week until Week 50. The efficacy however started to plateau after Week 6 with no further improvement post Week 12. This effect is likely due to lower trough concentrations achieved in BAROQUE than predicted from PK data from historic studies (MSC-1000, MSC1001 and MOR103C104). The reason for the lower than expected exposure to GSK3196165 in RA participants in BAROQUE is being investigated. The PK of GSK3196165 was linear over the tested dose range (IV; 0.025 – 3 mg/kg and SC; 22.5 – 180 mg), which is consistent with the PK profile of a mAb against soluble cytokine [GSK Document Number 2017N353526_00]. However, GSK3196165 clearance in healthy volunteers (HV) was 3 times higher (0.93, confidence interval [CI]: 0.83 – 1.04 L/day) than generally reported for a mAb (0.3 L/day) and the half-life ($t_{1/2}$) of 12 days was shorter than a typical mAb. In addition, the SC bioavailability (0.34, CI: 0.26 – 0.44) was lower than expected for a mAb. In RA participants, the apparent clearance (CL/F) after SC administration of GSK3196165 was 2.4 times higher than HV and the estimated $t_{1/2}$ was 10 days.

In this study, the dosing frequency will be increased to every week to overcome the higher CL/F and lower $t_{1/2}$ of 10 days. The GM-CSF-GSK3196165 complex data from BAROQUE also supports weekly administration as an optimal dosing regimen for GSK3196165. This dosing frequency with a 90 and 150 mg dose is predicted to result in steady-state pre-dose concentrations of 1500 and 2500 ng/mL, respectively. Based on a longitudinal exposure-response model of DAS28(CRP), a dose of 90 mg SC every week is predicted to provide clinically meaningful efficacy similar to the 180 mg regimen in the BAROQUE study and in line with other RA targeted DMARDs, whilst 150 mg SC every week dose is predicted to provide greater efficacy to that achieved in BAROQUE.

Figure 1 Comparison of PK/PD Model Predicted Median Change from Baseline in DAS28(CRP) given 3 Dose Regimens of GSK3196165: 180 mg Weekly for 5 Weeks Followed by Every Other Week (BAROQUE Regimen), 90 mg Weekly and 150 mg Weekly



Based on dose-response relationship at Week 4 (matching the weekly dose regimen to be used in this study) the 90 mg and 150 mg doses translate into a ED70 and ED80 respectively. Logistic regression analysis of ACR20 and ACR50 response at Week 12, also indicated higher trough concentrations are associated with a higher response rate. The predicted ACR20 response rate for the 90 mg and 150 mg weekly doses are 63% and 69%, respectively.

Furthermore, the safety profile of GSK3196165 in BAROQUE was acceptable at all doses with no apparent dose response in the incidence of AEs or SAEs. More details are provided in the GSK3196165 IB.

Given the GSK3196165 half-life of 10 days, steady-state is expected to be reached after 5 weekly doses (as in BAROQUE), therefore GSK3196165 concentrations with the 150 mg every week dosing regimen should not exceed concentrations studied in BAROQUE. The highest dose of 150 mg weekly provides a 3 to 5-fold safety margin to the 5 mg/kg dose in the 26-week monkey toxicology study where no foamy alveolar macrophages were observed (NOEL).

In summary, PK, exposure-response, dose-response and safety data from the BAROQUE study, supported by modelling strongly support the selection of the 90 mg and 150 mg weekly doses, where 90 mg is expected to provide clinically-meaningful efficacy at levels similar to BAROQUE and existing targeted DMARDs, and 150 mg is predicted to provide greater clinical benefit. Both doses are also covered by an appropriate safety margin.

Tofacitinib

The tofacitinib dose has been selected based on the recommended approved dose (5 mg BID) in the countries where the study is intended to be executed.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit. This will be the Week 52 visit for those participants who transition into the long-term follow-up study or the safety follow-up visit for all other participants.

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

5. STUDY POPULATION

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

Investigators should review and update the vaccination status of potential participants as per local guidelines for adult vaccination prior to entering them into the study (refer to EULAR recommendations where no local guidelines are available [Furer, 2019]), with particular attention to the vaccination status of participants over 65 years of age. All participants who have not received the herpes zoster vaccine at study entry will be recommended to complete vaccination >30 days prior to randomisation. All participants may receive inactivated flu vaccines during the study at the discretion of the investigator.

Note that "Inadequate response" to prior treatment in this population, is defined as: In the opinion of the investigator, after at least 3 months of treatment the participant experienced insufficient efficacy or loss of response (e.g. no EULAR response; failure to achieve ACR20; any other clinical criteria recommended per local guidelines that would trigger a change of treatment), or the participant discontinued treatment due to intolerability or toxicity irrespective of treatment duration.

5.1. Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Age ≥18 years at the time of signing informed consent.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Meets ACR/EULAR 2010 RA Classification Criteria (see study reference manual [SRM]) with a duration of RA disease of ≥6 months at time of screening and participant not diagnosed before 16 years of age.

3. Must have active disease at both screening and baseline, as defined by having both:
    a. ≥6/68 tender/painful joints (TJC), and
    b. ≥6/66 swollen joints (SJC).

    If surgical treatment of a joint has been performed, that joint cannot be counted in the TJC or SJC for enrolment purposes
4. Must have a high sensitivity C-reactive protein (hsCRP) measurement ≥3 mg/L at screening.
5. Must meet Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA (see SRM).
6. Must have at least 1 bone erosion present on hand/wrist or foot radiographs confirmed by central reading at screening.
7. Must have inadequate response, despite currently taking at least one and at most two concomitant csDMARDs for at least 12 weeks prior to Day 1, from the following:
    a. Methotrexate (MTX): weekly 15-25 mg oral or injected, for at least 12 weeks at the maximum tolerated dose prior to Day 1, with no change in route of administration in this time. A lower dose of ≥7.5 mg/week is acceptable if reduced for reasons of intolerance to MTX, e.g. nausea/vomiting, hepatic or hematologic toxicity, or per local requirement (there must be clear documentation in the medical record). Exception: A lower dose of 6 mg/week is allowed if the minimum locally approved or recommended dose is lower than 7.5 mg/week.
    b. Hydroxychloroquine up to 400 mg/day or chloroquine up to 250 mg/day.
    c. Sulfasalazine up to 3000 mg/day.
    d. Leflunomide up to 20 mg/day. Note: concomitant use of leflunomide and methotrexate is not allowed, for safety reasons.
    e. Bucillamine up to 100 mg/day (or up to 300 mg/day if permitted per local requirements).
    f. Iguratimod up to 50 mg/day.

    NOTE: The dose of csDMARD(s) **must be stable and tolerated for at least 8 weeks prior to Day 1** and should remain stable throughout the study from screening to end of treatment period, except adjustment for safety reasons. See Section 6.5.

    In addition, participants with prior bDMARD exposure: Prior exposure to one or more bDMARDs is permitted. The prior bDMARD exposure may have been with or without combination with a csDMARD. Prior bDMARD therapy must be discontinued before randomisation per the guidance in Section 6.5.2 Prohibited Therapies.

WEIGHT
8. Body weight ≥ 40 kg

SEX
9. Male or female participants are eligible to participate so long as they meet and agree to abide by the contraceptive criteria detailed in Appendix 4.

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

OTHER SAFETY-RELATED
11. For participants on MTX: Must be willing to continue or initiate treatment with oral folic acid (at least 5 mg/week) or equivalent and be treated during the entire study (mandatory co-medication for MTX treatment).

5.2. Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria apply:

MEDICAL CONDITIONS

1. Active infections (including localised infections), or history of recurrent infections (excluding recurrent fungal infections of the nail bed), or has required management of acute or chronic infections, as follows:
    - Currently taking any suppressive anti-infective therapy for a chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria) OR
    - Hospitalisation for treatment of infection within 26 weeks of Day 1 OR
    - Use of parenteral (IV) or intramuscular (IM) antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 26 weeks of Day 1 or oral antimicrobials (apart from INH use for latent TB treatment) within 14 days of Day 1.
2. Symptomatic herpes zoster within 3 months prior to screening.
3. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
4. Known infection with human immunodeficiency virus (HIV) or positive test at screening.
5. History of infected joint prosthesis at any time, with the prosthesis still in situ. History of chronic leg ulcers, permanent in-dwelling catheters, chronic sinusitis, recurrent chest infections or recurrent urinary tract infections.

6. Any baseline symptomatology that in the investigator's opinion would confound the early detection of pulmonary alveolar proteinosis based upon clinical features, such as persistent cough (CTC Grade ≥2) or persistent dyspnoea (dyspnoea scale Grade ≥2).
7. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.
8. Current acute or chronic Hepatitis B and/or Hepatitis C.
9. Current or history of renal disease or estimated glomerular filtration rate (eGFR) by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) calculation <60 mL/min/1.73m^2 at screening.
10. Breast cancer within the past 10 years or lymphoma, leukaemia, or any other malignancy within the past 5 years except for cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease, or basal cell or squamous epithelial cancers of the skin that have been resected with no evidence of recurrence or metastatic disease for at least 3 years.
11. History of any lymphoproliferative disorder, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, or signs and symptoms suggestive of current lymphatic disease.
12. History or presence of significant other concomitant illness according to the Investigator judgment such as, but not limited to cardiovascular (including Stage III or IV cardiac failure according to New York Heart Association classification, myocardial infarction within 3 months, unstable angina pectoris, uncontrolled hypertension, uncontrolled hypercholesterolemia, uncontrolled diabetes mellitus, VTE requiring anticoagulation), neurological, endocrinological, gastrointestinal (including diverticulitis), hepatic disease, metabolic, lymphatic disease, or previous renal transplant that would adversely affect the participant's participation in this study.
13. Any condition or contraindication as addressed in the local product information or local clinical practice for tofacitinib that would preclude the participant from participating in this protocol. For all participants, investigators should carefully review potential risk factors related to VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) and review the risk of infection in participants older than 65 years of age. Refer to the risk table for tofacitinib in Section 2.3.1.
14. History of other inflammatory rheumatologic or systemic autoimmune disorder, other than Sjögren's syndrome secondary to RA, that may confound the evaluation of the effect of the study intervention such as mixed connective tissue disease, psoriatic arthritis, juvenile chronic arthritis, spondyloarthritis, Felty's Syndrome, systemic lupus erythematosus, scleroderma, Crohn's disease, ulcerative colitis, or vasculitis.
15. Presence of fibromyalgia that, in the investigator's opinion, would make it difficult to appropriately assess RA activity for the purposes of this study.
16. Undergone any major surgery within 8 weeks prior to study entry or will require major surgery during the study that, in the opinion of the investigator in consultation with the medical monitor, would pose an unacceptable risk to the participant.

17. Current or previous active Mycobacterium tuberculosis (TB) regardless of treatment.
18. Evidence of latent TB (as documented by a positive QuantiFERON-TB Gold plus test or T-SPOT.TB test at screening, no findings on medical history or clinical examination consistent with active TB, and a normal chest radiograph) except for participants that either:
    - Are willing to complete at least 4 weeks of anti-TB therapy as per WHO or national guidelines prior to randomisation and agree to complete the remainder of treatment while in the study OR
    - Are documented as having evidence of satisfactory anti-TB treatment as per WHO or national guidelines within the last 5 years following review by a physician specialising in TB.
19. Previous close contact with a person with active TB and did not receive satisfactory anti-tuberculosis treatment as per WHO or national guidelines.
20. Significant allergies to humanised monoclonal antibodies.
21. Clinically significant multiple or severe drug allergies or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
22. Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

PRIOR/CONCOMITANT THERAPY

23. Any prior treatment antagonising GM-CSF or its receptor.
24. Any prior treatment with Janus kinase (JAK) inhibitor(s) (either experimental or approved) including, but not limited to tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib.
25. Participants who are expected to be non-compliant with restrictions on medications and vaccinations prior to the study, during the study or during the 8-week safety follow-up of the study. See Table 3 in Section 6.5.2 for details of prohibited medications/treatments and Table 2 in Section 6.5.1 for details of permitted medications/treatments.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

26. Current enrolment or past participation within the last 42 days before randomisation in any other clinical study involving an investigational study treatment or any other type of medical research.

DIAGNOSTIC ASSESSMENTS

27. Alanine transferase (ALT) or aspartate transaminase (AST) >1.5 x upper limit of normal (ULN).

28. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
29. Has a positive test for hepatitis B virus (HBV) defined as either:
    - positive for hepatitis B surface antigen (HBsAg) or
    - positive for hepatitis B core antibody (HBcAb) and positive for HBV deoxyribonucleic acid (DNA).
30. Positive test for hepatitis C antibody at screening. 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.
31. Haemoglobin ≤9 g/dL; white blood cell (WBC) count ≤3.0 x 10^9/L; platelet count ≤100 x 10^9/L; absolute neutrophil count (ANC) <1.0 x 10^9/L; lymphocyte count ≤0.75 x 10^9/L at screening.
32. Abnormal chest radiograph within 12 weeks of screening judged by the investigator as clinically-significant.

OTHER EXCLUSIONS

33. Pregnant or lactating, or women planning to become pregnant or initiating breastfeeding.
34. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within a year prior to Day 1.
35. History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

5.3. Lifestyle Considerations

5.3.1. Dietary Restrictions

Participants must refrain from consumption of grapefruit and grapefruit juice from 5 days before the start of study intervention until after the final assessment visit.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with the agreement of the Medical Monitor. The entire screening process must be repeated (except for the chest X-ray if performed within 12

weeks of the re-screening period, and hands and feet x-ray, if the original screening hands/feet x-ray was performed within 4 weeks of the re-screening period and passed central reading).

A QuantiFERON-TB Gold plus test may be repeated once during screening if the initial result is indeterminate, alternatively a T-SPOT.TB test may be used following an indeterminate result. This is not considered a rescreening. If the repeat test is positive or indeterminate, the participant will be considered to have active or latent TB.

For those participants requiring Isoniazid (INH) therapy for latent TB, LFTs must be assessed following 3 weeks of INH treatment in screening. Participants will fail screening if ALT >1.5 x ULN is identified; these participants may be re-screened if ALT elevation resolves to ALT <1.5 x ULN during ongoing INH therapy following discussion with the medical monitor.

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

Retesting within screening window of any blood sample withdrawn due to sample handling problems, breakage or sample integrity is not considered a rescreening.

Further details regarding the procedure for re-screening can be found in the SRM.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

An overview of the study interventions is provided in Table 1. Investigators should note the following:

- Study SC injection should be administered weekly, on the same day each week. The weekly SC injections of study intervention should rotate between the thighs and abdomen.
- Study oral capsules should be taken twice daily (one in morning, one in evening).
- A window of ±2 days is acceptable for the SC injection (minimum gap of 5 days between each dose, for no more than 2 consecutive doses). Participants should return to their 7 day dosing schedule as soon as possible thereafter.
- Participants must receive their SC injection at the site and be monitored for general safety for 1 hour after the injection at Weeks 0, 1, 12, and 13; the safety monitoring at Weeks 12 and 13 is due to the switch of the placebo participants to

active intervention at the Week 12 visit. Safety monitoring will include monitoring for systemic hypersensitivity and local injection site reactions.

- Until such time as GSK3196165 becomes available in a pre-filled syringe, every SC injection must be delivered by an unblinded administrator and the syringe must be shielded from the participant at all times, to avoid unblinding.

- If/when GSK3196165 becomes available in a pre-filled syringe, participants may be permitted to receive some of their SC injections at home; in this case, the investigator should first ensure the participant (or caregiver) is able to correctly administer the injection from PFS. PFS for home dosing will be dispensed every 4 weeks as a 4-week supply. Any participant who doses at home must be instructed to contact the site immediately if they experience any symptoms following dosing.

- Where possible, assessment visits should be scheduled to coincide with the weekly administration of study SC injection, **the injection will then be performed at the site, after completion of PK sampling** (see Section 1.3).

- Participants who are initially dosed with SC injections of study intervention supplied from vials, should continue to be dosed from the vials until at least Week 12 to coincide with the timing of the primary endpoint unless this is impractical due to supply issues; these participants may be switched to SC injections from the pre-filled syringes after Week 12, if sufficient supply is available.

- Participants who are initially dosed with SC injections of study intervention from the pre-filled syringes should continue to be dosed in this manner for the duration of the study providing sufficient supplies are available.

- Participants who transition into the long-term extension study 209564, will receive their last weekly SC injection at Week 51 and will be instructed to take their last capsule of oral study intervention no later than 6pm on the evening before their Week 52 visit.

In parallel to receiving study intervention, all participants will receive a stable dose of background csDMARD(s) (refer to Section 6.5). Any participant whose background DMARD is MTX must also receive ≥5 mg/week folic (or folinic) acid orally (dosing regimen at the discretion of the investigator). Dose modifications to background DMARDs are discussed in Section 6.6.2.

All local standard-of-care practices for the administration of csDMARD(s), including laboratory testing, follow-up care, contraindications, and (for MTX) folic acid administration should be performed throughout the study.

Table 1 Overview of Study Intervention

ARM Name	GSK3196165 90 mg	GSK3196165 150 mg	Placebo*		Tofacitinib
Intervention Name	GSK3196165 (Approved Name not yet assigned)	GSK3196165 (Approved Name not yet assigned)	Placebo to GSK3196165	Placebo to tofacitinib	Xeljanz
Type	Biologic	Biologic	Placebo to Biologic	Placebo Drug	Drug
Dose Formulation	Solution in vial (1.2 mL) or PFS (1.0 mL)	Solution in vial (1.2 mL) or PFS (1.0 mL)	Sterile 0.9% (w/v) sodium chloride solution or PFS (1.0 mL)	Capsule (containing lactose)	Capsule (over-encapsulated tablet)
Unit Dose Strength(s)	180 mg/vial (180 mg/1.2 mL) PFS 90 mg/mL	180 mg/vial (180 mg/1.2 mL) PFS 150 mg/mL	Not applicable	Not applicable	5 mg
Dosage Level(s)	90 mg once-weekly	150 mg once weekly	Weekly injection	One capsule BID	5 mg BID (10 mg/day)
Route of Administration	SC injection	SC injection	SC injection	Oral	Oral
IMP and NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Locally approved sodium chloride solution may be sourced at site or	Provided centrally by the Sponsor	Provided centrally by the Sponsor

ARM Name	**GSK3196165 90 mg**	**GSK3196165 150 mg**	**Placebo***		**Tofacitinib**
			provided centrally. PFS provided centrally by the Sponsor		
Dosing instructions	Vials: withdraw 0.6 mL into a small syringe and dose immediately; discard remaining material. PFS: Inject all	Vials: withdraw 1.0 mL into a small syringe and dose immediately; discard remaining material. PFS: Inject all	Withdraw 1.0 mL into a small syringe and dose immediately; discard remaining material. PFS: Inject all	Instruct participant to take 1 capsule in the morning and 1 capsule in the evening	Instruct participant to take 1 capsule in the morning and 1 capsule in the evening
Special instructions	Avoid excessive shaking of GSK3196165 vials as this could lead to product precipitation. Do not administer with other drugs concomitantly in the same syringe	Avoid excessive shaking of GSK3196165 vials as this could lead to product precipitation. Do not administer with other drugs concomitantly in the same syringe	None	None	None
Packaging and Labelling	Study Intervention will be provided in a single use vial or PFS in an individual carton and labelled as required per country requirement	Study Intervention will be provided in a single use vial or PFS in an individual carton and labelled as required	Commercial saline may be sourced at site or provided centrally / PFS will be provided for single-use in an individual carton and labelled as required	Study Intervention will be provided in a bottle containing 31 capsules and labelled as required per country requirement	Study Intervention will be provided in a bottle containing 31 capsules and labelled as required per country requirement

ARM Name	**GSK3196165 90 mg**	**GSK3196165 150 mg**	**Placebo***		**Tofacitinib**
		per country requirement	per country requirement		
Current/Former Name(s) or Alias(es)	GSK3196165, otilimab, anti-human GM-CSF monoclonal Ab, MOR103, MOR04357	GSK3196165, otilimab, anti-human GM-CSF monoclonal Ab, MOR103, MOR04357	Not applicable	Not applicable	Xeljanz, tofacitinib, Jakvinus, Jaquinus, CP-690,550

* Placebo consists of 3 arms to Week 12, after which participants will be switched to 1 of the 3 active intervention arms.
PFS = prefilled syringe; GM-CSF = granulocyte macrophage colony stimulating factor; Ab = antibody
GSK3196165 in vials and placebo will be administered SC, using syringes and needles commonly used for SC administration; compatibility with commonly used syringes and needles has been demonstrated.

6.1.1. Medical Devices

- The medical devices provided for use in this study are injection devices:
    - a prefilled syringe (PFS) containing 150 mg or 90 mg otilimab solution, or placebo, assembled into a safety syringe device (SSD)

  The otilimab PFS/SSD devices used in the study are representative of the devices and regionally appropriate device instructions planned to be marketed for the product.
- The components that comprise the otilimab and placebo PFS/SSD, including glass barrel with prestaked needle, flange, plunger and needle guard are sourced for GSK by a third party provider. The otilimab and placebo PFS is filled and assembled with the safety syringe components by GSK (or its affiliates).
- The instructions for use (IFU) for these injection devices are provided in the study reference manual (SRM).
- The otilimab and placebo PFS instructions were developed and optimised as a result of formative human factors (HF) studies and are representative of those that are planned for the product. The summary HF information will be provided in the regulatory submission.
- All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

- The site pharmacist or unblinded administrator 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 SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally randomised using Interactive Response Technology (IRT). Before the study is initiated, the log in information and directions for the IRT will be provided to each site. Study intervention will be dispensed at the study visits summarised in the SoA for the treatment period (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK or designee prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Participants will be randomised in a ratio of 6:6:3:1:1:1 to receive study intervention (Section 1.2 and Section 6.1). Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, all participants will receive oral capsules twice daily and once-weekly SC injections. Until such time as a matched placebo becomes available for GSK3196165, every SC injection must be delivered by an unblinded administrator and the syringe must be shielded from the participant to avoid unblinding.

An unblinded pharmacist (or unblinded designee) will be responsible for the dispensation of the study intervention and will endeavour to ensure that there are no differences in time taken to dispense between the different intervention arms. While the study drug is supplied in vials, care will be taken to ensure that participants are not able to see the injection volume, syringe size or colour of liquid. The syringe should be prepared away from view of the participant, and appropriate shielding or masking of the syringe applied prior to administration.

In addition, investigators and site staff will not have access to ongoing post-randomisation hsCRP/ESR analyses and should refrain from performing either routine ESR or CRP assessments unless clinically indicated for AE assessment. Furthermore, the results of the PK analyses of GSK3196165 will not be provided to the sites.

Dose modifications to the oral study intervention will not be permitted in this study as it will have the potential to unblind the treatment assignments. For this reason, the eligibility criteria have been designed to exclude potential participants that may require a

dose reduction for safety reasons and any concomitant medications that may require a dose reduction will also be prohibited.

In order to reduce bias, an independent joint assessor will perform all joint assessments (Section 8.1.1).

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomisation/dispensing has been done accurately.

A participant may continue in the study if that participant's intervention assignment is unblinded.

GSK's Pharma 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.

6.4. Study Intervention Compliance

GSK3196165 or matching placebo will be administered by SC injection at the times indicated in the SoA (Section 1.3). Participants should receive all doses per schedule, however exceptional circumstances may lead to a dose being missed. If a dose is missed, the dose may be rescheduled to a new date/time providing the new date is within the SoA window for the missed dose. If the dose cannot be rescheduled within the visit window, the dose must not be given outside the window and must be marked as missed in the IRT. After a missed dosed, further dosing may continue per SoA with the following requirements:

- Except for doses temporarily interrupted for safety reasons, the investigator must meet to discuss compliance with the study intervention with any participant who appears to be non-compliant.

- If the participant continues to be non-compliant and missed further doses, the investigator may decide to permanently discontinue the participant from study intervention and initiate standard of care. The participant will be encouraged to continue to attend study visits until Week 52.

A record of the number of study intervention injections dispensed to and taken by each participant must be maintained by the site staff and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the CRF.

Compliance with tofacitinib and matching placebo capsules will be assessed through querying the participant during the site visits and documented in the source documents. A record of the number of capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention

start and stop dates, including dates for intervention delays will also be recorded in the CRF.

6.5. Prior and Concomitant Therapies

Due to effect of cytokines on the CYP450 enzymes (Section 2.3.1) initiation or discontinuation of study intervention may have clinically relevant effect for CYP substrates with a narrow therapeutic index e.g. warfarin and theophylline. Where a CYP3A4 substrate drug is co-administered during the study, in addition to recording the initial dose and any dosage changes over time in the CRF, the results of any therapeutic monitoring (e.g. INR results), if available, should also be recorded.

Investigators should exercise caution when study intervention is co-administered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc.

6.5.1. Permitted Therapies

Medications or treatments deemed necessary by the investigator to provide supportive care will be permitted during the study except when administration would occur during a time of restricted use, as in Table 2, or if the medication is specifically excluded, as in Section 6.5.2. The permitted dose is the usual marketed dose approved in the country in which the study is being conducted. Any use of these medications must be recorded in the eCRF, 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. The requirements for use of specific permitted medications/treatments are listed in Table 2.

Table 2 Requirements for Use of Specific Permitted Medications/Treatments

Medications/Treatments	Restriction		
	Prior to study treatment period	**During study treatment period** Day 1 to Week 52	**During 8-week follow-up**
Conventional synthetic DMARDs Participants must currently be taking at least one and at most two of the following concomitant csDMARDs			
Methotrexate 15-25mg/week oral or injected. A lower dose of ≥7.5 mg/week is acceptable if reduced for reasons of intolerance to MTX. e.g. hepatic or hematologic toxicity, or per local requirement (this must be clearly documented in medical records). Exception: A lower dose of 6 mg/week is only allowed if the minimum locally approved or recommended dose is lower than 7.5 mg/week.	At least one and at most two required (must have received at least 12 weeks treatment prior to Day 1, with stable and tolerated dose for at least 8 weeks prior to Day 1)	At least one and at most two required (dose must remain stable except adjustment for safety reasons)	Permitted
Hydroxychloroquine up to 400 mg/day			
Chloroquine up to 250 mg/day			
Sulfasalazine up to 3000 mg/day			
Leflunomide up to 20 mg/day			
Bucillamine up to 100 mg/day (or up to 300 mg/day if permitted per local requirements)			
Iguratimod up to 50 mg/day			
Corticosteroids			
Stable dosing regimen of oral corticosteroids ≤10 mg/day prednisolone or equivalent.	Permitted (dose must be stable 4 weeks prior to Day 1 and during screening if longer, with no changes except for safety reasons)	Permitted (dose must remain stable except for safety reasons)	Permitted
Intra-articular corticosteroids	Prohibited within 4 weeks prior to Day 1 and during screening, if longer.	Permitted after Week 12 (Post week 12, the number of IA steroid injections should be limited to 2 injections through Week 52, administration should not occur during the 4 weeks prior to Week 24 or Week 52. The site(s) of injection must be recorded)	Permitted
Inhaled steroids, topical steroids or topical immunosuppressive agents (e.g., eye drops, creams)	Permitted	Permitted	Permitted

Medications/Treatments	**Restriction**		
	Prior to study treatment period	**During study treatment period** Day 1 to Week 52	**During 8-week follow-up**
Analgesics			
Acetaminophen (paracetamol) **taken as rescue for RA pain:** up to a maximum of 4g/day or locally approved maximum (if lower).	Permitted as needed (but not within 24 hours of Day 1 baseline visit)	Permitted as needed (but not within 24 hours of assessment visits)	Permitted
NSAIDs including aspirin and selective cyclooxygenase inhibitors. • *In this study, aspirin is considered a NSAID, except for low-doses (e.g. 75-150 mg/day) prescribed for cardiovascular or cerebrovascular disease.*	Permitted **Participants on regular doses:** Dosing regimen must be stable 7 days prior to Day 1, no changes except for safety reasons. Do not discontinue in advance of visits.	Permitted **Participants on stable, regular doses:** From Day 1 to Week 12, dose regimen must not change except for safety reasons. Do not discontinue in advance of visits. After Week 12, any new analgesic or change in regimen should not occur within 24h of assessment visits.	Permitted
Weak opioid analgesics (e.g. tramadol up to 400 mg/day, codeine)	**Participants on PRN prescription:** Record each dose during screening, or frequency with start/end dates, in CRF. Should not be taken within 24h of Day 1 baseline visit.	**Participants on PRN prescription:** Record each dose, or frequency with start/end dates, in CRF. Should not be taken within 24h of assessment visits.	
Strong opioid analgesics (e.g. morphine, hydromorphone, oxycodone, hydrocodone, fentanyl, meperidine, methadone)	Prohibited within 4 weeks prior to Day 1 and during screening, if longer.	Permitted after Week 12 After week 12, PRN or regular doses may be considered, but any new analgesic or change in regimen should not occur within 24h of assessment visits. **Participants on PRN prescription:** Record each dose, or frequency with start/end dates, in CRF. Should not be taken within 24h of assessment visits.	Permitted
Other Medications			
Intra-articular Hyaluronic acid and any other intra-articular compounds used as lubricant in the joints.	Prohibited within 2 weeks prior to Day 1 and during screening, if longer.	Prohibited within 2 weeks prior to Week 12, Week 24 and Week 52 assessments.	Permitted

Prior to any dose changes in csDMARD(s) or oral corticosteroids, it is recommended that the Investigator contacts the medical monitor to discuss and agree with the dose change.

Use of analgesics is restricted during the first 12 weeks of study intervention and thereafter, investigators should follow routine clinical practice to manage RA pain (see Table 2). Any new analgesic or change in analgesic use must be recorded in the concomitant medication eCRF.

Other medications (including vitamins, herbal and dietary supplements) will be considered on a case-by-case basis and will be permitted if in the opinion of the Investigator, after consultation with the medical monitor as necessary, the medication will not interfere with the study procedures or compromise participant safety.

6.5.2. Prohibited Therapies

Medications prohibited or restricted prior to the study, during the study and/or during the safety follow-up of the study are listed in Table 3, along with any period of exclusion which must be applied.

Table 3 Prohibited Medications/Treatments

Medications/Treatments		Restriction		
		Prior to study treatment period	**During study treatment period** Day 1 to Week 52	**During 8-week follow-up**
Treatments affecting GM-CSF pathway				
Any treatment antagonising GM-CSF or its receptor		Prohibited (**Exclusion criterion**)	Prohibited (except study intervention)	Prohibited
Conventional synthetic DMARDs				
Combination treatment with MTX and Leflunomide		Discontinue at least 12 weeks prior to Day 1	Prohibited	No restriction
Combination treatment of 3 or more csDMARDs		Discontinue at least 4 weeks prior to Day 1	Prohibited	No restriction
Azathioprine alone or in combination with Methotrexate		Discontinue at least 4 weeks prior to Day 1	Prohibited	No restriction
Tacrolimus Not permitted as background medication		Discontinue at least 4 weeks prior to Day 1	Prohibited	No restriction
Hydroxychloroquine, chloroquine, sulfasalazine, minocycline, cyclosporin, bucillamine, iguratimod. If not being continued as background medication during the study.		Discontinue at least 4 weeks prior to Day 1	Prohibited	No restriction
Leflunomide If not being continued as background medication during the study.	Without washout treatment	Discontinue at least 12 weeks prior to Day 1	Prohibited	No restriction
	With washout treatment for 11 days with oral cholestyramine (8 g three times daily) or charcoal (50 g four times daily)	Washout treatment must complete at least 2 weeks prior to Day 1	Prohibited	No restriction

Medications/Treatments	Restriction		
	Prior to study treatment period	**During study treatment period** Day 1 to Week 52	**During 8-week follow-up**
Other csDMARDs If not being continued as background medication during the study.	Discontinue at least 4 weeks prior to Day 1	Prohibited	No restriction
Biologic DMARDs			
Etanercept (including its biosimilars).	Discontinue at least 4 weeks prior to Day 1	Prohibited	Prohibited
Any cell-depleting therapies, e.g., anti-CD20.	Discontinue at least 52 weeks prior to Day 1.	Prohibited	Prohibited
Any other biologic DMARDs (experimental or approved)	Discontinue at least 8 weeks prior to Day 1.	Prohibited	Prohibited
Targeted synthetic DMARDs			
Janus kinase (JAK) inhibitors , experimental or approved (e.g. tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib).	Prohibited (Exclusion criterion)	Prohibited (except study intervention)	Prohibited
Other (non-JAKi) tsDMARDs either experimental or approved.	Discontinue at least 4 weeks or 5 half-lives, (whichever is longer) prior to Day 1.	Prohibited	Prohibited
Other RA therapies			
Plasmapheresis or intravenous immunoglobulin (IVIG) or use of plasma filtering devices (eg. Staph protein A column (Prosorba))	Discontinue at least 26 weeks prior to Day 1.	Prohibited	Prohibited
Corticosteroids			
Dose changes in oral corticosteroids ≤10 mg/day prednisolone or equivalent	Prohibited 4 weeks prior to Day 1, and during screening if longer, except for safety reasons	Prohibited (except for safety reasons)	No restriction
Oral corticosteroids >10 mg/day prednisolone or equivalent	Discontinue or reduce to ≤10 mg/day, at least 4 weeks prior to Day 1.	Prohibited (except for safety reasons)	No restriction
Intra-muscular or intravenous corticosteroids	Discontinue at least 4 weeks prior to Day 1, and during screening if longer.	Prohibited (except for safety reasons)	No restriction
Other Medications			
Potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole). One or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Potent CYP3A4 inducers (e.g., rifampin).	**Refer to SRM for additional guidance**	Prohibited	No restriction

Medications/Treatments	Restriction		
	Prior to study treatment period	**During study treatment period** Day 1 to Week 52	**During 8-week follow-up**
Vaccine Immunisations Note: Investigators should review and update the vaccination status of potential participants as per local guidelines for adult vaccination prior to entering them into the study (refer to EULAR recommendations where no local guidelines are available [Furer, 2019]), with particular attention to the vaccination status of participants over 65 years of age. All participants who have not received the herpes zoster vaccine at study entry will be recommended to complete vaccination >30 days prior to randomisation. All participants may receive inactivated flu vaccines during the study at the discretion of the investigator.			
Live-attenuated vaccinations	Discontinue at least 30 days prior to Day 1	Prohibited	Prohibited
BCG vaccination	Discontinue at least 365 days prior to Day 1.	Prohibited	Prohibited

6.5.3. Rescue Medicine

Acetaminophen (paracetamol) is permitted as needed, both prior to and during the study as rescue medicine for RA pain management, up to 4g/day or to the maximum permitted under local label (if lower than 4g/day). However, acetaminophen (paracetamol) must **not** be taken within 24 hours prior to the baseline (Day 1) or any assessment visit.

Any use of rescue medication must be recorded in the appropriate concomitant medication form, in the CRF.

6.6. Dose Modification

6.6.1. Dose Modification of Study Intervention

Dose reduction of the SC and/or oral study interventions is not permitted in this study.

6.6.2. Dose Modification of Background Therapy

Dose reduction or temporary interruption of the background csDMARD medication(s) may be performed at any time for safety reasons (e.g. intolerance or toxicity) but must be clearly documented. If clinically indicated, csDMARD may be re-started following an interruption and increased back to the dose taken prior to the change.

Dose modifications for reasons other than safety are not permitted during the study treatment period.

6.7. Intervention after the End of the Study

Participants who complete the 52-week treatment period visit may have the option to transition into long term extension study 209564. Exceptionally, participants who missed their final SC dose at Week 51 in this study may still be eligible, after consultation with the medical monitor. Participants receiving GSK3196165 in this study will continue to receive the same dose in the extension study. Participants receiving tofacitinib in this

study will be re-randomised in a 1:1 ratio to either GSK3196165 90 mg or GSK3196165 150 mg once-weekly in the extension study.

Participants who do not transition into long term extension study 209564, will not receive any further treatment with GSK3196165 but will be treated according to local standard of care for RA disease.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

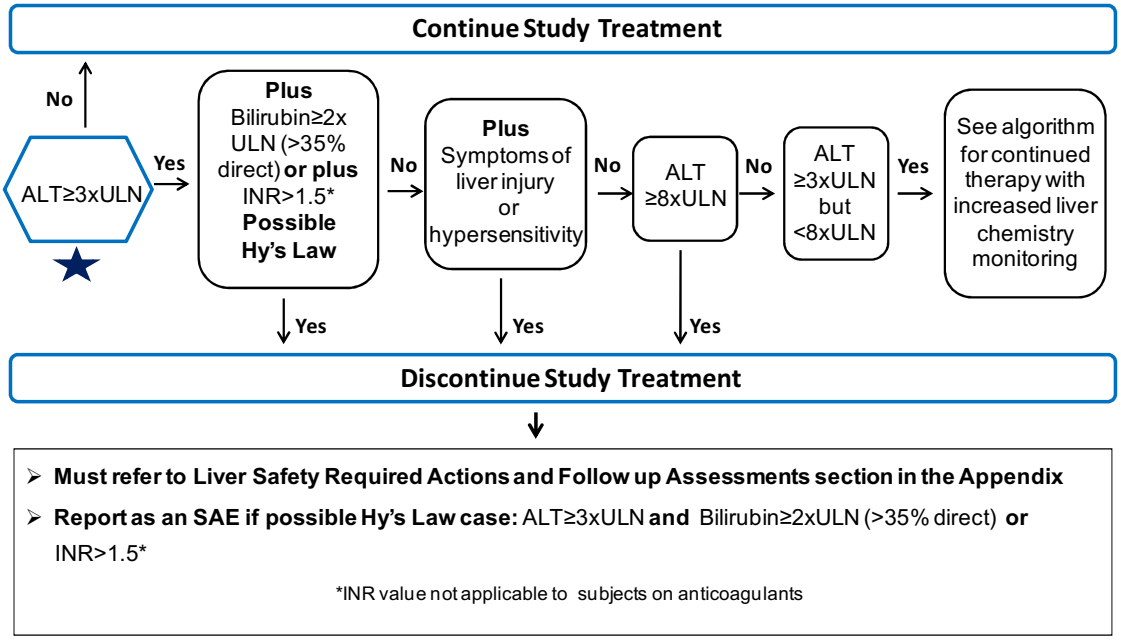
In rare instances, it may be necessary for a participant to permanently discontinue study intervention (oral capsules and SC injection). A participant will permanently discontinue study intervention if there is no longer a positive risk:benefit ratio at any time point in the study as determined by the investigator. If study intervention is permanently discontinued, the participant will, where possible, remain in the study and continue with study visits in order to be evaluated for efficacy and safety. These participants will not be eligible to participate in long term extension study 209564.

7.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study intervention for abnormal liver tests is required when a participant meets one of the conditions outlined in the algorithms. Additionally, study intervention must be discontinued if there are any clinical signs/symptoms suggestive of hepatic decompensation such as ascites and hepatic encephalopathy.

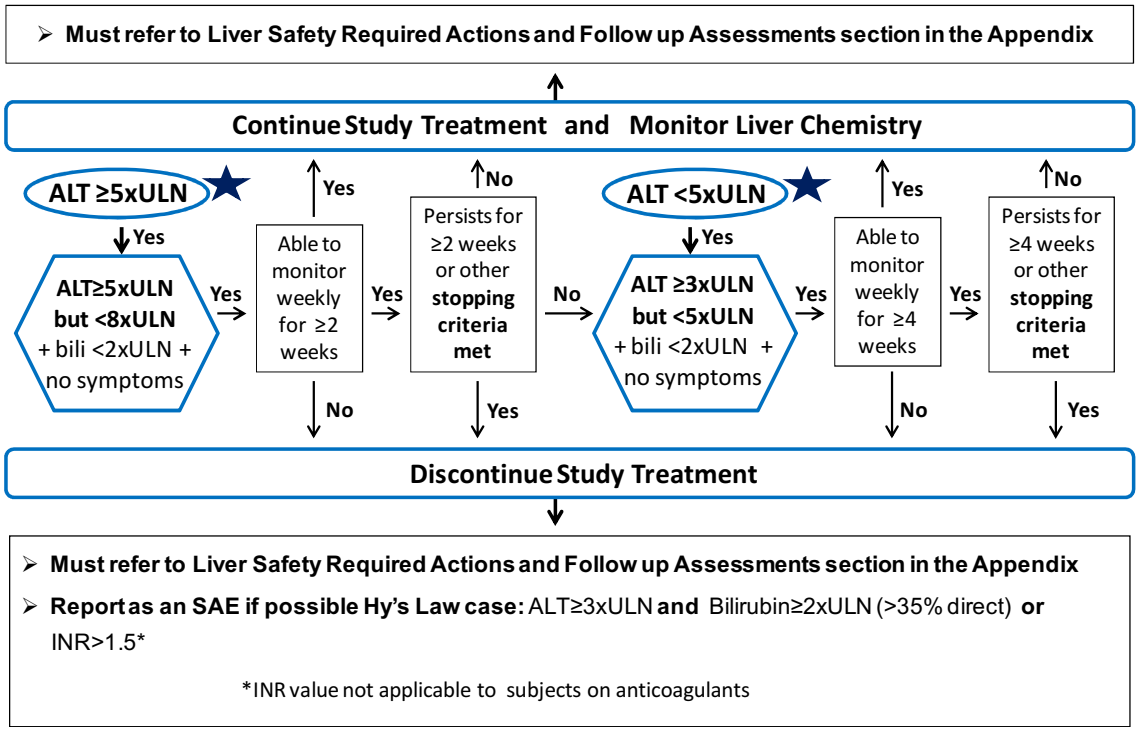
Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



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

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



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

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

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

7.1.2. Other Stopping Criteria

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

- VTE, including PE and DVT, requiring anti-coagulation
- Pregnancy (see Section 8.3.5 and Appendix 4).
- Confirmed pulmonary alveolar proteinosis (see Section 8.2.6).
- Serious hypersensitivity reactions (see Section 8.3.7).
- Other serious or severe adverse events or other significant medical event, at the discretion of the investigator, after consultation with the Medical Monitor.

- HBV DNA level ≥200 IU/mL or HBV DNA detected at any level with recent increase in hepatic transaminases (see Figure 2 in Section 8.2.8).
- HBV DNA positive (any level ≤200 IU/mL) and on repeat testing within 1 week (see Figure 2 in Section 8.2.8) either:
    - HBV DNA positive (any level) OR
    - HBV surface antigen positive OR
    - increase in hepatic transaminases.
- New latent or active TB infection (see Section 8.2.7.4).
- Gastrointestinal perforation.
- Absolute neutrophil count (ANC) <0.5 x 10^9/L.
- Lymphocyte count <0.5 x 10^9/L.
- Severe renal impairment (eGFR <30 mL/min/1.73m^2) and confirmed upon repeat testing.
- Introduction of prohibited therapies or dosages where continuation of the study intervention would place the participant at risk in the opinion of the investigator and medical monitor.

7.1.3. Temporary Discontinuation

7.1.3.1. Respiratory Symptoms

Study intervention will be temporarily discontinued if a participant develops a persistent cough (CTCAE Grade ≥ 2) [NCI, 2017] or persistent dyspnoea (dyspnoea scale Grade ≥ 2) for 3 consecutive weeks (21 days). The participant should be referred to a pulmonologist for further assessment. Study intervention should remain suspended until the symptoms or signs that caused referral have resolved and/or the diagnosis has been determined and clinically significant events have been excluded by the pulmonologist. Participants with a confirmed diagnosis of pulmonary alveolar proteinosis must permanently discontinue study intervention (Section 7.1). Suggested pulmonary assessment and management algorithms are provided in a separate Pulmonary Safety Guidance Document in the SRM.

7.1.3.2. Serious and Opportunistic Infections

If a serious or opportunistic infection or sepsis develops, temporarily discontinue study intervention until the infection is controlled and discuss further management with the medical monitor.

7.1.3.3. Haematologic Abnormalities

Study intervention will be temporarily discontinued upon confirmatory (local) repeat test, for the following haematological abnormalities:

- White blood cell (WBC) count <2.0 x 10^9/L.

- ANC ≤1.0 x 10^9/L.
- Lymphocyte count ≤0.75 x 10^9/L
- Decrease in haemoglobin >2g/dL or haemoglobin <8.0g/dL. Dosing should be interrupted until haemoglobin values have normalised.

The local repeat test must be performed and assessed within 7 days (ideally 3-5 days), with additional sample(s) sent for central testing.

If study intervention is temporarily discontinued, the abnormality must be reported as an AE and a further repeat test should be performed within 7 days of discontinuation. The medical monitor should be consulted if the repeat test is still abnormal. Study intervention can be restarted if the haematological parameters rise above these values.

7.1.3.4. TB Reactivation

Study intervention may be temporarily discontinued for the following after consultation with the medical monitor:

- Suspected TB reactivation (see Section 8.2.7.4).

7.1.3.5. Renal Abnormalities

Study intervention will be temporarily discontinued for the following renal abnormality:

- Moderate to severe renal impairment (eGFR ≥30 to <45 mL/min/1.73m^2).

A repeat test must be performed locally and assessed within 7 days with additional sample(s) sent for central testing. The medical monitor should be consulted if the repeat test is still abnormal and a further repeat test performed again within 7 days. Study intervention can be restarted if renal function improves to ≥45 mL/min/1.73m^2.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted following the procedures at the Week 52 visit, as shown in the SoA (Section 1.3). A safety follow-up visit should be scheduled at 8 weeks post last dose of study SC intervention.
- The participant will be permanently discontinued both from the study intervention and withdrawn 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.

7.3. Lost to Follow Up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

8.1.1. Joint Assessments

An evaluation of all 68 joints for tenderness and 66 joints for swelling will be performed by an independent joint evaluator. Replaced or fused joints are considered non-evaluable and will not be included in joint evaluations. The reason for absence of the evaluations of those joints must be recorded. If a joint has undergone intra-articular injection of corticosteroid during the course of the study, the injected joint must be recorded.

One or more independent assessors, who have documented experience in performing joint assessments, will be designated at each trial site to perform joint assessments. Preferably the same independent assessor will perform all joint assessment for the same participant throughout the trial. The principal investigator must ensure that the independent joint assessor has documented experience and he/she is adhering to locally accepted and implemented standards. This also applies if the independent joint assessor is replaced during the trial.

The independent joint assessor should have no other contact with the participant during the trial, must not be the treating physician (investigator), should not discuss the clinical status of the participant with them during the joint assessment nor with other site

personnel, and will not be permitted to review the participant's medical records, the eCRF, nor any of the previous joint assessments.

The procedure for joint assessments is provided in the SRM.

8.1.2. Physician's Global Assessment of Arthritis

Investigators will complete a global assessment of RA disease activity using the physician global assessment item (PhGA), a visual analogue scale (VAS) with anchors "0" (CCI) to "100" (CCI), respectively.

8.1.3. Joint X-Rays

Radiographic progression of structural joint damage will be assessed using X-rays of the hands and feet. All X-rays will be read centrally by the imaging CRO and will be assessed for the presence or absence of erosion(s). X-rays will be taken at screening to confirm eligibility.

8.1.4. Patient Reported Outcomes

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

CCI

8.1.4.1. Patient's Assessment of Arthritis Pain

Participants will assess the severity of their arthritis pain over the past week, using a 100 unit VAS, with anchors "0" (CCI) and "100" (CCI).

The results of this question will be used for the HAQ-DI, where the local version of HAQ-DI asks the same question.

8.1.4.2. Patient's Global Assessment of Arthritis

Participants will complete a global assessment of disease activity using the patient global assessment (PtGA) item, a VAS with anchors "0" (CCI) to "100" (CCI).

8.1.4.3. Health Assessment Questionnaire – Disability Index (HAQ-DI)

The functional status of the participant will be assessed by means of the Disability Index of the Stanford Health Assessment Questionnaire (HAQ-DI). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in eight functional areas [Fries, 1980]: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities.

CCI

CCI

8.1.4.7. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue questionnaire is a validated patient-reported measure developed originally to assess fatigue in individuals with cancer. The FACIT-fatigue has subsequently been used and validated in numerous chronic conditions, including RA.

8.1.4.8. SF-36 Short Form Health Survey

Health-related quality of life (HRQL) will be assessed using the participant-completed Medical Outcomes Study (MOS) Short-Form 36 (SF-36) which is a generic health survey that contains 36 questions covering eight domains of health. The SF-36 yields an eight-scale profile of functional health and well-being scores as well as physical and mental component health summary scores. The version 2, 1-week recall questionnaire will be used.

CCI

CCI [redacted]

8.2. Safety Assessments

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

In the event that pulmonary follow-up criteria are triggered, all sites must have access to a pulmonologist (see Section 7.1.3.1 and Section 8.2.6).

8.2.1. Dyspnoea Assessments

The dyspnoea scale grades the effect of breathlessness on daily activities and measures perceived respiratory disability. The scale will be completed by the investigator in consultation with the participant. Dyspnoea will be reported on a rating scale from 0 (CCI [redacted]) through 4 (CCI [redacted]).

8.2.2. Physical Examinations

- A complete physical examination (e.g. at the Screening visit) 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.
- All physical examinations will include monitoring for signs and symptoms of TB (see Section 8.2.7).

8.2.3. Electrocardiograms

- 12-lead ECG measurements should be recorded pre-dose, and where possible before vital sign measurements and blood draws.
- Participants should be in a quiet setting without distractions and rest in a supine position for at least 5 or 10 minutes before ECG collection.
- Triplicate 12-lead ECG measurements will be obtained at screening with single ECG measurements obtained post-baseline 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.

- At the screening visit where triplicate ECG are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- ECG traces will be read locally.

8.2.4. Vital Signs

- Vital signs should be measured pre-dose, and where possible before blood draws.
- Temperature, pulse rate, respiratory rate and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. The participant should use the same position throughout all visits.
- All blood pressure readings will be recorded using an appropriate cuff size with the same arm being used throughout the study.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- When the timing of these measurements coincides with blood collection, the blood pressure and heart rate should be obtained first.

8.2.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA in Section 1.3 for the timing and frequency.
- All study-required laboratory assessments will be performed by a central laboratory except erythrocyte sedimentation rate (ESR), dipstick urinalysis, and urine pregnancy tests which will be analysed locally.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- In this study, the **key** laboratory parameters are WBCs, lipids, haemoglobin, platelets, lymphocytes, neutrophils and liver function tests.
- Participants who develop hyperlipidemia should be managed according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)].
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.2.6. Pulmonary Assessments

Pulmonary assessments are a key aspect of the safety monitoring in this study. The following pulmonary assessments will be performed as specified in the SoA (Section 1.3).

- Chest X-ray (posteroanterior).
- Cough assessment.
- Dyspnoea assessment (see Section 8.2.1).
- Lung auscultation.
- Pulse oximetry.
- Pulmonary function tests (PFTs) – spirometry (FEV_1 and FVC) at baseline (or prior to Day 1) only or as required by the pulmonologist in the event of participant referrals for further assessment.

In the event of any new or clinically significant pulmonary abnormalities that may develop during the study (e.g., increased shortness of breath/dyspnoea, or unexplained and persistent coughing), it is recommended that the participant be referred to a pulmonologist for further assessment.

If, at any time during the study, a participant reports new onset or an increase (if present at baseline) in cough (CTC Grade ≥2) or dyspnoea (Grade ≥2), they must be questioned again (either by phone or during the site visit) on a weekly basis for 3 further consecutive weeks or until the symptoms resolve, if earlier. Any new onset or worsening cough and/or dyspnoea must be reported as an AE.

If a participant experiences persistent cough Grade ≥2 for three consecutive weeks (≥21 days) or persistent dyspnoea Grade ≥2 for three consecutive weeks (≥21 days), study intervention must be temporarily discontinued immediately, and the participant undergo a local pulmonologist review within 1-2 days. Chest X-ray and repeat spirometry must be performed within 1 week in addition to any other assessments deemed appropriate by the consulting pulmonologist. The study intervention must be temporarily discontinued as per the pulmonary guidance document until the symptoms or signs that caused referral have resolved and/or the underlying diagnosis has been determined and clinically

significant events have been excluded by the pulmonologist. Pulmonary assessment/management algorithms are provided in a separate Pulmonary Safety Guidance Document in the SRM.

The participant may undergo additional pulmonary imaging (high-resolution computed tomography [HRCT]) or other tests during the study to investigate pulmonary abnormalities; the Pulmonary Adjudication Committee (PAC), IDMC or SRT may request copies of any reports or images for central review.

Any participant with a diagnosis of pulmonary alveolar proteinosis must permanently discontinue study intervention (Section 7.1.2).

8.2.7. Tuberculosis Monitoring

8.2.7.1. Tuberculosis Status Definitions

In this study the following definitions for active TB, latent TB and adequate treatment of latent TB will be utilised.

Active TB is defined as:

- Microbiological evidence of TB (including, but not limited to, microscopy for acid-fast bacilli, mycobacterial culture, GeneXpert, or other validated PCR) in any clinical sample (including, but not limited to, sputum, pus, or biopsied tissue),

OR

- Findings on medical history or clinical examination and/or chest radiograph consistent with active TB as assessed by a physician specialising in TB, sufficient to warrant empirical treatment for active TB even in the absence of microbiological evidence of TB.

Latent TB is defined as:

- A positive QuantiFERON-TB Gold plus test or T-SPOT.TB test, no findings on medical history or clinical examination consistent with active TB and a normal chest radiograph.

Adequate latent TB treatment status

For participants that have received treatment for latent TB within the previous 5 years, a participant is considered to have received adequate treatment if a physician specialising in TB agrees that:

- sufficient evidence exists demonstrating that completion of treatment has occurred AND

- the participant has no findings on medical history or clinical examination consistent with active TB, and a normal chest radiograph.

Appropriate treatment for latent TB is considered to be:

- Completion of at least 6 months of INH or an alternative regimen consistent with WHO or national guidelines.
- Participants who received treatment more than 5 years ago for latent TB infection and who remain QuantiFERON-TB Gold plus or T-SPOT.TB test positive will need to complete treatment for latent TB prior to study entry as per Section 8.2.7.3.

8.2.7.2. Tuberculosis Testing

In this study the following testing for TB must be followed:

- The QuantiFERON-TB Gold plus test will be used in countries where it is available. Where QuantiFERON-TB Gold plus test is not available T-SPOT.TB will be used.
- A QuantiFERON-TB Gold plus test may be repeated once during screening if the initial result is indeterminate, alternatively a T-SPOT.TB test may be used following an indeterminate result. This is not considered a rescreening.
- Unscheduled TB testing should be performed if a participant is known or suspected to have come in close contact with someone who has untreated **active** TB.

8.2.7.3. Treatment of Latent TB During the Study

Participants diagnosed with latent TB during screening will need to complete a course of at least 6 months of INH therapy during the study including at least 4 weeks of therapy prior to randomisation.

Following 3 weeks of INH treatment in screening, LFTs must be assessed. Participants will fail screening if ALT >1.5 x ULN is identified, these participants may be re-screened if ALT elevation resolves to ALT <x 1.5 ULN during ongoing INH therapy following discussion with the medical monitor. Participants who are randomised will require LFT assessment every 4 weeks during the study.

8.2.7.4. Monitoring for TB Infection and Re-activation During the Study

Routine monitoring for the signs and symptoms of TB will be performed during this study as part of every full or brief physical exam (see SoA in Section 1.3).

If at any point during the study, the investigator suspects that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken including consultation with a physician specialising in TB. The investigator should discuss with the medical monitor and interruption of study intervention should be considered.

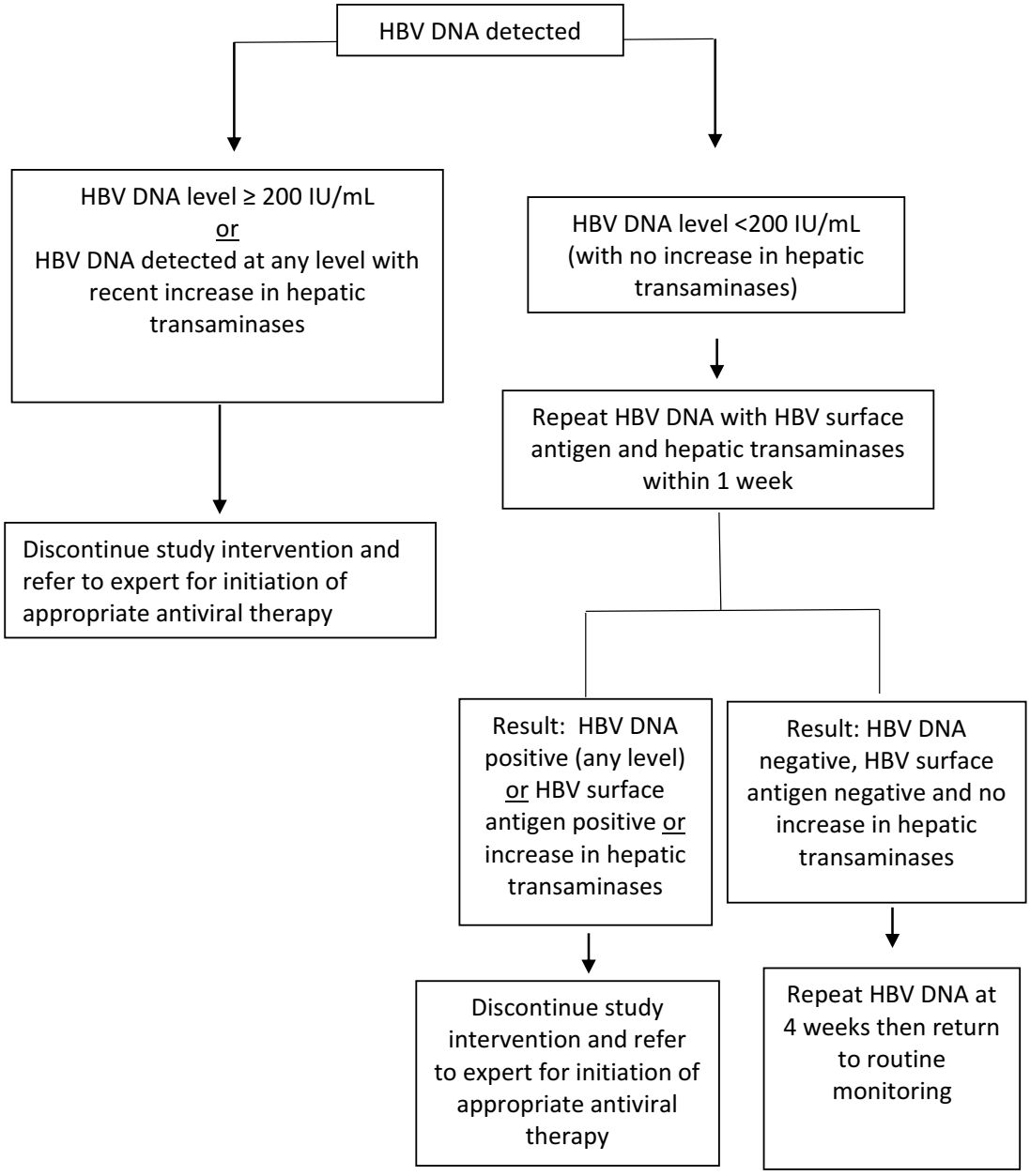
A QuantiFERON-TB Gold Plus test or a T.SPOT.TB test must be performed as part of the Week 48 assessment (see SoA in Section 1.3). If a participant has a positive result at Week 48 who previously had a negative result at study start, then the participant must be referred to a physician specialising in TB to determine if the participant has active or latent TB.

If TB infection is diagnosed, study intervention must be discontinued.

8.2.8. Hepatitis B Monitoring

All participants with positive HBcAb results will have HBV DNA levels monitored throughout the study as summarised in Figure 2.

Figure 2 Monitoring of HBV DNA Levels in HBcAb Positive Participants



From the start of study intervention, HBV DNA levels will be assessed every 4 weeks to Week 24, then every 8 weeks to Week 40 and then every 12 weeks to Week 52.

8.2.8.1. Risk of Reactivation in Participants Positive for Hepatitis B Core Antibody (HBcAb)

Participants who are HBcAb positive, will be informed of the risk of reactivation and that if this occurs treatment with antiviral therapy, such as with nucleo(s)tide analogues such as entecavir or tenofovir, will be needed.

8.2.8.2. Treatment of Participants Who Are HBcAb Positive and Who Develop Detectable HBV DNA Requiring Initiation of Antiviral Therapy

HBcAb positive participants who become positive for HBV DNA and require antiviral therapy must have study intervention discontinued. The participant must also be referred to a hepatologist or infectious diseases expert so that treatment advice regarding whether to commence anti-viral therapy is received within 7 days of HBV DNA elevation being identified. The participant should then be reviewed by the expert within 14 days of HBV DNA elevation being identified and managed as per local guidelines or under EASL or AASLD guidelines if none are available.

8.2.8.3. Follow Up of Participants Treated With Anti-viral Therapy

All participants will be followed up within the study by the investigator in addition to local expert follow up. After completion of the study, participants should be followed up as per local expert opinion based on guideline recommendations.

8.3. Adverse Events and Serious Adverse Events

- The definitions of an AE or SAE can be found in Appendix 3.
- The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).
- Participants will be assessed for cough or dyspnoea at selected visits as specified in the SoA (Section 1.3. The investigator will complete the CTC cough scale if a cough is present and will record dyspnoea as per the dyspnoea scale. Lung auscultation and pulse oximetry will also be performed at the visits specified in the SoA (Section 1.3).
- If a participant, at times other than scheduled visits, reports new onset or an increase (if present at baseline) in cough (CTCAE Grade ≥2) or dyspnoea (dyspnoea scale Grade ≥2), the participant will be questioned (in clinic or by phone) on a weekly basis for 3 further consecutive weeks or until symptoms resolve, if earlier. Any new onset or worsening cough and/or dyspnoea must be reported as an AE.

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

- All SAEs will be collected from the start of study intervention until the follow-up visit (for participants who do not enter the long-term safety study) or the Week 52 visit (for participants who enter the long-term safety study) at the time points specified in the SoA (Section 1.3).
- In addition, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study. **In China** (and where this is a local requirement) all SAEs will be collected from the time of signing informed consent form.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. 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, and non-serious AEs of special interest (as defined in Section 8.3.7), will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). 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 a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of 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.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 8 weeks after the last SC dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Female participants who become pregnant after the start of study intervention must permanently discontinue study intervention but can continue to be followed in the study if they wish (Section 7.1.2). If the participant does not wish to continue in the study, follow guidance in Section 7.2.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Cardiovascular and Death Events

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

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

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

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

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

This information should be recorded in the specific CV CRF/eCRF within one week of when the AE/SAE(s) are first reported.

8.3.7. AEs of Special Interest

The potential risks with GSK3196165 are discussed in Section 2.3.1.

Adverse events of special interest GSK3196165 include:

- Serious infections
- Opportunistic infections
- TB and TB reactivation
- Neutropenia ≥ Grade 3 (<1.0 x 10^9/L)
- Pulmonary alveolar proteinosis
- Hypersensitivity reactions
- Injection site reactions
- Persistent cough (CTCAE Grade ≥2)
- Persistent dyspnoea (dyspnoea scale Grade ≥2).

8.3.8. Medical Device Deficiencies

In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Appendix 9.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.8.1 Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 9.

8.3.8.2 Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.8.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the sponsor using the Medical Device Deficiency Report Form (provided in the Pharmacy Manual), within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the sponsor device complaints email address, as provided in the Pharmacy Manual.
- The sponsor will be the contact for the receipt of device deficiency reports.
- Refer to the Pharmacy Manual for further guidance.

8.3.8.4 Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal

responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4. Treatment of Overdose

For this study, any dose of GSK3196165 or tofacitinib greater than the dose used in this study, or used more frequently than permitted (GSK3196165 once-weekly, tofacitinib twice daily) will be considered an overdose. It should be noted that the minimum permitted time between dosing with GSK3196165 is 5 days but it is strongly recommended that dosing should revert back to 7 days as soon as possible.

No specific treatment is recommended for an overdose of GSK3196165, and the investigator should treat as clinically indicated. Investigators should refer to the approved product label or local prescribing information for treatment of an overdose of tofacitinib.

In the event of a potential overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis within 3-5 days from the date of the last dose of study SC intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Contact the unblinded CRA/Monitor with the quantity and duration of the overdose to be documented.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

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8.9. Immunogenicity Assessments

Whole blood samples of approximately 6 mL will be collected from all participants and divided into suitable portions for immunogenicity assessments of anti-drug antibody (ADA) development. Antibodies to GSK3196165 will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Serum samples should also be collected at the final visit from participants who discontinued study intervention or are withdrawn from the study. In addition to scheduled immunogenicity assessments, "event-driven" testing will be performed in the context of serious hypersensitivity reactions or AEs deemed to be clinically significant in the opinion of the investigator resulting in discontinuation from study intervention.

Serum samples will be screened for antibodies binding to GSK3196165 and the titre of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to GSK3196165 and/or further characterise the immunogenicity of GSK3196165. The serum sample collected at Day 1 will also be analysed for anti-GM-CSF auto-antibodies and free GM-CSF levels.

The detection and characterisation of antibodies to GSK3196165 will be performed using validated assay methods by or under the supervision of the sponsor. Antibodies may be further characterised and/or evaluated for their ability to neutralise the activity of the study intervention(s). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis.

8.10. Medical Resource Utilisation and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of the study is to determine whether GSK3196165 is superior to placebo in the treatment of participants with moderately to severely active RA despite csDMARD treatment (i.e. csDMARD-IR), as assessed by the proportion of participants achieving ACR20 response at Week 12.

The study will test the null hypothesis that there is no difference between 150 mg dose of GSK3196165 and placebo in the proportion of participants achieving ACR20 response at Week 12 versus the alternative hypothesis that the 150 mg dose of GSK3196165 differs from placebo in the proportion of participants achieving ACR20 response at Week 12.

9.2. Sample Size Determination

Approximately 3000-3600 participants will be screened to achieve between 1500 and 1800 randomly assigned to study intervention. Approximately 1500 evaluable participants are expected to be included in the primary analysis, of whom approximately 1350 are expected to complete the Week 12 visit. When the approximate target of 1500 participants is reached, recruitment may continue up to a maximum of 1800 participants to ensure sufficient numbers in the key Asian country subgroup.

For the purpose of analyses up to Week 12, the placebo-sequence groups will be pooled into a single placebo arm.

The minimum sample size of 1500 will provide:

- >99% power to detect a 25% difference between GSK3196165 and placebo in the ACR20 response at Week 12 (55% vs 30%) based on a 2-sided significance level of 0.05 using a pooled z-test. The least significant difference this sample size will detect is 7.2%
- >99% power to detect a 20% difference between GSK3196165 and placebo in the CDAI-LDA response at Week 12 (37% vs 17%) based on a 2-sided significance level of 0.025 using a pooled z-test. The least significant difference this sample size will detect is 7.2%
- Approximately 82% power for the non-inferiority analysis of ACR20 response rate at Week 12 between GSK3196165 and tofacitinib groups, where a response rate of 60% in each group, a non-inferiority margin of 12% and a 1 sided significance level of 0.0125 using a pooled z-test are assumed. The non-inferiority margin was calculated using the FDA fixed margin approach [FDA, 2016]. With this sample size, the difference in proportions between tofacitinib and GSK3196165 can be up to 3% in favour of tofacitinib and still conclude non-inferiority. In order to conclude superiority, the difference in proportions must be at least 8% in favour of GSK3196165.

The above sample size and power estimates were obtained from PASS version 12.0.2.

9.3. Sample Size Sensitivity

The power of the primary analysis of the study will be affected by changes in the assumed response rate. The effect on power under varying response rates on both placebo and GSK3196165 assuming a fixed sample size of 500 in the GSK3196165 arm and 250 on the placebo arm based on a 2-sided significance level of 0.05 using a pooled z-test are shown in Table 4.

Table 4 Power for ACR20 Response at Week 12 Under Varying Response Rates on GSK3196165 and Placebo

Placebo Response Rate	GSK3196165 Response Rate		
	50%	55%	60%
30%	>99%	>99%	>99%
35%	98%	>99%	>99%
40%	74%	97%	>99%

The power of the non-inferiority analysis will be affected by changes in the assumed response rate. The effect on power under varying response rates on both tofacitinib and GSK3196165 assuming a fixed sample size of 500 in the GSK3196165 arm and 250 on the tofacitinib arm, and a fixed non-inferiority margin of 12% based on a 1 sided significance level of 0.0125 using a pooled z-test are shown in Table 5.

Table 5 Power for Non-Inferiority Analysis on ACR20 Response at Week 12 Under Varying Response Rates on GSK3196165 and Tofacitinib

Tofacitinib Response Rate	GSK3196165 Response Rate		
	58%	60%	62%
58%	82%	92%	98%
60%	65%	82%	93%
62%	44%	66%	83%

9.4. Populations for Analyses

For purposes of analyses, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Intent-to-Treat (ITT)	All randomised participants who receive at least one dose of study intervention.
Per-protocol (PP)	All randomised participants who are compliant with intervention, who do not have significant protocol violations, and whose investigator site does not have any GCP issues that require reporting to the regulatory agencies.

Population	Description
Safety	All randomised participants who take at least 1 dose of study intervention. Participants will be analysed according to the intervention they actually received.

The primary analysis population will be the ITT population. In addition, the primary and major secondary analyses will be repeated using the PP population. Full details of all protocol violations that lead to exclusion from the PP population will be listed in the Reporting and Analysis plan (RAP).

9.5. Statistical Analyses

Full details of all analyses will be described in the RAP.

The primary analysis will be performed when the minimum target sample size of 1500 has been achieved. All inferences will be drawn from the primary analysis.

The proposed sequence of primary and key secondary endpoints is:

1. ACR20 at Week 12
2. CDAI LDA at Week 12
3. HAQ-DI at Week 12.

In order to preserve the type I error, each endpoint will be assessed sequentially using a step-down approach where statistical significance can be claimed for the second endpoint only if the first endpoint in the sequence meets the requirements for significance.

Additionally, as there are two doses of GSK3196165 within each endpoint, each to be compared with placebo, a step-down procedure, where the high dose will be tested first, will be used within each endpoint, i.e. the high dose (150 mg) at a given endpoint can achieve significance only if the high dose at the prior endpoint is significant; the low dose (90 mg) at a given endpoint can achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint are significant. For each endpoint, and for each GSK3196165 dose group, the comparison with placebo will be conducted using a 2-sided significance level of either 0.05 or 0.025.

Following all comparisons with placebo, assuming that the full sequence of endpoints meets the requirements for significance, the step down approach will be used for the non-inferiority comparison with tofacitinib on the ACR20 endpoint using a 1-sided significance level of 0.0125.

A graphical presentation of the step-down procedure is provided in Appendix 8.

9.5.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The proportion of participants with ACR20 response will be summarised using counts and proportions of responders, and analysed using a Generalised Estimating Equations (GEE) model, comparing intervention group with placebo at each time point, with fixed effects of intervention, visit, baseline swollen joint count (66), baseline tender joint count (68), previously failed medication, intervention-by-visit interaction and a random effect of participant.
Key Secondary	The proportion of participants achieving CDAI LDA response will be analysed using the same method as described for the primary endpoint, however this model will include fixed effects of intervention, visit, baseline CDAI Total Score, intervention-by-visit interaction and a random effect of participant. The HAQ-DI will be expressed as a change from baseline and will be analysed using a mixed effect repeated measures model (MMRM) with fixed effects of intervention, visit, baseline value, intervention-by-visit interaction and a random effect of participant. An unstructured covariance structure will be used to model the between and within-participant errors, however if this analysis fails to converge, other structures will be tested. The Kenward-Roger method will be used to estimate the degrees of freedom. Least Squares means will be used for the statistical comparisons; CIs will also be reported. Intervention group comparisons versus placebo at Week 12 and other visits will be tested.
Additional Secondary and Exploratory	Full details on all additional analyses will be described in the RAP.

9.5.2. Estimand Strategy

The main intercurrent (post-randomisation) event anticipated to impact on the interpretation of the treatment effect for the primary objective is discontinuation of study intervention.

The estimand for the primary comparison will be defined using:

1. Population: defined through the inclusion/exclusion criteria.
2. Variable: Proportion of participants at Week 12 with ACR20 response.
3. Intercurrent Event: the participant withdrew from study intervention.
4. Population Level Summary: Comparisons of proportions between the active groups and placebo.

The primary estimand used will be the treatment policy estimand. This follows the principle that participants should be followed up, assessed and analysed irrespective of compliance to planned intervention. This strategy answers the question of what the effect is of assigning participants to an intervention. Therefore, if a participant discontinues study intervention but efficacy data continues to be collected, their data will be analysed as if they were still on the original randomised intervention. If a participant discontinues study intervention and data does not continue to be collected or if missing data occurs while on study intervention, their missing data will be imputed using multiple imputation. Full details on the missing data techniques will be provided in the RAP.

Further details on any sensitivity estimators and supplementary estimands used to assess the primary objective and any estimands used to assess the secondary objectives will be provided in the RAP.

9.5.3. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	For safety data, no formal hypotheses will be tested. Incidence of AEs, SAEs, and AESIs, including laboratory tests, vital signs, pulmonary function tests and 12-Lead ECGs will be displayed in the form of listings, frequencies, summary statistics, graphs, and statistical analyses where appropriate. Interpretation will be aided by clinical expertise. Full details, including example outputs, will be documented in the RAP.

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9.6. Interim Analyses

The primary analysis will be conducted when the planned target of 1500 randomised participants has been reached. No interim analysis with respect to this population is planned. However, if at the time of reaching approximately 1500 randomised participants a sufficient number of participants that are required for the key Asian country subgroups is not reached, then recruitment in these countries may continue. Participants who have already been enrolled from Asian country subgroups at the time of reaching the 1500 target will be included in the primary analysis. Double-blinding will be maintained for any subjects continuing in the study at the time of the primary analysis. The primary analysis will be the basis of all inferences. If enrolment continues beyond the planned target of 1500 randomised participants, secondary analyses will be conducted upon completion of enrolment/follow-up for the entire study population, based on all randomised subjects.

9.6.1. Data Monitoring Committee (DMC)

An IDMC will be utilised in this study to ensure ongoing objective medical and/or statistical review of safety data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study. See Section 10.1.5 for further details.

Full details of the data to be reviewed and membership of the committee will be available in the charter which will be available prior to the first participant's visit.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The 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 or the participant's legally authorised representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An Independent Data Monitoring Committee (IDMC), a Major Adverse Cardiac Event/Gastrointestinal Perforation (MACE/GI Perforation) Adjudication Committee and a Pulmonary Adjudication Committee (PAC) will be utilised in this study, in addition to the routine sponsor review of blinded safety data that will occur approximately every 4 weeks during the period of study conduct.

The overall responsibility of the IDMC is to protect the ethical and safety interests of participants recruited into this study while protecting as far as possible the scientific validity of the data. The IDMC and Adjudication Committees will include physicians with relevant clinical expertise and a statistician, none of whom is affiliated with the sponsor. The IDMC will adopt a staggered approach to reviewing unblinded data. The initial early review, frequency of further reviews and the safety data included, will be detailed in the IDMC charter.

The MACE/GI Perforation Adjudication Committee and PAC will function as detailed in the IDMC charter.

10.1.6. 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 multicentre 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.

10.1.7. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomisation 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 anonymised 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.

10.1.8. 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.
- This study uses a number of assessments and questionnaires to evaluate the participant's symptoms and impacts at a particular moment in time (see efficacy assessments listed in Section 8.1). These patient-reported outcomes and impact instruments completed directly by participants, investigators and joint assessors as source records (e.g. site tablet or electronic clinical outcome assessment (eCOA) portal) contribute to the secondary and exploratory endpoints and must not be changed or overwritten (with the exception of administrative/operational data items), in order to minimise bias.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organisations).
- 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.
- 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.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Source Document Acknowledgement.

10.1.10. Study and Site Closure

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

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the central laboratory except for ESR, dipstick urinalysis, and urine pregnancy tests, which will be analysed locally.
- Except for ESR, dipstick urinalysis, and urine pregnancy tests, local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or safety evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- 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.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) for WOCBP should be conducted once every 4 weeks to Week 16 and then every 8 weeks to Week 52 during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) will also be conducted at the safety follow up visit.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation of a WOCBP in the study.

Table 6 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Haemoglobin			
	Haematocrit			
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase (AP)	Albumin

Laboratory Assessments	**Parameters**			
	Albumin/globulin ratio	Phosphate	Creatine Phosphokinase (CPK)	High sensitivity C-reactive protein (hsCRP)
	γ-Glutamyl transpeptidase (GGT)	Lactate dehydrogenase (LDH)		
Lipid profile	Total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein-cholesterol, triglycerides and other lipoprotein tests as needed			
Urinalysis	• Performed locally by dipstick			
Urine pregnancy test	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]			
Other Tests	• Follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) • Highly sensitive serum hCG pregnancy test (as needed for women of childbearing potential)[2] • Serology [HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), HBV DNA, HCV RNA, and hepatitis C virus antibody], rheumatoid factor (RF), ACPA (anti-CCP), hsCRP, ESR, QuantiFERON-TB Gold plus test (or, if unavailable, T-Spot TB) • eGFR calculated by the CKD-EPI calculation. • All study-required laboratory assessments will be performed by a central laboratory, except ESR, dipstick urinalysis and urine pregnancy tests which will be performed locally. Only the results of tests performed locally will be recorded in the eCRF. Details for recording the post-randomisation ESR values will be provided in the SRM			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6. All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (>35% direct bilirubin) or ALT ≥ 3 × ULN and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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. This includes results of PK analyses, ESR (performed locally by an unblinded independent study team member) and hsCRP. The only exception is the result of ESR and hsCRP at the participant's final assessment visit, if the participant is moving to the extension study.

Note: Monitoring of CRP/hsCRP during the course of this study by local measurements, is not permitted, in order to protect the blind. However individual local measured CRP/hsCRP may be performed if required for safety reasons.

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

- This Appendix contains definitions and procedures required for AEs and SAEs which do not involve Medical Devices used in this study (see Section 6.1.1 for the list of medical devices).
- Refer to Appendix 9 for definitions and reporting requirements of Medical Device AEs, SAEs, incidents and deficiencies.

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 (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

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

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during 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. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

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

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

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one 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 utilised 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 a SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF

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

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

10.4.1. Definitions:

10.4.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

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

10.4.1.2. Women in the following categories are not considered WOCBP

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

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

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomised partner   • *Note: Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

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

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

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

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

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention but can continue in the study and attend all clinic visits if she wishes.

10.4.4. Contraception Eligibility Criteria for Female and Male Participants

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 8 weeks after last dose of study SC intervention:

- Refrain from donating sperm

PLUS, either:

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

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom AND female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year (as described in Section 10.4.2) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

b. Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is NOT a woman of childbearing potential (WOCBP) as defined in Section 10.4.1.

  OR

  - Is a WOCBP and using a contraceptive method that is highly effective with a failure rate of <1% per year(see Section 10.4.2), for 30 days before the first dose of study intervention, during the intervention period and at least 8 weeks after the last dose of study SC intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. Additionally, WOCBP using hormonal contraceptives, including oral, injections, implants, and patches, are required to use a secondary method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- In addition to contraception requirements for blinded study medication as outlined above, participants should follow csDMARD local labelling.
- A WOCBP must have both:
  - A confirmed menstrual period prior to the first dose of study intervention

  AND

- A negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

  If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Pregnancy tests for WOCBP are specified in the SoA (Section 1.3).

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK3196165 or RA and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3196165, and RA. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analysed if it is hypothesised that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK3196165 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3196165 (or study interventions of this class) or RA continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

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

Phase 3-4 liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology

Phase 3-4 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><td>Symptomatic</td><td colspan="2">Any clinical signs/symptoms suggestive of hepatic decompensation such as ascites and hepatic encephalopathy</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete a SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
• If restart/rechallenge not allowed or not granted, permanently discontinue study intervention and continue participant in the</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained less than 8 weeks after last dose[5]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin ≥ 2xULN</td></tr>
</table>

study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilise or return to within baseline	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR >1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

4. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase 3-4 liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥ 5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥ 3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥ 5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalise or return to within baseline.

References

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

10.7. Appendix 7: Summary of composite endpoints

These composite endpoints are derived using the data collected from assessments described in Section 8.1.

10.7.1. ACR

The American College of Rheumatology's definition for calculating improvement in RA (ACR20) is calculated as a 20% improvement from baseline in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and ACR70 are calculated with the respective percent improvement.

The specific components of the ACR Assessments that will be used in this study are:

- Tender/Painful Joint count (68).
- Swollen Joint Count (66).
- Pain VAS.
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.
- Acute-phase reactant (hsCRP or ESR).
- Health Assessment Questionnaire – Disability Index (HAQ-DI).

10.7.2. Disease Activity Score

The Disease Activity Score (DAS) assessment is a derived measurement with differential weighting given to each component. The DAS 28(CRP) or DAS 28(ESR) will be calculated at each assessment timepoint.

The components of the DAS 28 arthritis assessment include:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).
- hsCRP or ESR.
- Patient's Global Assessment of Arthritis.

10.7.3. Clinical Disease Activity Index (CDAI)

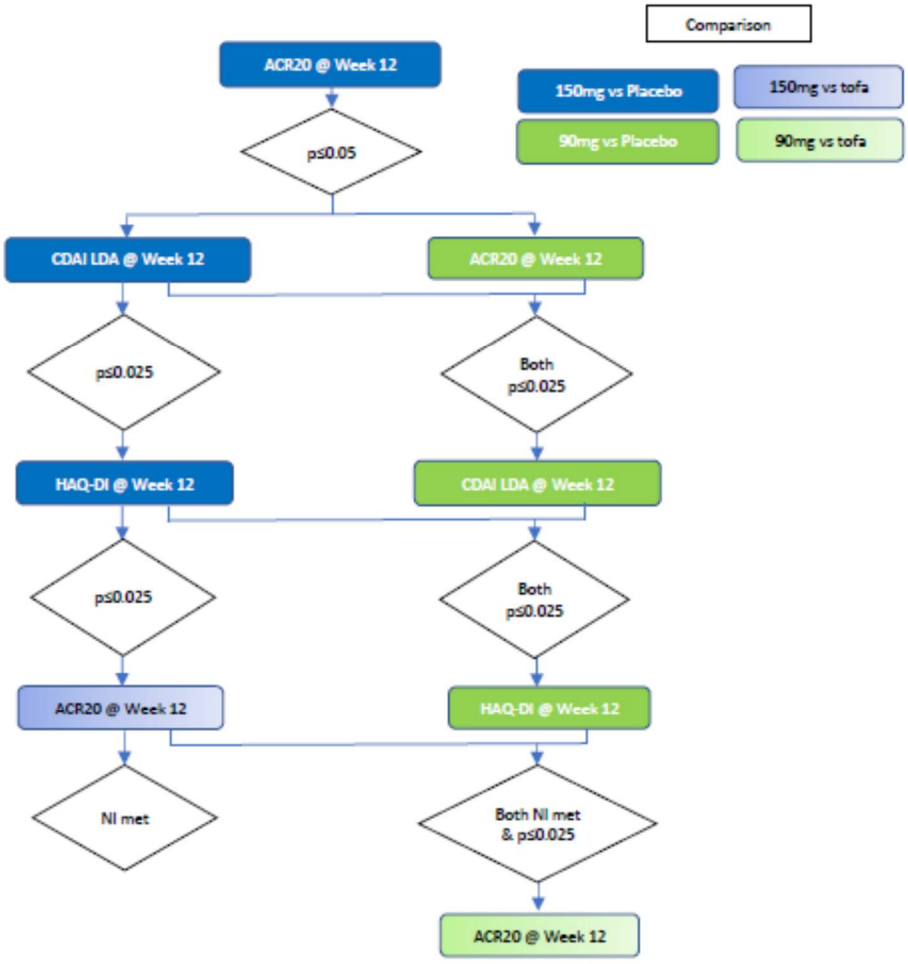
The CDAI for rheumatoid arthritis is a clinical composite score to determine disease severity using only clinical data. The CDAI score will be calculated at each assessment timepoint.

The components of the CDAI include:

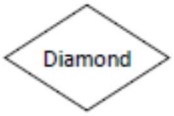
- Tender/Painful Joint Count (28).

- Swollen Joint Count (28).
- Patient's Global Assessment of Arthritis.
- Physician's Global Assessment of Arthritis.

10.8. Appendix 8: Hierarchy Options to Demonstrate Superiority or Non-inferiority of Each Dose of GSK3196165 Versus Placebo or Tofacitinib, Respectively



Explanation of Figure:

Testing continues along a given arrow until a  is false.

All testing stops when testing along all arrows stops.

The figure shows the steps to testing, but significance of a particular test (denoted by each box) is determined by whether *that test* is significant, provided the box itself was reached while stepping down the testing hierarchy.

Note: NI = Non-inferiority.

10.9. Appendix 9: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

- The detection and documentation procedures described in this Appendix apply to the medical devices provided for use in the study as detailed in Section 6.1.1. Refer to Appendix 3 for all other AE/SAE reporting not involving a medical device.
- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.

10.9.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.9.2. Definition of Medical Device SAE, SADE and USADE

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

A Medical Device SAE is a Medical Device AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. 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 2. A permanent impairment of a body structure or a body function, 3. Inpatient or prolonged hospitalization, Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
Serious Adverse Device Effect (SADE) definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3.1).

10.9.3. Definition of Device Deficiency

Device Deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

10.9.4. Recording and Follow-Up of Medical Device AE and/or SAE and Device Deficiencies

Medical Device AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF. • It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency CRF page.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one 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 a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs 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.
- Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- 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/device deficiency, the investigator must document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change his/her opinion of causality in light of follow-up information and send a 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 Medical Device AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.9.5. Reporting of Medical Device SAEs

Medical Device SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor **or the SAE coordinator** by telephone.
- Contacts for SAE reporting can be found in SRM.

Medical Device SAE Reporting to GSK via Paper CRF

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

10.9.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. For medical device deficiencies with no associated AE or SAE please refer to Section 8.3.8.4.

- Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- GSK shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in the SRM.

10.10. Appendix 10: Country-specific requirements

Not Applicable.

10.11. Appendix 11: Abbreviations and Trademarks

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ACR20/50/70	20%/50%/70% improvement in American College of Rheumatology Criteria
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AP	Alkaline phosphatase
AST	Aspartate transaminase
BCG	Bacillus Calmette-Guérin
bDMARD	Biologic disease-modifying antirheumatic drug
BID	Twice daily
CDAI	Clinical disease activity index
CD20	Cluster of differentiation antigen 20
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COX	Cyclo-oxygenase
CPK	Creatine phosphokinase
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
CTFG	Clinical Trial Facilitation Group
CTC	Common terminology criteria
DAS28	Disease activity score including 28 different joints
DAS28(CRP)	Disease activity score including 28 different joints with CRP value
DAS28(ESR)	Disease activity score including 28 different joints with ESR value
DNA	Deoxyribonucleic acid
DMARD	Disease-modifying antirheumatic drug
DRE	Disease-related event
DVT	Deep vein thrombosis
EASL	European Association for the Study of the Liver
EBV	Epstein Barr Virus
ECG	Electrocardiogram
CCI [redacted]	
eCRF	Electronic case report form
ED	Effective dose
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FACIT	Functional assessment of chronic illness therapy
FEV_1	Forced expiratory volume in one second

FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GEE	Generalised Estimating Equation
GFR	Glomerular filtration rate
GM-CSF	Granulocyte-macrophage colony stimulating factor
GSK	GlaxoSmithKline
HAQ-DI	Health Assessment Questionnaire Disability Index
hCG	Human chorionic gonadotropin
HF	Human Factors
HOA	Hand osteoarthritis
HRCT	High-resolution computed tomography
HRT	Hormone replacement therapy
hsCRP	High sensitivity C-reactive protein
HV	Healthy volunteer
IA	Intra-articular
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Institutional ethics committee
IFU	Instructions For Use
IgM	Immunoglobulin M
IL	Interleukin
IM	Intramuscular
IMP	Investigational medicinal product
INH	Isoniazid
INR	International normalised ratio
IP	Investigational product
IR	Inadequate response
IRB	Institutional review board
IRT	Interactive Response Technology
ITT	Intent to Treat
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVIG	Intravenous immunoglobulin
JAK	Janus Kinase
kg	Kilogram
L	Litre
LAM	Lactational amenorrhoea method
LDA	Low disease activity
LDH	Lactate dehydrogenase
LFT	Liver function test
LTE	Long-term extension

mAb	Monoclonal antibody
MCV	Mean cell volume
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Millilitre
MMP	Matrix metalloproteinase
MMRM	Mixed Model for Repeated Measures
MOS	Medical Outcomes Study
MS	Multiple sclerosis
MSDS	Material safety data sheet
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NCEP	National Cholesterol Educational Program
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOEL	No observed effect level
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
PAC	Pulmonary Adjudication Committee
PAP	Pulmonary alveolar proteinosis
PCP	Pneumocystis Pneumonia
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PE	Pulmonary embolism
PFS	Prefilled syringe
PFT	Pulmonary function test
PP	Per Protocol
PRN	Pro re nata (as needed)
CCI [redacted]	
PtGA	Patient's Global Assessment of Arthritis
PhGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetics
RA	Rheumatoid arthritis
RAP	Reporting and analysis plan
RF	Rheumatoid factor
RNA	Ribonucleic acid
SC	Subcutaneous
SAE	Serious adverse event
SJC	Swollen joint count
SF-36	Short form (36)
SRM	Study Reference Manual
SRT	Safety Review Team
SSD	Safety Syringe Device
TB	*Mycobacterium tuberculosis*

TE	Target engagement
TJC	Tender joint count
TNFα	Tumor necrosis factor alpha
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
TST	Tuberculin skin test
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VTE	Venous thromboembolism
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Jakvinus
Jaquinus
MedDRA
CCI [redacted]
Prosorba
QuantiFERON
T.SPOT TB
Xeljanz

10.12. Appendix 12: Protocol Amendment History

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

Protocol Amendment 01 22 MAY 2019

Overall Rationale for the Amendment: Correction of contraceptive requirements for Women of Child Bearing Potential (WOCBP) and additional clarifications.

Section # and Name	Description of Change	Brief Rationale
Section 10.4.4 Contraception Eligibility Criteria for Female and Male Participants	Correction of bullet 'b' for WOCBP, to remove "with low user dependency" wording and remove requirement for "two" methods except if hormonal contraceptives are used.	Corrected to align with the Investigator Brochure (IB) Development Core Safety Information and the Study Risk Assessment (see Section 2.3).
Section 8.1.4 Patient reported outcomes	Clarification that some (exploratory) PROs will only be implemented if and when translations are available.	Some PROs may be delayed or may not be available in all languages for the global study.
Section 5.1 Inclusion criteria and **Section 6.5.1 Permitted therapies**	Maximum allowed dose of Bucillamine increased to 300 mg/day if permitted per local requirements.	Enable dosing of permitted regimen in countries including Republic of Korea/China.
Section 1.3 SoA, Section 2.3.1 Study risk table and **Section 5.4 Screen Failures**	Correction, a baseline chest X-ray and hands/feet X-ray <u>are</u> required during rescreening (if not carried out recently), but a hands/feet x-ray is <u>not</u> required at early withdrawal, if carried out recently.	Correction of requirements.
Section 6.5.2 Prohibited therapies	Washout period for Marijuana corrected to "at least 4 weeks prior to Day 1."	Correction.
Section 8.6.1 Target engagement and **Section 8.9 Immunogenicity**	Clarification that free GM-CSF levels will be measured at baseline using excess material from immunogenicity sample.	Clarification of procedure.
Section 1.3 SoA	Footnotes updated for above changes.	Guidance.
Section 9 Statistical Considerations	Correction of hypothesis to state 150 mg dose, and addition of stratification factor to the model specification.	Align hypothesis with multiple testing hierarchy and adjust for stratification factor in the model.
All sections	Minor grammatical and typographical corrections to improve readability.	

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CCI [redacted]

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CCI [redacted]

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