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Official Title of Study: A multi-centre long-term extension study to assess the safety and efficacy of GSK3196165 in the treatment of rheumatoid arthritis

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TITLE PAGE

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Compound Name: Otilimab

Study Phase: Phase 3

Short Title: Long-term safety and efficacy of GSK3196165 in the treatment of rheumatoid arthritis.

Study Name: contRAst-X

Sponsor Name and Legal Registered Address:

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PPD

PPD

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A multi-centre long-term extension study to assess the safety and efficacy of GSK3196165 in the treatment of rheumatoid arthritis.

Short Title: Long-term safety and efficacy of GSK3196165 in the treatment of rheumatoid arthritis.

Rationale: This is a long-term safety and efficacy study. The participants in this study will be adults with rheumatoid arthritis (RA) who have completed the treatment phase of a qualifying GSK3196165 clinical study (including phase 3 studies contRAst 1 (201790), contRAst 2 (201791) and contRAst 3 (202018)) and who, in the investigator's judgement will benefit from extended treatment with GSK3196165. The primary aim of this study is to provide long-term safety data for GSK3196165, dosed at 90 mg or 150 mg every week.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To determine the long-term safety of GSK3196165 at weekly doses of 90 mg or 150 mg for the treatment of participants with moderately to severely active rheumatoid arthritis (RA).	• Incidence of adverse events (AEs) and serious adverse events (SAEs) and adverse events of special interests (AESI). • Change from baseline* in key laboratory parameters. • Proportion of participants with NCI-CTCAE ≥Grade 3 haematological/clinical chemistry abnormalities.
Secondary	
To determine the long-term efficacy of GSK3196165.	Proportion of participants at Weeks 24, 48 and every 48 weeks thereafter, achieving: • CDAI total score ≤10 (CDAI LDA) • CDAI total score ≤2.8 (CDAI Remission) • DAS28-CRP <2.6 and DAS28-ESR <2.6 (DAS28 remission). • ACR and EULAR Remission (Boolean and SDAI). Absolute values at Weeks 24, 48 and every 48 weeks thereafter for: • CDAI total score. • DAS28-CRP & DAS28-ESR. • van der Heijde mTSS score (participants from 201790 and 201791 only)

Objectives	Endpoints
To determine effects of GSK3196165 on Patient Reported Outcomes (PROs).	**Patient Reported Endpoints** Absolute values at Weeks 24, 48 and every 48 weeks thereafter for: • HAQ-DI. • Arthritis pain VAS. • The physical and mental component scores and the domain scores of SF-36. • FACIT-Fatigue.
To determine the immunogenic potential of GSK3196165.	**Immunogenicity Endpoints** • Anti-GSK3196165 antibodies

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; SDAI = simplified disease activity index; mTSS = modified total Sharp score; ESR = erythrocyte sedimentation rate; AEs = adverse events; SAEs = serious adverse events; FACIT = functional assessment of chronic illness therapy; AESI = adverse event of special interest; NCI-CTCAE = National Cancer Institute common terminology criteria for adverse events; RA = rheumatoid arthritis; SF-36 = short form-36.

*See Statistical Analyses section.

Overall Design: This is a long-term safety and efficacy study in participants with RA who have completed treatment in one of the qualifying GSK3196165 clinical studies. Participants who have not developed any discontinuation criteria in their qualifying study and who consent to take part in this study will be assessed for eligibility upon completion of their final assessment visit within their qualifying study. Eligible participants will be enrolled and receive weekly GSK3196165 90 mg or 150 mg by subcutaneous (SC) injection.

The anticipated study duration is approximately 4 years which will enable participants to receive treatment with GSK3196165 until it is expected to become commercially available. The study duration may be increased if necessary to align with revised commercial availability, or reduced, if an alternative early access (or equivalent) programme is started, or if development of GSK3196165 in RA is stopped. An individual participant's treatment duration in this study is expected to be between 1-4 years depending on a number of factors, including: continued efficacy response of the participant, safety and tolerance of the study drug, consent of the participant to continue with study assessments, the opinion of the investigator and the development status of the drug. All participants will have a safety follow-up visit 8 weeks after their last dose of study intervention.

Participants will continue to receive the same background conventional synthetic disease modifying antirheumatic drug(s) (csDMARD) treatment as they received in their qualifying study. However, if clinically indicated, a participant's background csDMARD(s) dose may be changed, including dose reduction/discontinuation per the guidance within protocol, starting from Week 12 (or from Week 24, for participants who joined from 202018).

During the course of this extension study, it is expected that an autoinjector (AI) device will become available to supplement/replace the pre-filled syringes (PFS). When the AI device becomes available, a sub-study of approximately 200 new participants who join the extension study at this time, will examine AI device usability and steady state PK.

Disclosure Statement: This is a parallel group treatment study with two arms that are initially participant and investigator blinded. A participant's treatment allocation will remain blinded at least until their qualifying study has been reported.

Number of Participants: It is anticipated that approximately 3000 participants from the qualifying studies already planned (201790, 201791 and 202018) may be eligible to participate in this long-term extension study. This number may increase if the number of qualifying studies increases. All subjects will be considered evaluable.

Intervention Groups and Duration: Upon successful enrolment to this study, participants will be assigned by interactive response technology (IRT) to receive GSK3196165 90 mg or 150 mg weekly SC injection as follows:

- Participants who were receiving GSK3196165 in their qualifying study will continue to receive GSK3196165 at the same dose level (90 mg or 150 mg weekly), in this study.

- Participants who were receiving a comparator (e.g. tofacitinib or sarilumab) in their qualifying study will be re-randomised, in a ratio of 1:1, to receive either GSK3196165 90 mg or 150 mg weekly.

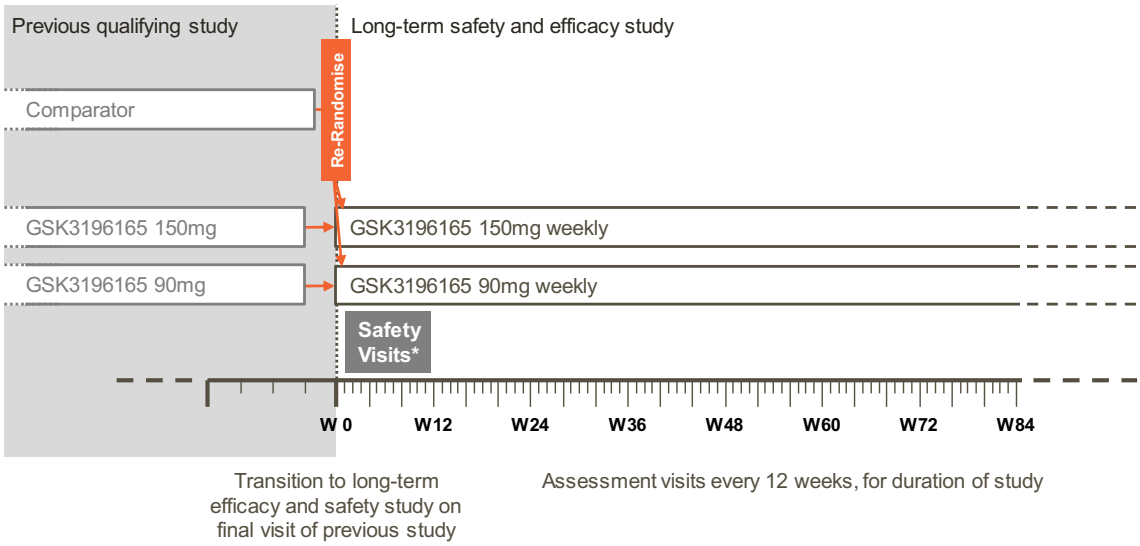
Note: If it is determined at any time (for example, at the time of the primary analysis of the qualifying studies) that one of the doses does not have a positive benefit:risk profile, then this arm may be discontinued and all patients transferred to the remaining dose arm.

Independent Data Monitoring Committee: Yes.

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

Pulmonary Adjudication Committee: Yes.

1.2. Schema



*__Safety visits:__ All participants must be monitored for safety for 1 hour post-dose for their first two doses in this study (Week 0 and Week 1). In addition, participants joining from study 202018, will attend for a safety visit at Week 4.

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. The physician global assessment (PhGA) should then take place, followed by other assessments (including safety), ECGs, vital signs and blood draws, before dosing.
- CCI [redacted] 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, so that the participant may receive their dose at site on visit days.** The injection will then be performed at the site, *after* completion of study assessments, CCI [redacted] and other blood draws.
- All participants must be monitored for safety, for 1 hour post-dose for their first two doses in this study (Week 0 and Week 1).

1.3.1. SoA – Treatment Period

	Study activities \ Assessment visit Week	Visit (Visit windows: W1-4 ±2 days; W12-W48 ±1 week; W60 onwards ±2 weeks)							Repeat every 48 weeks until EoS			
		Day 1[1,3] Week 0	Week 1[3]	Week 4[4]	Week 12	Week 24	Week 36	Week 48	Week 60 (then W108, W156…)	Week 72 (then W120, W168…)	Week 84 (then W132, W180…)	Week 96 (then W144, W192…)
	Informed consent	X										
	Eligibility (Inclusion/Exclusion)	X										
	Randomisation	X										
PROs	HAQ-DI, Arthritis pain VAS, PtGA[5]	X[2]			X	X	X	X	X	X	X	X
PROs	SF-36, FACIT-Fatigue[5]	X[2]			X	X	X	X		X		X
PROs	AI sub-study usability questionnaire[5,13]				X							
Assessments	12-lead ECG[6]	X[2]						X				X
Assessments	Vital signs	X[2]	X	X	X	X	X	X	X	X	X	X
Assessments	Physical Exam (B - brief, F - full)	F[2]	B	B	B	B	B	F	B	B	B	F
Assessments	Dyspnoea & Cough assessment, Lung Auscultation, Pulse Oximetry	X[2]	X	X	X	X	X	X	X	X	X	X
Assessments	Swollen (66) & Tender (68) joint count[7]	X[2]			X	X	X	X	X	X	X	X
Assessments	Physician Global Assessment[8]	X[2]			X	X	X	X	X	X	X	X
Assessments	Hands and Feet x-ray[9]					X		X				X
Assessments	Chest X-ray (posteroanterior)							X				X
Labs and blood draws	Hematology, Chemistry, Urinalysis	X[2]	X	X	X	X	X	X	X	X	X	X
Labs and blood draws	Lipid profile					X		X				X
Labs and blood draws	Urine pregnancy test[10]	X[2]	<---------- Every 8 weeks ---------->									
Labs and blood draws	hsCRP, ESR[11]	X[2]			X	X	X	X	X	X	X	X
Labs and blood draws	TB testing							X				X
Labs and blood draws	CCI											
Labs and blood draws	Immunogenicity blood sampling[14]	X[2]				X		X		X		X
Labs and blood draws	CCI											
Dose	Dispense treatment	X	X	<---------- Every 4 weeks ---------->								
Dose	Weekly study treatment SC injection	X[3] [14]	X[3]	<---------- X ---------->								
	SAE/AE and AESI review	<---------- X ---------->										
	Concomitant medication review	<---------- X ---------->										
	AE/conmed phone call **if no site visit**[15]	<------ Every 4 weeks to Week 48, then every 6 weeks to Week 96 ------>										

Notes

1. Participants wishing to enrol in contRAst-X should complete Day 1 study activities on the day of their qualifying study final assessment visit or if not possible, within 7 days. **Exceptions to this must be agreed with the medical monitor.**
2. Pre-dose Day 1 assessments will not be collected as part of *this* study if enrolment is on the same day as the qualifying study final assessment visit, or within 7 days.
3. All participants must be monitored for 1 hour post-dose on Weeks 0 and 1 (because some participants will be receiving GSK3196165 for the first time).
4. Safety visit for participants from 202018 only (to monitor safety when switching from biologic comparator).
5. PROs should be completed before any other assessments, procedures or consultations, to avoid influencing participants' perception.
6. ECGs should be performed before vital signs and blood draws, with triplicate ECGs at pre-dose Day 1.[2]
7. Where possible the same assessor should perform all joint assessments for an individual participant.
8. Where possible, the same individual should perform all physician global assessments for an individual participant.
9. Participants from 201790 and 201791 only.
10. For women of child-bearing potential.
11. ESR measured locally using kit provided by the central laboratory.

CCI [redacted]

15. Window for AE/conmed call is +/-1 week.

1.3.2. SoA – Safety follow-up (8 weeks after last dose of study intervention)

	Safety follow-up visit procedures Last dose + 8 weeks ↓
Assessments	Vital signs
	Full Physical Exam
	Dyspnoea & Cough assessment, Lung Auscultation, Pulse Oximetry
	Concomitant Medication Review
	SAE/AE review
Labs	Haematology, Chemistry, Urinalysis (dipstick), Urine pregnancy test (women of child bearing potential only)
	Immunogenicity blood sampling

1.3.3. Assessments for Early Withdrawal from Study

Follow the Week 96 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 study intervention.

*Note: A hands/feet x-ray should not be performed at early withdrawal if one has been carried out within 8 weeks of the early withdrawal date, as part of study procedures, and a chest x-ray should not be performed if one has been carried out within 12 weeks of the early withdrawal.

CCI

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

This is a long-term study, primarily to assess safety, with efficacy assessment as a secondary objective. The participants in this study will be adults with rheumatoid arthritis (RA) who have completed the treatment phase of a qualifying GSK3196165 clinical study (including Phase 3 studies 201790, 201791 and 202018) and who, in the investigator's and participant's judgement will benefit from extended treatment with GSK3196165. The aim of this study is to provide long-term safety and efficacy data for GSK3196165, dosed at 90 mg or 150 mg every week.

2.2. Background

RA is a chronic, systemic inflammatory autoimmune disease, characterised by a symmetrical polyarthritis that can be associated with substantial disability and morbidity.

Since RA is a chronic disease, patients will require treatment for a long period of time and it is important to study the long-term safety and efficacy of the continuous treatment with GSK3196165 over several years.

More detailed information on RA and the mechanism of action of GSK3196165 may be found in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

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 29 days after receiving a single dose of 1.5 mg/kg but	**Eligibility Criteria (Section 5):** Exclusion of participants with: • Evidence of untreated latent Mycobacterium tuberculosis (TB) (unless willing to undergo TB therapy or have successfully undergone TB therapy). • Current or previous active TB regardless of treatment. **Monitoring:** • Serious and opportunistic infections, TB and TB reactivation are categorised as adverse events of special interest (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). • Monitoring for TB and TB re-activation throughout the study (Section 8.2.7.4). • Participants diagnosed with latent TB will need to complete a course of at least 6 months of isoniazid (INH) therapy during the study. For the first 4 weeks of INH therapy, the participant must be temporarily discontinued from study intervention (Section

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	recovered after treatment with antibiotics. In Phase II completed studies, no significant infections or opportunistic infections were reported.	8.2.7.3). **Withdrawal Criteria:** Temporarily discontinue the study intervention for: • Serious infections until the infection has resolved. • Suspected TB reactivation. • New diagnosis of latent TB • WBC count < 2 x 10^9/L Permanently discontinue the study intervention for: • New active TB infection • HBV DNA level ≥ 200 IU/mL or HBV DNA detected at any level with recent increase in hepatic transaminases (see Figure 1 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 1 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 dyspnoea and pulmonary infection.	**Monitoring:** • PAP is categorized as an AESI. 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
	The duration of exposure to GSK3196165 in this study may be approximately 4 years. 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:** 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. **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):** Exclusion of participants with: • 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 should they develop (also contained within the ICF)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Hypersensitivity to be managed appropriately per local guidelines/medical judgement • All participants must be monitored for 1 hour post dose on Weeks 0 and 1. **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; injection site reactions to be reported as an AE. • Monitor for injection site reactions throughout study. • Injection sites will be 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 haematopoiesis [Stanley, 1994]. **Clinical Data:** Neutropenia has been observed in completed studies of GSK3196165; however, no clinically significant cases have been observed.	**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 **Withdrawal Criteria:** • Temporarily discontinue study intervention for the following haematological abnormality until resolved (Section 7.1.3.3): • Absolute neutrophil count (ANC) ≤ 1 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 post partum development of offspring in the mouse	**Eligibility Criteria (Section 5 and Appendix 4):** • Women of child bearing potential (WOCBP) and males to meet contraceptive requirements.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	[Robertson, 1999; Robertson, 2007]. **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 healthy volunteer (HV) participant and 1 in an multiple sclerosis (MS) participant. Both pregnancies were electively terminated. The effect of GSK3196165 on human pregnancy is unknown.	**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. **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 completed studies in the GSK3196165 program.	**Eligibility Criteria (Section 5):** Exclusion of participants who: • Develop a new cancer or malignancy except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured by the investigator • Have developed any lymphoproliferative disorder, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, or signs and symptoms suggestive of current lymphatic disease

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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]. Participants who discontinue from background csDMARD/MTX will have extra immunogenicity samples collected following discontinuation. **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. **Clinical Data:** In clinical trials to date, there is no evidence that anti-GSK3196165 antibodies affect GSK3196165 serum concentrations.	• Blood samples will be tested for ADAs to GSK3196165 on week 0 (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 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).	• Information will be collected on concomitant warfarin use (e.g. International normalized ratio (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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	
Study Procedures		
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 400 mL of whole blood will be collected from each participant over the course of the study (assuming a 4-year treatment period, including extra assessments for csDMARD tapering and AI sub-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. • 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 during study (annual Chest X-ray) • 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. This study aims to establish if structural bone damage does or does not deteriorate after treatment with GSK3196165.	• Minimal procedures performed to assess structural joint damage in patients from qualifying studies 201790 and 201791 (annual X-ray) • Exposure to radiation from X-rays is far less than the exposure to natural radiation. • 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 and autoinjector 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.

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] and namilumab [Taylor, 2019] were able to reduce RA disease activity and pain. In addition, results from BAROQUE (GSK Study 201755) showed that all doses of GSK3196165 above 22.5 mg in combination with methotrexate (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, including the long term evaluation of clinical benefit and safety that will be achieved within this study.

All participants enrolled will have been deemed by the investigator as likely to benefit from receiving continuous treatment with GSK3196165 upon completion of the qualifying study and all will receive GSK3196165. Furthermore, each participant will continue to 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.

If it is determined at any time (for example, at the time of the primary analysis of the qualifying studies) that one of the doses does not have a positive benefit:risk profile, then this dose arm may be discontinued and all patients transferred to the remaining dose arm.

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, PAP, 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 9.5.1). Key safety data will be reviewed by the IDMC allowing ongoing assessment of the overall benefit:risk throughout the study. Full details 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 by long term administration to participants with RA.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To determine the long-term safety of GSK3196165 at weekly doses of 90 mg or 150 mg for the treatment of participants with moderately to severely active rheumatoid arthritis (RA).	• Incidence of adverse events (AEs) and serious adverse events (SAEs) and adverse events of special interests (AESI). • Change from baseline* in key laboratory parameters. • Proportion of participants with NCI-CTCAE ≥Grade 3 haematological/clinical chemistry abnormalities.
Secondary	
To determine the long-term efficacy of GSK3196165.	Proportion of participants at Weeks 24, 48 and every 48 weeks thereafter, achieving: • CDAI total score ≤10 (CDAI LDA) • CDAI total score ≤2.8 (CDAI Remission) • DAS28-CRP <2.6 and DAS28-ESR <2.6 (DAS28 remission). • ACR and EULAR Remission (Boolean and SDAI). Absolute values at Weeks 24, 48 and every 48 weeks thereafter for: • CDAI total score. • DAS28-CRP & DAS28-ESR. • van der Heijde mTSS score (participants from 201790 and 201791 only)
To determine effects of GSK3196165 on Patient Reported Outcomes.	**Patient Reported Endpoints** Absolute values at Weeks 24, 48 and every 48 weeks thereafter for: • HAQ-DI. • Arthritis pain VAS. • The physical and mental component scores and the domain scores of SF-36. • FACIT-Fatigue.
To determine the immunogenic potential of GSK3196165.	**Immunogenicity Endpoints** • Anti-GSK3196165 antibodies
CCI [redacted]	

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; SDAI = simplified disease activity index; mTSS = modified total Sharp score; ESR = erythrocyte sedimentation rate; AEs = adverse events; SAEs = serious adverse events; FACIT = functional assessment of chronic illness therapy; AESI = adverse event of special interest; NCI-CTCAE = National Cancer Institute common terminology criteria for adverse events; RA = rheumatoid arthritis; SF-36 = short form-36;

* See Statistical Analyses Section 9.4.

4. STUDY DESIGN

4.1. Overall Design

- This is a Phase 3, multicentre, long-term extension study, with the primary objective to assess the long-term safety of GSK3196165 in combination with csDMARDs in participants who have completed one of the qualifying studies with GSK3196165.

- The anticipated study duration is approximately 4 years, which will enable participants to receive treatment with GSK3196165 until it is expected to become commercially available. The study duration may be increased if necessary to align with revised commercial availability, or reduced, if an alternative early access (or equivalent) programme is started, or if development of GSK3196165 in RA is stopped. An individual participant's treatment duration in this study is expected to be between 1-4 years depending on a number of factors, including: continued efficacy response of the participant, safety and tolerance of the study drug, consent of the participant to continue with study assessments, the opinion of the investigator and the development status of the drug. All participants will have a safety follow-up visit 8 weeks after their last dose of study intervention.

- In order to avoid a prolonged break in treatment between studies, participants wishing to join this extension study should complete Day 1 study activities (including informed consent, eligibility assessment and randomisation) immediately

after completion of the final assessment visit of their qualifying study, preferably on the same day. There is no formal screening period in this extension study.

- If the participant is enrolled on the same day as the final assessment visit, or within 7 days following this, no collection of pre-dose assessments under this extension study is required and the participant may proceed to dosing (the data from their final assessment of the qualifying study will be used as pre-dose values for this study). With approval of the medical monitor, participants may be enrolled after 7 days following the completion of their qualifying study final assessment visit, in these cases pre-dose assessments per the SoA will be collected prior to dosing.
    - Note: Participants should be advised of this extension study in the weeks and months prior to the end of their qualifying study, to ensure they have enough time to consider this study prior to their final assessment visit on the qualifying study.
- Participants who consent and are eligible, will be enrolled and assigned to receive GSK3196165 90 mg or 150 mg weekly SC injection, by interactive response technology (IRT) as follows:
    - Participants who were receiving GSK3196165 in their qualifying study will be assigned by IRT to continue to receive GSK3196165 at the same dose level in this study.
    - Participants who were receiving a comparator (e.g. tofacitinib or sarilumab) in their qualifying study will be re-randomised by IRT, in a ratio of 1:1, to receive either GSK3196165 90 mg or 150 mg weekly, in this study.
- A participant's treatment allocation will remain blinded at least until their qualifying study has been reported.
- Participants will continue to receive the same background csDMARD treatment as they received in their qualifying study. However, if clinically indicated, a participant's background csDMARD(s) dose may be changed, CCI [redacted] See Section 6.6.2 for details about background csDMARD (including MTX) CCI [redacted]
- Participants who join from Study 201790 or Study 201791, or any other qualifying study/ies in which radiographic assessment of joints has been performed will continue to have radiographs of the hands and feet (see SoA, Section 1.3) to assess long-term radiographic progression of structural joint damage.

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4.2. Scientific Rationale for Study Design

Participation in this study will allow participants who have completed one of the qualifying GSK3196165 clinical studies to receive long-term treatment with GSK3196165 at doses of 90 mg or 150 mg weekly.

The data from this study will provide an evaluation of the long-term safety and efficacy outcomes of GSK3196165 in adults with RA.

4.3. Justification for Dose

The GSK3196165 doses of 90 mg and 150 mg weekly (SC) proposed for this study are the doses that were used in qualifying Phase 3 studies 201790, 201791 and 202018. These were selected based on the pharmacokinetic (PK) data, efficacy and safety data, and the exposure-response relationship for efficacy endpoints in the Phase 2b dose finding study (BAROQUE, 201755).

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 including the safety follow up visit, 8 weeks after the last dose.

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.

There is no formal screening period in this extension study. Clinical laboratory assessments will be collected in the qualifying study, approximately two to four weeks prior to the final assessment visit and assessed and managed as per the qualifying study protocol. Any temporary or permanent discontinuation of study medication resulting from these assessments must be considered against the eligibility criteria detailed in Section 5.1 and Section 5.2 below.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

TYPE OF PARTICIPANT
1. Participants with rheumatoid arthritis who are aged ≥18 years at the time of signing informed consent, who have completed one of the qualifying GSK3196165 clinical studies and who, in the opinion of the investigator, may benefit from treatment with GSK3196165.

WEIGHT
2. Body weight ≥40 kg

SEX
3. Male or female participants are eligible to participate as long as they meet the contraceptive eligibility criteria in Section 10.4.4 and agree to abide by the contraceptive requirements detailed in Appendix 4.

INFORMED CONSENT
4. 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
5. For participants on MTX: must be willing to continue treatment with oral folic acid (at least 5 mg/week) or equivalent while receiving MTX (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. Had study intervention permanently discontinued at any time during a qualifying study except any participant with a new diagnosis of latent TB at the end of study assessment in a qualifying study and currently undertaking or willing to complete at least 4 weeks of anti-TB treatment off study treatment, per WHO or national guidelines prior to re-commencing therapy and complete the remainder of anti-TB

treatment while on study.

2. Evidence of latent TB (as documented by 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) except for participants that
    - Are currently undertaking or willing to complete at least 4 weeks of anti-TB therapy off study treatment, as per WHO or national guidelines prior to re-commencing study treatment and agree to complete the remainder of anti-TB treatment while in the study OR
    - Had documented evidence of satisfactory anti-TB treatment as per WHO or national guidelines following review by a physician specialising in TB on entry to a qualifying study.
3. Current or previous active Mycobacterium tuberculosis (TB) regardless of treatment.
4. Were temporarily discontinued from study intervention at the time of the final study visit of a qualifying study and, in the opinion of the investigator, participation in the extension study poses an unacceptable risk for the patient's participation.
5. A new cancer or malignancy except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured by the investigator.
6. Have developed any lymphoproliferative disorder during a qualifying study, such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, or signs and symptoms suggestive of current lymphatic disease.
7. Have significant uncontrolled cardiovascular, cerebrovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neuropsychiatric disorders, or abnormal laboratory values that developed during a qualifying study that, in the opinion of the investigator, poses an unacceptable risk for the patient's participation.

PRIOR/CONCOMITANT THERAPY

8. 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 Section 6.5.2 for details of prohibited medications/treatments and Section 6.5.1 for details of permitted medications/treatments.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

9. Participants who are currently participating in any interventional clinical study other than a qualifying GSK3196165 clinical study.

DIAGNOSTIC ASSESSMENTS
10. Abnormal chest radiograph within the last 12 weeks judged by the investigator as clinically-significant.

OTHER EXCLUSIONS
11. Pregnant or lactating, or women planning to become pregnant or initiating breastfeeding
12. 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 Restrictions

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into the study. There is no formal screening period in this extension study, however 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 at the time of eligibility assessment (screen failure) cannot be reconsidered at a later point in time, "rescreening" is not permitted.

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 SC injection should be administered to the abdomen, thigh or upper arm, and should preferably be rotated left and right, or to a different site, 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.

- All participants must receive their Week 0 and Week 1 SC injections **at site, with general safety monitoring for 1 hour post-dose.** Safety monitoring will include monitoring for systemic hypersensitivity and local injection site reactions.

- **Where possible, assessment visits should be scheduled to coincide with the weekly administration of study SC injection, so that the participant may receive their dose at site on visit days.** The injection will then be performed at the site, *after* completion of study assessments, CCI and other blood draws (see Section 1.3).

- Any participant who doses at home must be instructed to contact the site immediately if they experience any symptoms of a drug reaction following dosing.

- When available the active treatment will be supplied in an autoinjector format. Until this time treatment will be supplied in PFS (or from vials, if PFS are not available).

- Study intervention for each arm is expected to be supplied in volume-matched PFS or AI for the duration of this study. However, if at any time while the study is blinded to site or participant, the study intervention is supplied from vials (for example, if supply of PFS or AI is interrupted), an unblinded administrator must prepare and administer the injection, keeping the syringe and vial shielded from the participant at all times. If this situation occurs, additional guidance will be provided in an updated pharmacy manual or addendum.

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Table 1 Overview of Study Intervention

ARM Name	**GSK3196165 90 mg**	**GSK3196165 150 mg**
Intervention Name	GSK3196165	GSK3196165
Type	Biologic	Biologic
Dose Formulation	Solution in vial (1.2 mL), solution in PFS (1.0mL) and solution in AI (1.0 mL)	Solution in vial (1.2 mL), solution in PFS (1.0mL) and solution in AI (1.0 mL)
Unit Dose Strength(s)	Vial: 150mg/mL PFS and AI: 90 mg/mL	Vial: 150mg/mL PFS and AI: 150 mg/mL
Dosage Level(s)	90 mg once weekly	150 mg once weekly
Route of Administration	SC injection	SC injection
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Dosing instructions	PFS and AI: Inject all per instructions for use (IFU). Vial: withdraw **0.6 mL** into a small syringe and dose immediately; discard remaining material.	PFS and AI: Inject all per instructions for use (IFU). Vial: withdraw **1.0 mL** into a small syringe and dose immediately; discard remaining material.
Special instructions	Avoid excessive shaking of vials, PFS and AI, as this could lead to product precipitation.	Avoid excessive shaking of vials, PFS and AI, as this could lead to product precipitation.
Packaging and Labelling	Study Intervention will be provided in a single use vial, PFS or AI in an individual carton and labelled as required per country requirement.	Study Intervention will be provided in a single use vial, PFS or AI in an individual carton and labelled as required per country requirement.
Current/Former Name(s) or Alias(es)	otilimab Anti human GM-CSF monoclonal Ab MOR103 MOR04357	otilimab Anti human GM-CSF monoclonal Ab MOR103 MOR04357

PFS = prefilled syringe; AI = Autoinjector; GM-CSF = granulocyte macrophage colony stimulating factor; Ab = antibody, IFU= Instructions for use.

GSK3196165 in vials will be administered SC, using syringes and needles commonly used for SC administration; compatibility with commonly used syringes and needles has been demonstrated.

6.1.2. Medical Devices

- The medical devices provided for use in this study are injection devices: a prefilled syringe (PFS) assembled into a safety syringe device (SSD) and a prefilled syringe contained within an autoinjector (AI). The 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 PFS and SSD, including glass barrel with prestaked needle and plunger are sourced for GSK by a third party provider. The prefilled syringe is filled and assembled with the safety syringe components by GSK (or its affiliates).
- The AI components are manufactured for GSK by a third party. The autoinjector components are assembled with the prefilled syringe by GSK (or its affiliates).
- The instructions for use (IFU) for these injection devices are provided in the study reference manual (SRM). The 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 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 or patients with sufficient training may 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 or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants who received GSK3196165 in their qualifying study will continue in this study on the same dose. Participants who received a comparator in their qualifying study will be centrally randomised using IRT in a ratio of 1:1 to either GSK3196165 90 mg or 150 mg. 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 1.3.1). 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 CRF, as applicable.

Participants who were **not** receiving weekly GSK3196165 90 mg or 150 mg in their qualifying study, will be randomised by the IRT in a ratio of 1:1, to one of these two treatment arms on Day 1. Participants who were receiving GSK3196165 90 mg or 150 mg in their qualifying study will be allocated by IRT to the same dose level in this study.

Study intervention will be dispensed at the study visits summarized in the SoA for the treatment period (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

A participant's treatment allocation will remain blinded at least until their qualifying study has been reported. A participant may continue in the study if that participant's intervention assignment is unblinded.

Although it is expected that study intervention for each arm will be supplied in volume-matched PFS or AI for the duration of this study, an interruption to supply of PFS or AI could require supply of intervention in fixed concentration vials. If such a situation occurs, at a time while the study is blinded to site or participant, sites will need to ensure the blind is maintained. An unblinded pharmacist (or unblinded designee) would then be responsible for the dispensation of the study intervention from vial, and an unblinded administrator would be responsible for administration of the SC injection, keeping the syringe and vial shielded from the participant at all times. If this situation occurs, additional guidance will be provided in an updated pharmacy manual or addendum.

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 will be administered by site staff to participants at the site or participants will have the option to self-administer using pre-filled syringes or auto-injector for weekly SC administration at home. A record of the number of syringes or auto-injectors 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.

6.5. Concomitant Therapy

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, theophylline levels), 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. unless such time that this risk is negated by results from the preceding phase 3 studies.

6.5.1. Permitted Therapies

Medications or treatments deemed necessary by the investigator to provide adequate supportive care will be permitted during the study unless specifically excluded in Section 6.5.2. These medications, if permitted and taken during the study, must be recorded in the CRF, 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 below.

- Investigators should follow routine clinical practice to manage RA pain. Any new analgesic or oral corticosteroid use or change in dose should not take place within 24 hours before a study assessment visit and must be recorded in the concomitant medication CRF.

- Other medications (including vitamins, herbal and dietary supplements) will be permitted if in the opinion of the investigator, the medication will not interfere with the study procedures or compromise participant safety. These must be recorded in the concomitant medication CRF.
- Background MTX/csDMARD change, dose reduction or discontinuation is permitted as per guidance in Section 6.6.2.
- At most two concomitant background csDMARDs are permitted as follows:
  a. Methotrexate (MTX): up to 25mg per week whether oral or injected.
  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. Tacrolimus up to 3 mg/day.
  f. Bucillamine up to 100 mg/day (or up to 300 mg/day if permitted per local requirements).
  g. Iguratimod up to 50 mg/day.
- All participants may receive inactivated flu vaccines during the study at the discretion of the investigator.

6.5.2. Prohibited Therapies

Medications prohibited or restricted are as follows:

- Treatment with any targeted synthetic DMARD (tsDMARD) or biologic DMARD (bDMARD) is prohibited between the last administration of study dose in the qualifying study and Day 1 of this study, during the study treatment period and during safety follow-up (8 weeks after the last study dose).
- Treatment with more than two csDMARDs or combination of leflunomide and MTX is prohibited between the last administration of study dose in the qualifying study and Day 1 of this study, during the study treatment period and during safety follow-up (8 weeks after the last study dose).
- Live or attenuated vaccinations are prohibited between the last administration of study dose in the qualifying study and Day 1 of this study, during the study treatment period and during safety follow-up (8 weeks after the last study dose).
- Plasmapheresis or intravenous immunoglobulin (IVIG) or use of Staph protein A column (Prosorba) are prohibited within 26 weeks of Day 1, during the study treatment period and during safety follow-up (8 weeks after the last study dose).
- Any treatment antagonizing GM-CSF or its receptor (other than study treatment) is prohibited prior to and during the study and during safety follow-up (8 weeks after the last study dose).
- csDMARDs which are not listed in Section 6.5.1 are prohibited.

6.6. Dose Modification

6.6.1. Dose Modification of Study Intervention

Dose modification of the SC study interventions is not permitted in this study.

6.6.2. Dose Modification of Background csDMARD treatment

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

Dose modification of background csDMARD(s) (including MTX) **for reasons other than safety** are permitted with the following guidance:

- From week 12 onwards (for participants from 201790 and 201791) or from week 24 onward (for participants from 202018), if clinically indicated (i.e. when a participant achieves CDAI low disease activity (CDAI ≤ 10) for 2 consecutive assessment visits), csDMARD dose reduction can be implemented. Instructions on dose reduction can be found below, with an example of MTX tapering. The dose reduction can continue while still clinically indicated.

- Any change in csDMARD treatment should be performed according to the investigator's practice and as tolerated by the participant, including restarting csDMARD and documented in the patient's records.

- In this study, MTX dose should not be reduced by more than 5 mg every 8 weeks [Fleischmann, 2005], except for safety reasons. The *recommended* minimum time between each 5 mg reduction is 12 weeks, to align with study visits. Longer periods between dose reductions and/or smaller dose reductions are permitted per investigators judgement and local guidance. See Table 2 below.

- CCI [redacted]

- If a participant flares during, or after, the csDMARD tapering/withdrawal, the participant may return to their previous dose of csDMARD(s) treatment, as clinically indicated.

Table 2 Example MTX Tapering table

	Visit (time since tapering started)				
Week / MTX dose	+0 weeks	+12 weeks	+24 weeks	+36 weeks	+48 weeks
25 mg	20 mg	15 mg	10 mg	5 mg	0 mg
20 mg	15 mg	10 mg	5 mg	0 mg	0 mg
15 mg	10 mg	5 mg	0 mg	0 mg	0 mg
10 mg	7.5 mg (or 5 mg)	0 mg	0 mg	0 mg	0 mg
7.5 mg	5 mg (or 2.5 mg)	0 mg	0 mg	0 mg	0 mg

This table shows for participants tapering off MTX, the *recommended* minimum 12 weeks between each 5 mg reduction, to align with study visits. Longer periods between dose reductions and/or smaller dose reductions are permitted, per investigator's judgement and local guidance.

6.7. Intervention after the End of the Study

Participants will be treated according to local standard of care for RA disease after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

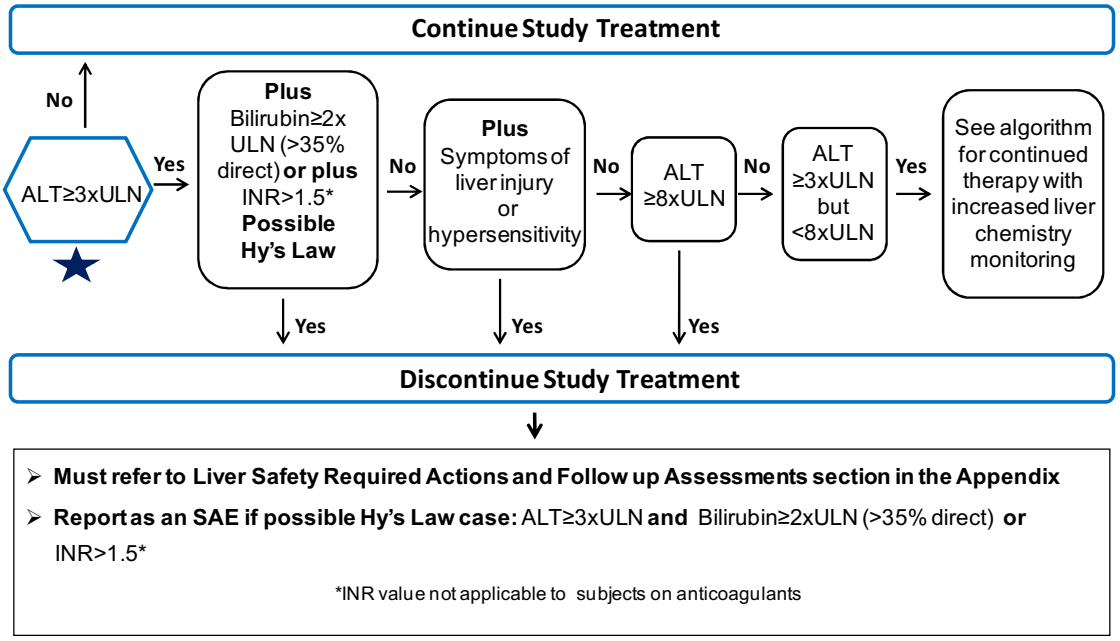
In rare instances, it may be necessary for a participant to permanently discontinue study intervention. A participant will permanently discontinue study intervention if there is no longer a positive risk:benefit ratio at any time point in the study as determined by the investigator. If study intervention is permanently discontinued, refer to Section 1.3.3 (Assessments for Early Withdrawal from Study) for assessments to be collected at the time of discontinuation of study intervention and for scheduling of safety follow-up.

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.

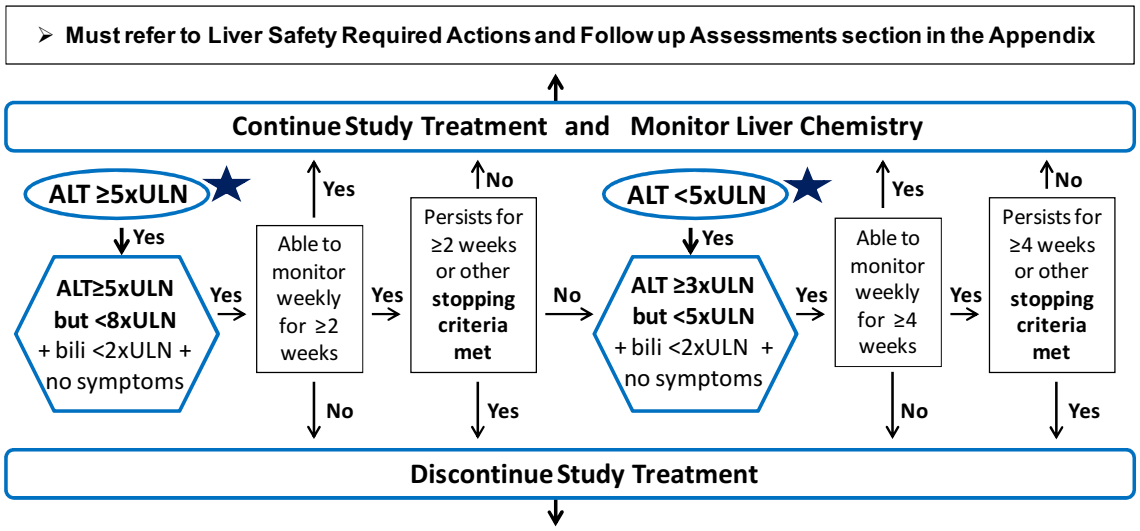
Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



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

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 5.

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 normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 5.

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 withdrawn from study intervention if any of the following criteria are met:

- Pregnancy (see Section 8.3.5 and Appendix 4).
- Confirmed pulmonary alveolar proteinosis (see Section 8.2.6).
- Serious hypersensitivity reactions, including anaphylaxis (see Section 8.3.7).
- Other serious or severe adverse events, at the discretion of the investigator, after consultation with the Medical Monitor (see Section 8.3.7).

- HBV DNA level ≥ 200 IU/mL or HBV DNA detected at any level with recent increase in hepatic transaminases (see Figure 1 in Section 8.2.8)
- HBV DNA positive (any level < 200 IU/mL) and on repeat testing within 1 week (see Figure 1 in Section 8.2.8) either:
    - HBV DNA positive (any level) OR
    - HBV surface antigen positive OR
    - increase in hepatic transaminases.
- New active TB infection (see Section 8.2.7.4).
- 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 (see Section 6.5.2).

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 8.2.6). 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 for the following haematological abnormalities that must be reported as an AE. These should be promptly re-tested, ideally within 3-5 days:

- White blood cell (WBC) count <2.0 x 10^9/L.
- ANC ≤ 1.0 x 10^9/L.
- Lymphocyte count <0.5 x 10^9/L.

Do not restart study intervention until the haematological parameters rise above these values and monitor the participant until the event has resolved. Note that for the above haematological abnormalities, a repeat test must be performed locally and assessed within 7 days with additional samples 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.

7.1.3.4. TB Reactivation

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

- Suspected TB reactivation (see Section 8.2.7.4).

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, behavioral, compliance or administrative reasons.
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted and safety follow-up visit scheduled. Refer to Section 1.3.3 (Assessments for Early Withdrawal from Study) for assessments to be collected at the time of discontinuation of study intervention and for scheduling of safety follow-up.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

  If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled assessment or dispensing 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.
- A thorough eligibility review must be completed to confirm that potential participants meet all required study entry criteria. The investigator will maintain a log to record details of all participants assessed and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's prior qualifying study and obtained before signing of ICF for this long-term extension study, may be utilised for eligibility assessments and/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 amount of blood collected from each participant over the duration of the study (assuming a 4-year treatment period), including extra assessments for csDMARD tapering and AI sub-study, will not exceed 400 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 a 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 in the eCRF at that time.

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

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" [redacted] to "100" [redacted] respectively.

8.1.3. Patient Reported Outcomes

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

8.1.3.1. 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.

8.1.3.2. 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" [redacted] and "100" [redacted]

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

8.1.3.3. 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" [redacted] to "100" [redacted]

8.1.3.4. 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 acute recall questionnaire will be used.

8.1.3.5. 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.

8.2. 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 (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 (not breathless at rest or on exertion) through 4 (breathless at rest).

8.2.2. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Smoking status will be recorded, height and weight will 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 baseline (pre-dose Day 1), with single ECG measurements obtained at all other time points, 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.
- 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), T.SPOT TB, 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 (pre-dose Day 1) or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline (pre-dose Day 1) 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.

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 increase (if present at baseline [pre-dose Day 1]) in cough (CTCAE Grade ≥2) or dyspnoea (dyspnoea scale Grade ≥2), they must be asked again (either by phone or during the site visit) 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.

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 PAP 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 polymerase chain reaction (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 TB treatment status

For participants that have received treatment for latent TB within 5 years prior to the qualifying study entry, 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.

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.

8.2.7.3. Treatment of Latent TB During the Study

If a participant had a positive QuantiFERON-TB Gold Plus test result (or a positive T.SPOT.TB test result) at the end of their qualifying study, who previously had a negative result at study start, then the participant must have been referred to a physician specialising in TB to determine if the participant has active or latent TB as per TB exclusion criteria (see Section 5.2). If active TB infection is diagnosed, then the participant will not be eligible for this study (see Section 7.1.2).

Participants diagnosed with latent TB will need to complete a course of at least 6 months of INH therapy during the study:

- If diagnosed prior to study commencement, then at least 4 weeks of therapy should occur prior to commencement of study intervention.

- If diagnosed during the study, then the participant must temporarily discontinue study intervention and complete 4 weeks of INH therapy. Participants may only start or re-commence study treatment once ALT elevation resolves to ALT < 3 x ULN during ongoing INH therapy. Participants with persisting ALT ≥ 3 x ULN must be discussed with the GSK medical monitor.

Participants will require safety monitoring of blood haematology and liver biochemistry every 4 weeks during INH therapy. Should elevated levels rise above the liver stopping criteria for participants receiving INH within the study then participants should be withdrawn from 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 physical exam (see SoA in Section 1.3). In addition, annual TB test must be performed.

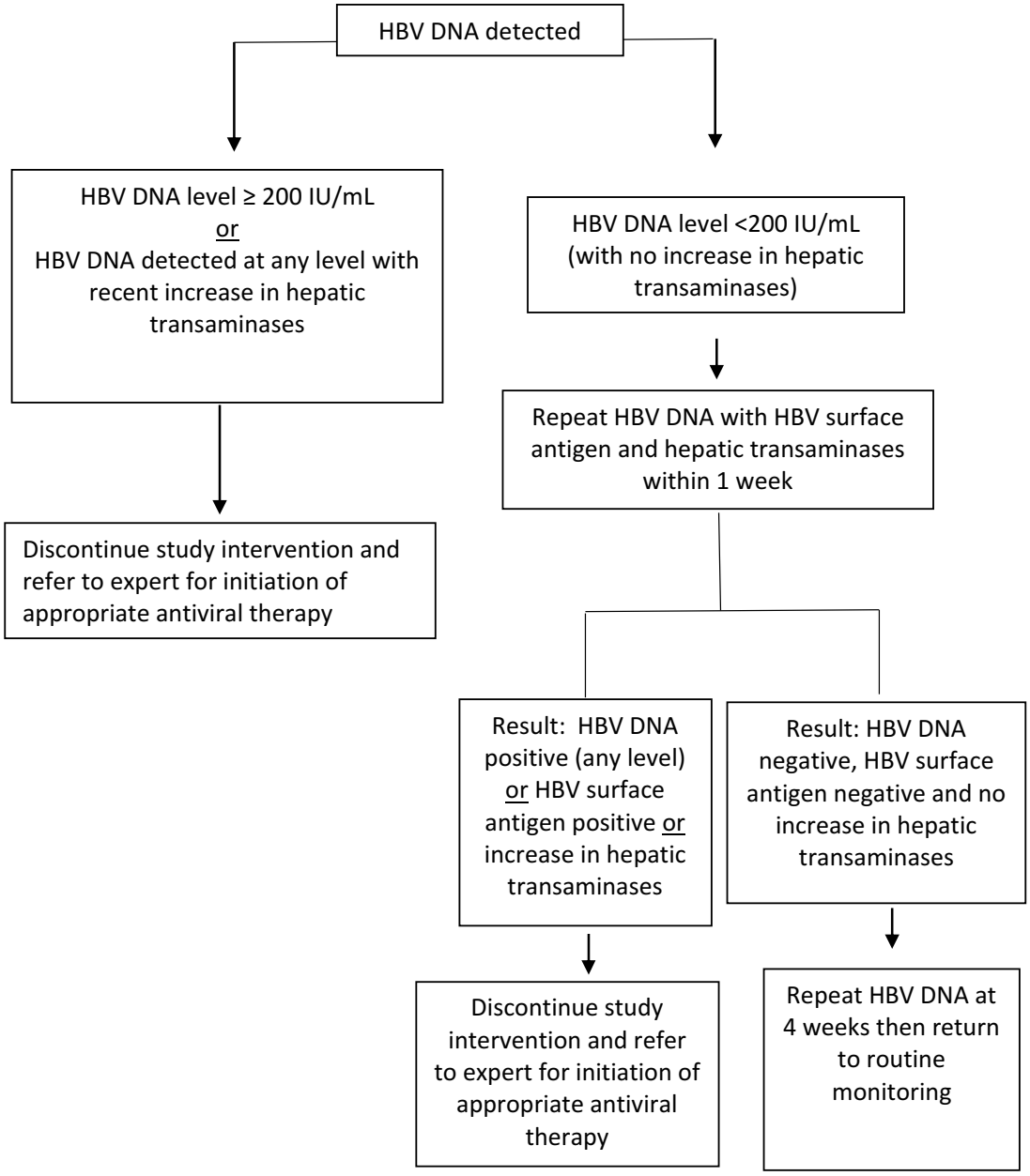
If at any point during the study, the investigator suspects that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken including consultation with a physician specializing in TB. The investigator should discuss with the medical monitor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

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

8.2.8. Hepatitis B Monitoring

All participants with positive HBcAb results from qualifying study, will have HBV DNA levels monitored throughout the study as summarized in Figure 1.

Figure 1 Monitoring of HBV DNA Levels in HBcAb Positive Participants



HBV DNA levels will be assessed every 4 weeks up to Week 12 in these participants, then every 8 weeks to Week 36 and then every 12 weeks for the duration of the study. This increased monitoring at the start of this study is important because some participants will have changed their treatment from comparator in qualifying study, to GSK3196165 in this study.

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 like 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 definitions of device-related safety events, (adverse device effects (ADEs) and serious adverse device effects (SADEs)), can be found in Appendix 7. Device deficiencies are covered in Section 8.3.8.

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 determine the severity of the cough based on CTCAE grading scale and will record the grade of dyspnoea. 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 [pre-dose Day 1]) 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 AEs and SAEs will be collected from the time of signing the informed consent form until the follow-up visit at the time points specified in the SoA (Section 1.3).
- 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 SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants which commence after the start of study intervention and until 8 weeks after the last dose will be collected and followed through the end of pregnancy.
- 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 be permanently discontinue study intervention and be withdrawn from the study following 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 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 (AESIs) for 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

Medical devices are being provided for use in this in the form of pre-filled syringes assembled into either a safety syringe or autoinjector device. 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 7.

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 7.

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 fulfill 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 greater than the highest dose used in this study (150 mg once-weekly) will be considered an overdose. It should be noted that the minimum time between dosing with GSK3916165 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.

In the event of an 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 intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Contact the unblinded CRA 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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8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

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 titer 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 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

There are no formal statistical hypotheses to be tested: this study is designed to describe the long-term safety and efficacy of GSK3196165.

9.2. Sample Size Determination

There are no formal statistical sample size calculations. Sample size will be determined by the number of participants who choose to continue after completion of their qualifying GSK3196165 study. All subjects will be considered evaluable.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

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

The primary analysis population will be the Safety Population.

9.4. Statistical Analyses

The primary objective of this study is to assess long-term safety. Data will be summarised descriptively.

For assessment of change from baseline in safety assessments, baseline will be the pre-dose assessment(s) on the day of the participant's scheduled first dose of GSK3196165 in their qualifying study, or at the start of this study (if the participant did not receive GSK3196165 in their qualifying study). For descriptive efficacy assessments (except x-ray data), baseline from the pre-dose assessment on entry to this study will be used. For x-ray data, baseline will be defined in the Charter for Independent Imaging Assessment.

Results will be presented split by GSK3196165 dose in this study and treatment arm from the qualifying study.

Where important for interpretation, safety data from the qualifying study will be included in the results tables.

Full details of all data analyses will be provided in the reporting and analysis plan (RAP). Any changes to the original planned analysis provided in this section of the protocol will be described in the RAP and/or the Clinical Study Report.

9.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
All	All analyses will be descriptive in nature. Data will be summarised using frequency counts, proportions, summary statistics, graphs and listings. In particular, incidence rates will be calculated for AEs, SAEs and AESIs, and the proportions of participants with laboratory abnormalities (NCI-CTCAE ≥ Grade 3) will be calculated.

9.4.2. Efficacy & Patient-Reported Outcome Analyses

Endpoint	Statistical Analysis Methods
All	All analyses will be descriptive in nature. Data will be summarised using summary statistics, frequency counts, proportions, graphs and listings.

9.4.3. Other Analyses

Details for exploratory endpoints will be provided in the RAP.

Exploratory endpoints may be presented separately from the main clinical study report (CSR).

9.5. Interim Analyses

Several unblinded analyses for regulatory purposes are planned. The first unblinded interim analysis of the data in this continuation study is planned to coincide with the primary analysis of the Phase 3 qualifying studies 201790, 201791 and 202018 in order to analyse and submit this long-term data to regulatory authorities. Additional unblinded interim analyses may be required to support, for example, subsequent safety updates to regulatory authorities, and the final analysis will be conducted after all patients have completed the study.

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

9.5.1. Independent Data Monitoring Committee (IDMC)

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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

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

10.1.5. Committees Structure

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 utilized 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, PAC and IDMC will function as detailed in their respective charters.

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 multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.7. 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 subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for all participants who joined from the same qualifying study, after that qualifying study has reported.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.8. 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 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 minimize 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 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 3 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.
- 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 eligibilty pregnancy criteria.
    - Pregnancy testing (urine or serum as required by local regulations) for WOCBP will be conducted once every 8 weeks during study treatment period.
    - 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 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	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	• 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 [Hepatitis B surface antigen (HBsAg), HBV DNA], 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.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international 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.

The following results will not be reported to investigative sites or the study team involved in the conduct of the study:

- CCI [redacted]

Note: ESR/CRP/hsCRP are not blinded in this study and additional local testing (outside of the study) may be performed when necessary.

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 GSK Medical Devices used in this study (see Section 6.1.2 for the list of GSK medical devices).
- Refer to Appendix 7 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 (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., 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 fulfills 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 (e.g, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
• **Possible Hy's Law Case:** ALT ≥3xULN and Bilirubin ≥2 xULN (>35% direct) or INR > 1.5* *INR value not applicable to participants on anticoagulants
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 to GSK in lieu of completion of the GSK AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category 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 an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

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: 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

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • Permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments	• 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[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of

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, stabilize 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, stabilize or return to within baseline	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. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. 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 normalize 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.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369

10.6. Appendix 6:Summary of composite endpoints

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

10.6.1. Disease Activity Score (DAS)

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.
- PtGA.

10.6.2. 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).
- PtGA.
- PhGA.

10.6.3. ACR and EULAR Remission (Boolean and SDAI)

ACR/EULAR remission in rheumatoid arthritis clinical trials [Felson, 2011] will be assessed using both Boolean and SDAI definitions, at each assessment timepoint.

For the Boolean definition, this includes:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).
- hsCRP.
- PtGA.

For the SDAI definition, this includes:

- Tender/Painful Joint Count (28).
- Swollen Joint Count (28).
- hsCRP.
- PtGA.
- PhGA.

10.7. Appendix 7: 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 all GSK medical devices provided for use in the study (see Section 6.1.2 for the list of GSK medical devices). Refer to Appendix 3 for all other AE/SAE reporting not involving a GSK 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.

10.7.1. 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.

10.7.2. 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).

10.7.3. 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.

10.7.4. 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.

10.7.5. 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.

10.7.6. 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.

- 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.

10.8. Appendix 8: Country-specific requirements

10.9. Appendix 9: Abbreviations and Trademarks

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACR	American College of Rheumatology
ADA	Anti-Drug Antibody
ADE	Adverse Device Effect
AE	Adverse event
AESI	Adverse event of special interest
AI	Auto Injector
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AP	Alkaline phosphatase
AST	Aspartate transaminase
bDMARD	Biologic disease modifying antirheumatic drug
CDAI	Clinical disease activity index
CIOMS	Council for International Organisations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPK	Creatine phosphokinase
CRF	Case report form
CRP	C-reactive protein
csDMARD	Conventional synthetic disease modifying antirheumatic drug
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CV	Coefficient Variance
CYP	Cytochrome
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
EASL	European Association for the Study of the Liver
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCRF	Electronic case report form
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FACIT	Functional assessment of chronic illness therapy
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony stimulating factor
GSK	GlaxoSmithKline
HAQ-DI	Health Assessment Questionnaire Disability Index
HBcAb	Hepatitis B core Antibody

HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HF	Human factors
HRCT	High-resolution computed tomography
HRQL	Health Related Quality of Life
HRT	Hormone replacement therapy
HV	Healthy volunteer
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IgM	Immunoglobulin M
IEC	Institutional Ethics Committee
IFU	Instructions for use
IMP	Investigational medicinal product
INH	Isoniazid
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IRT	Interactive Response Technology
kg	Kilogram
L	Litre
LAM	Lactational amenorrhoea method
LDH	Lactate dehydrogenase
MACE	Major Adverse Cardiac Event
MCV	Mean cell volume
MCH	Mean corpuscular haemoglobin
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
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
NIMP	Non-investigational medicinal product
PAC	Pulmonary Adjudication Committee

PAP	Pulmonary alveolar proteinosis
PCR	Polymerase chain reaction
PFS	Prefilled syringe
PtGA	Patient's Global Assessment of Arthritis
PhGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetics
PRO	Patient Reported Outcomes
RA	Rheumatoid arthritis
RAP	Reporting and analysis plan
RF	Rheumatoid factor
RNA	Ribose nucleic acid
SC	Subcutaneous
SAE	Serious adverse event
SADE	Serious Adverse Device Effect
SF-36	Short form (36)
SoA	Schedule of Activitites
SRM	Study Reference Manual
SRT	Safety Review Team
TB	*Mycobacterium tuberculosis*
CCI	
TNFα	Tumor necrosis factor alpha
tsDMARD	Targeted synthetic disease modifying antirheumatic drug
USADE	Unanticipated Serious Adverse Device Effect
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WBC	White Blood Cell
WOCBP	Woman of Childbearing Potential

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