Statistical Analysis Plan

Study ID: 209564

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

NCT ID: NCT04333147

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TITLE PAGE

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

Study Number: 209564

Compound Number: GSK3196165

Compound Name: Otilimab

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

Acronym: contRAst-X

Sponsor Name: GlaxoSmithKline Research & Development Limited

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	12 Jan 2023	Original version (14-OCT-2019)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report for Study 209564. Due to the termination of the entire Rheumatoid Arthritis programme, no interim analyses will be performed. Details of the planned final analyses are provided herein.

Additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. 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 interest (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 and DAS28-ESR • van der Heijde mTSS score [2] (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

Objectives	Endpoints
	• 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 events of special interest; NCI-CTCAE = National Cancer Institute common terminology criteria for adverse events; RA = rheumatoid arthritis; SF-36 = short form-36; CCI [redacted] PFS = pre-filled syringe.

* See SAP Section 4.1.2 Baseline Definition

CCI [redacted]

[2] At the time of study termination, most participants did not have the required number of X-rays performed (i.e., Week 24 and Week 48) for these to be read as per the reading charter. Additionally, most of the readings of the available X-rays had been assessed by only one reader, but adjudication had not yet occurred as per the reading charter. Therefore, these partial data will be listed with no analysis of the mTSS endpoints.

1.1.2. Estimands

The primary clinical questions of interest in this study relate to AEs, AESIs, SAEs, change from baseline in key laboratory parameters, and NCI-CTCAE ≥ Grade 3 haematological/clinical chemistry abnormalities. In the case of AEs, AESIs and SAEs, the question of interest is "What is the incidence of an event with otilimab 90 mg and 150 mg in participants with moderately or severely active rheumatoid arthritis, regardless of permanent treatment discontinuation, intake of prohibited medication and change in background medication?"

Estimand for the Primary Objective

The estimand will be defined as follows:

A. Treatment conditions: otilimab 90 mg and otilimab 150 mg.
B. Population: Participants with moderately or severely active RA on background csDMARD therapy.
C. Variable: AEs, AESIs and SAEs over the entire study i.e., using data up to Safety follow-up.
D. Intercurrent Events (IE):
    - permanent treatment discontinuation
    - prohibited medication taken while on study intervention
    - change in background therapy while on study intervention

    For all types of IE, the treatment policy estimand is being used as it provides evidence of safety regardless of whether the participants took drug as per the protocol and is most closely reflective of usual clinical practice.

E. Summary measure: frequency of an event i.e., AEs, AESIs, SAEs.

The incidence of AEs, AESIs, and SAEs will be estimated for each treatment group regardless of whether these IE have occurred or not. Data will continue to be collected after the occurrence of the IE, until the participant either completes the study or withdraws from the study before completion.

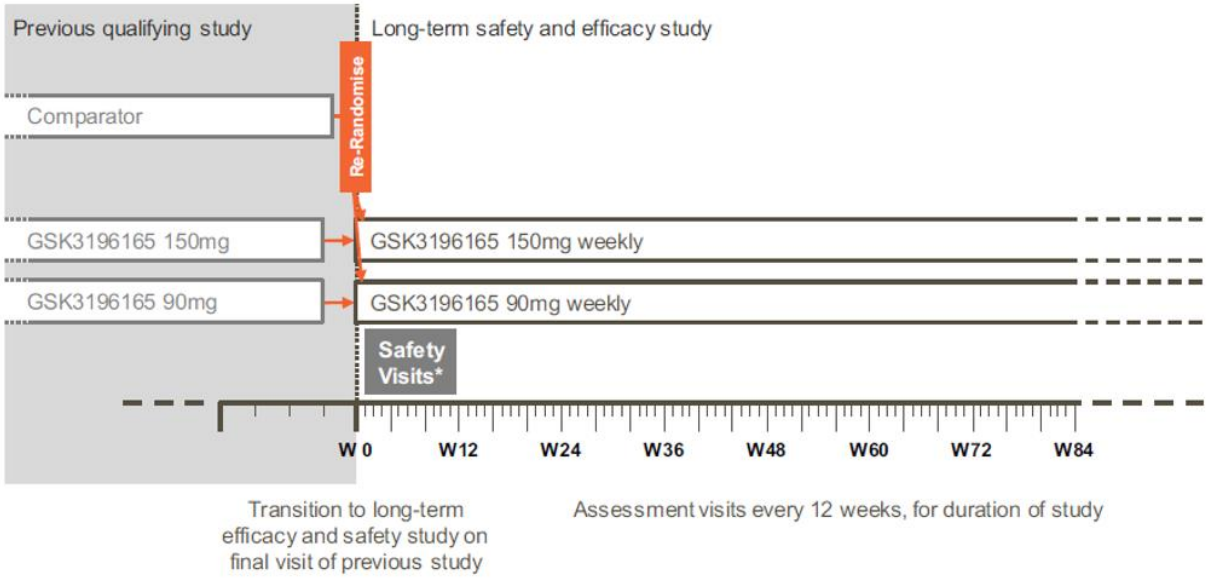
Similarly, for change from baseline in key laboratory parameters, the estimand would be the same as above, except components C and E will be defined as:

- C. Variable: change from baseline at discrete timepoints during the study
- E. Summary measure: mean change from baseline

Similarly, for NCI-CTCAE ≥ Grade 3 haematological/clinical chemistry abnormalities, the estimand would be the same as above, except components C and E will be defined as:

- C. Variable: NCI-CTCAE ≥ Grade 3 haematological/clinical chemistry abnormalities over the entire study
- E. Summary measure: frequency of Grade 3 or more abnormalities.

1.2. Study Design

Overview of Study Design and Key Features	
 * 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 follow-up visit at Week 4.	
Design Features	• Global Phase 3, multicentre, long term extension study in adult participants with rheumatoid arthritis (RA) who have completed treatment in one of the qualifying GSK3196165 clinical studies and who, in the investigator's judgement will benefit from extended treatment with GSK3196165. • Participants are expected to be treated for 1-4 years [1]. • Every participant will receive either GSK3196165 90 mg or 150 mg subcutaneous (SC) injection weekly. • Participants from study 202018 who received sarilumab will receive otilimab two weeks after their last sarilumab dose. • Study intervention for a given participant will remain blinded at least until the applicable qualifying study has been unblinded. • No formal screening period, eligible participants should complete Day 1 assessments following completion of final qualifying study assessment. Typically, the final day of the qualifying study serves as Day 1 of study 209564. • All participants will have a safety follow up visit 8 weeks after their last dose of study intervention.
Study intervention	• GSK3196165 90 mg or 150 mg, SC injection weekly, administered by pre-filled syringe (PFS) or an autoinjector (AI) device, if available (see Protocol Section 6.1).

Overview of Study Design and Key Features	
	• The AI device will be made available to selected sites for use in a sub-study, see Protocol Section 4.1. • Participants will continue to receive the same background conventional synthetic disease modifying antirheumatic drug(s) (csDMARD) treatment as received in their qualifying study.
Study intervention Assignment	• Participants randomised to GSK3196165 in the qualifying study will continue to receive GSK3196165 at the same dose level in study 209564. Those randomised to comparator drug (i.e., tofacitinib or sarilumab) in the qualifying study will be re-randomised, in a ratio 1:1, to receive either GSK3196165 90 mg or 150 mg weekly, in this study (see Protocol Section 4.1).
Final Analyses	Note, a blinded read out of the AI sub-study was conducted to provide data on the AI device questionnaire plus AEs (SAP submitted to IND 121958 – Sequence 0099, Serial Number – 0095; GSK document number TMF-133338010). [1] Due to study termination all participants are expected to return for an early withdrawal visit and Safety Follow-up. The final (end-of-study) analysis will be conducted when all participants have completed these visits per the protocol.

2. STATISTICAL HYPOTHESES

There is no placebo control or active reference arm in study 209564 to assess the treatment effect of GSK3196165. Therefore, no formal hypotheses will be tested: study 209564 is a descriptive summary of the endpoints.

2.1. Multiplicity Adjustment

Multiplicity adjustment is not applicable.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility, see Protocol Section 5.4.	• Study Population
Enrolled	• All participants who enrolled in study 209564 (who were randomized or received study intervention or underwent a post screening study procedure) and signed the ICF. • Note screening failures (who never passed screening) and participants screened but never enrolled into the study (met eligibility but not enrolled) are excluded from the Enrolled analysis set.	• Study Population
Randomised	• All enrolled participants who were randomised to study intervention in the qualifying study and allocated or re-randomised to study treatment in study 209564 (see Section 1.2).	• Study Population
Safety	• All enrolled participants who received at least one dose of study intervention. • Data should be reported according to the actual treatment.	• Safety
ITT	• All enrolled participants who received at least one dose of study intervention • Data will be reported according to the randomised study intervention.	• Efficacy
CCI [redacted]		

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Data will be presented by GSK3196165 dose level (90 mg or 150 mg) in study 209564 alone. Additionally, data (not presented in figures) will be presented by GSK3196165 dose level of study 209564 and previous exposure (Naïve, 12 weeks, 24 weeks, 40 weeks, 52 weeks) in the qualifying study based on actual treatment arm, unless otherwise indicated. Note: Naïve comprises participants who received either sarilumab or tofacitinib in the qualifying studies, who are now exposed for the first time to GSK3196165 in study 209564.

Unless otherwise specified, continuous data will be summarised using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarised as the number and percentage of participants in each category.

Pandemic measures for COVID-19 started before participants enrolled in study 209564. Therefore, any required summaries by pre- and post- pandemic measures will not be produced.

Listings not mentioned explicitly in this document may be made available through the RAPIDO data viewer. The RAPIDO data viewer allows viewing and searching within the clinical database without the need for statistical outputs.

4.1.2. Baseline Definition

Baseline will be defined as Day 1 of study 209564, unless otherwise stated.

Data not collected at the start of study 209564 (e.g., date of RA diagnosis, ACPA and RF status) will be taken from the qualifying study either from eCRF data prior to the study or at Day 1 (pre-dose). For some assessments, not available or missing at Day 1 of study 209564, baseline will be the latest pre-dose assessment that is available prior to starting study 209564.

For assessment of change or shift 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 study 209564 (if the participant did not receive GSK3196165 in their qualifying study).

4.2. Primary Endpoint Analyses

The primary objective of study 209564 is Safety, which will be evaluated by the incidence of adverse events, serious adverse events (SAEs) and AEs of special interest (AESI) and changes from baseline in key laboratory parameters, and proportion of participants with NCI-CTCAE ≥ Grade 3 haematological/clinical chemistry abnormalities. Planned analyses of these endpoints are described in Section 4.5 Safety Analyses.

4.3. Secondary Endpoint Analyses

Secondary endpoints include long-term efficacy, patient reported outcomes, and anti-GSK3196165 antibodies. The secondary endpoint analyses will be based on the ITT Analysis Set, unless otherwise specified.

Data for each secondary endpoint will be summarised using summary statistics, for each scheduled time-point.

4.3.1. Efficacy

4.3.1.1. Definition of endpoints

CDAI total score ≤ 10

The Clinical Disease Activity Index (CDAI) for RA is a clinical composite score to determine disease severity using only clinical data (see Protocol Section 10.6.2).

The components of the CDAI are:

- Tender/Painful Joint Count (evaluating 28 joints, TJC28)
- Swollen Joint Count (evaluating same 28 joints, SJC28)

- Patient's Global Assessment of Arthritis (PtGA)
- Physician's Global Assessment of Arthritis (PhGA)

A secondary efficacy endpoint of CDAI is the proportion of participants at Weeks 24, 48, and every 48 weeks thereafter, achieving CDAI LDA (CDAI total score ≤ 10).

The CDAI total score is calculated as the sum of the four component counts. Scores range from 0 to 76, where higher scores indicate more severe disease. If one of the components is missing at an individual assessment time-point, the CDAI total score for that assessment will be set to missing.

Note: PtGA and PhGA components are on a scale of 0-10, obtained by multiplying the collected visual analogue scale (VAS) score by 1/10 (see PhGA and PtGA explanation below).

CDAI total score ≤ 2.8

See CDAI total score ≤ 10 for details of the endpoint definition.

A secondary efficacy endpoint of the CDAI score is the proportion of participants at Week 24, 48 and every 48 weeks thereafter, achieving CDAI Remission (CDAI total score ≤ 2.8).

DAS28-CRP < 2.6 and DAS28-ESR < 2.6

The Disease Activity Score (DAS) is a measure of disease activity in RA based on 28 joints (DAS28) (see Protocol Section 10.6.1).

The components of the DAS28 arthritis assessment include:

- Tender/Painful Joint Count (TJC28)
- Swollen Joint Count (SJC28)
- High sensitivity C-reactive protein (hsCRP) (in mg/L) or Erythrocyte sedimentation rate (ESR) (in mm/hr)
- PtGA

Secondary endpoints of the DAS28 are:

- Proportion of participants at Week 24, 48 and every 48 weeks thereafter, achieving DAS28-CRP Remission (DAS28-CRP < 2.6)
- Proportion of participants at Week 24, 48 and every 48 weeks thereafter, achieving DAS28-ESR Remission (DAS28-ESR < 2.6)

The DAS28-CRP is calculated as:

$$\text{DAS28-CRP} = 0.56*\sqrt{TJC28} + 0.28*\sqrt{SJC28} + 0.36*\ln(\text{hsCRP}+1) + 0.014*\text{PtGA} + 0.96$$

If one of the components is missing at an individual assessment time-point, the DAS28-CRP value for that assessment will be set to missing.

The DAS28-ESR is calculated as:

$$\text{DAS28-ESR} = 0.56*\sqrt{TJC28} + 0.28*\sqrt{SJC28} + 0.7*\ln(\text{ESR}) + 0.014*\text{PtGA}$$

If one of the components is missing at an individual assessment time-point, the DAS28-ESR value for that assessment will be set to missing. An ESR value of 0 will be substituted with ESR=1 for the calculation of DAS28-ESR.

ACR and EULAR Remission

ACR/EULAR remission in RA clinical trials will be assessed using both Boolean and SDAI (Simple Disease Activity Index) definitions, at each assessment time-point (see Protocol Section 10.6.3; Table 2).

A secondary efficacy endpoint of ACR/EULAR remission is the proportion of participants at Weeks 24, 48 and every 48 weeks thereafter, achieving each definition separately.

Boolean definition

A participant must satisfy the following:

- TJC evaluating 68 joints (TJC68) ≤ 1
- SJC evaluating same joints, with the exception of hip (SJC66) ≤ 1
- hsCRP ≤ 1 mg/L
- PtGA ≤ 10

If one of the components is missing at an individual assessment point, Boolean-based remission for that assessment will be set to missing.

SDAI definition

A participant must have an SDAI ≤ 3.3. The SDAI is the sum of the tender/painful joint count and swollen joint count, employing 28 joints; PtGA and PhGA (on a scale of 0-10); and hsCRP (mg/L).

If one of the components is missing at an individual assessment point, the Index-based remission for that assessment will be set to missing.

CDAI total score

See CDAI total score ≤ 10 for details of the endpoint definition.

A secondary efficacy endpoint of CDAI is the absolute values of the CDAI total score at Weeks 24, 48 and every 48 weeks thereafter.

DAS28-CRP and DAS28-ESR scores

See DAS28-CRP < 2.6 and DAS28-ESR < 2.6 for details of the endpoint definition.

Secondary efficacy endpoints of DAS28 are the absolute values of the DAS-CRP and DAS-ESR at Weeks 24, 48 and every 48 weeks thereafter.

van der Heijde mTSS score

At the time of study termination, most participants did not have the required number of X-rays performed (Week 24 and Week 48) for these to be read as per the reading charter. Additionally, most of the readings of the available X-rays had been assessed by only one reader, but adjudication had not yet occurred as per the reading charter. Therefore, these partial data will be listed with no analyses of the mTSS scores.

Components of CDAI and DAS28

For the purpose of deriving the composite efficacy endpoints, the individual components used are described below, and a listing of the components will be provided.

TJC and SJC

An evaluation of all 68 joints for tenderness and 66 joints for swelling will be performed by a joint evaluator (see Protocol Section 8.1.1). The joint count is scored as a sum of the tender joints (TJC) and a sum of the swollen joints (SJC).

Joint counts will be calculated for 68 joints for tenderness (TJC68) and 66 joints for swelling (SJC66), and for a subset of 28 joints for tenderness/swelling (TJC28, SJC28). Table 1 shows the joints that are assessed for each tenderness/swelling count.

Table 1 Joints assessed for presence of tenderness and swelling

Joint	Location	Score	Joints of 66/68 joint count	Joints of 28/28 joint count
Temporomandibular (TMJ)	Jaw	2	●	
Sternoclavicular (SC)	Chest	2	●	
Acromioclavicular (AC)	Chest/Shoulder	2	●	
Shoulder		2	●	●
Elbow		2	●	●
Wrist		2	●	●
Metacarpophalangeal (MCP)	Base of fingers/thumb	10	●	●
Finger proximal interphalangeal (finger PIP)	Middle of fingers/thumb	10	●	●
Distal interphalangeal (DIP)	Tips of fingers	8	●	
Hip **(tenderness only)**		2	●	
Knee		2	●	●

Joint	Location	Score	Joints of 66/68 joint count	Joints of 28/28 joint count
Ankle		2	●	
Tarsus	Feet	2	●	
Metatarsophalangeal (MTP)	Base of toes	10	●	
Toe proximal interphalangeal (toe PIP)	Toes	10	●	

Notes:

1. Replaced or fused joints are considered non-evaluable in the swelling and tenderness assessment.
2. If there are missing observations for tender or swollen joints, then the remaining observations will be assessed and weighted by dividing the number present by number non-missing and by multiplying by 66/68/28/28 for the joint count.
3. If a joint has undergone inter-articular (IA) injection of corticosteroid during the study, this joint is recorded in the concomitant medication dataset. The joint will be considered as tender and swollen for 8 weeks post IA corticosteroid injection.

PhGA

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

PtGA

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

hsCRP

hsCRP (mg/L) a marker of inflammation in RA was collected as part of the laboratory assessments.

ESR

ESR (mm/hr) a marker of inflammation of RA was collected as part of the laboratory assessments.

4.3.1.2. Main analytical approach

Binary endpoints

The following secondary efficacy endpoints in Section 4.3.1.1 will be analysed as binary endpoints:

- CDAI total score ≤ 10

- CDAI total score ≤ 2.8
- DAS28-CRP < 2.6 and DAS28-ESR < 2.6
- ACR and EULAR remission

Binary endpoints will be summarised using counts and proportions of the number of participants meeting the specified criteria at each assessment visit. No missing data will be imputed.

Continuous endpoints

The following secondary efficacy endpoints in Section 4.3.1.1 will be analysed as continuous endpoints

- CDAI total score
- DAS28-CRP and DAS28-ESR

Continuous endpoints will be summarised using descriptive statistics at each assessment visit. No missing data will be imputed.

A listing of efficacy data will be provided.

4.3.2. Patient Reported Outcomes

4.3.2.1. Definition of endpoints

Health Assessment Questionnaire – Disability Index (HAQ-DI)

The functional status of the participant will be assessed by the Disability Index of the Stanford Health Assessment Questionnaire (HAQ-DI). The HAQ-DI is a 20-item measure that evaluates patient difficulty with activities of daily living over the past week, using a 4-point scale, where 0 indicates "without difficulty" and 3 indicates "unable to do". The 20 items are grouped into 8 functional categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Also identified are specific aids or devices utilized for assistance, as well as help needed from another person (aids/help). The highest component score in each functional area determines the score for that functional area unless aids/help are required. Participants who use equipment or physical assistance for a specific functional area, will have their score adjusted, as necessary, to represent disability more accurately.

A secondary PRO endpoint of the HAQ-DI is the absolute values of the HAQ-DI score at Week 24 and 48, and every 48 weeks thereafter.

The HAQ-DI score is calculated as the sum of the functional area scores divided by the number of functional areas answered. Higher overall score indicates greater disability (on a scale of 0 to 3). The HAQ-DI will be not computed when the participant provides answers in fewer than 6 functional areas.

Arthritis Pain VAS

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

A secondary PRO endpoint of the Pain VAS is the absolute values of the Pain VAS score at Week 24, 48 and every 48 weeks thereafter.

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.

The eight domains of health are:

- Physical functioning
- Role function – Physical aspect
- Bodily Pain
- General health perception
- Mental Health
- Role function – Emotional aspect
- Social functioning
- Vitality

Secondary PRO endpoints of the SF-36 are the absolute values of the SF-36 physical and mental component scores, and individual health domain scores, at Week 24 and 48, and every 48 weeks thereafter.

The SF-36 will be scored using the Quality Metrics SF-36 scoring software. All items, domains and summary scores, will be scored so that a higher score indicates a better health status.

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.

The FACIT-fatigue is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and functions, using a numeric rating scale 0 to 4 where 0 indicates CCI and 4 indicates CCI For item 7 CCI and item 8 CCI

[redacted], a higher score represents [redacted] for items 1 to 6 and 9 to 13, item scores must be reversed.

A secondary PRO endpoint of FACIT-[redacted] is the absolute values of the FACIT total score at Week 24 and 48, and every 48 weeks thereafter.

The total FACIT score is calculated as the sum of the individual item scores. The total score ranges from 0 to 52 where higher values represent [redacted]

4.3.2.2. Main analytical approach

All secondary PRO endpoints in Section 4.3.2.1 will be summarised as continuous endpoints.

Continuous endpoints will be summarised using descriptive statistics at each assessment visit. No missing data will be imputed.

4.3.3. Immunogenicity

4.3.3.1. Definition of endpoints

Serum samples for anti-drug antibody (ADA) measurements will be collected at Week 24 and 48 of each study year, and the follow-up visit (8 weeks after last dose of study intervention). Serum samples will be screened for antibodies binding to GSK3196165 and the titer of confirmed positive samples determined (see Protocol Section 8.9).

A secondary endpoint of immunogenicity is the proportion of participants with a confirmed positive for ADA to GSK3196165.

The detection and characterisation of antibodies to GSK3193165 will be performed using validated assay methods (see Protocol Section 8.9 for details of the assay methods).

4.3.3.2. Main analytical approach

Immunogenicity results will be summarised at each assessment visit and any time post-Day 1 of study 209564.

The results will be categorised for analysis as

- negative, or
- positive

Positive results will further be categorised (only for anytime post-Day 1 of study 209564) as

- transient positive (defined as a single positive immunogenic response where the previous visit is negative, that does not occur at the final assessment), or
- persistent positive (defined as a positive immunogenic response where the previous visit is positive, or the final study assessment is positive).

Any time post-Day 1 of study 209564, the highest result obtained for each participant will be summarised (lowest to highest result is: negative, Transient Positive, Persistent Positive).

Titers will be summarised by median, minimum and maximum.

Neutralizing antibody assay results will be summarised for participants with a positive ADA assay.

Additionally, an overall summary of all ADA results will be produced.

A listing of immunogenicity results will be provided.

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4.5. Safety Analyses

Safety is evaluated by AEs, changes in laboratory data, vital signs and ECG. The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

Incidence of AEs, SAEs and AESI and other important AEs, and changes from baseline in key laboratory parameters, and proportion of participants with NCI-CTCAE ≥ Grade 3 haematological/clinical chemistry abnormalities, are defined as the primary endpoints of study

209564 (see Section 1.1). These analyses are described in Section 4.5.2 Adverse Events and Section 4.5.3 Additional Safety Assessments.

4.5.1. Extent of Exposure

The extent of exposure to study intervention during study 209564 will be summarised.

- Number of participants exposed, and duration of exposure, using any device
- Number of missed injections, using any device

Duration of exposure to study intervention (in days) will be calculated for each participant, as

Duration of exposure in days =
(last injection date – first injection date + 7 days) – (number of missed injections × 7 days)

For any participants who died within the 7 days after injection, duration of exposure will be censored at the date of death.

Participants who did not have an injection date will be assigned 0 days of exposure.

Summary statistics will be produced for the duration of exposure. The number of participants with missed injections will be summarised as follows: 0, 1, 2 to 5, >5 missed injections.

In addition, the distribution of treatment exposure to GSK3196165 (without adjustment for missed doses) up to pre-defined ranges from Day 1 of study 209564 (< 24 weeks, > 24 to 48 weeks, >48 to 96 weeks, etc) will be summarised. Treatment exposure (in days) will be calculated for each participant as (last injection date – first injection date + 7 days).

Person-year exposure will be reported with and without missing doses.

Additionally, the number of participants that were administered study intervention by the AI device will be summarised overall and by country. For Japan only, AI device administrator details will be listed, where such data are collected.

A listing of study intervention including randomisation details (number and date) and exposure will be produced.

4.5.2. Adverse Events

An adverse event (AE) is considered study intervention emergent if the AE onset date is on or after the study intervention start date for study 209564 and on or before the Safety follow-up visit (8 weeks post-last dose).

AE summaries will be based on study intervention emergent events unless otherwise specified. Ongoing AEs and SAEs at the start of study 209564 (from qualifying study) will be summarised separately. All AE and SAE summaries will be by SOC and PT only unless otherwise specified.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary in use at the time of reporting) and grouped by SOC and PT, unless otherwise stated.

A listing of all AEs will be provided. Death and Cardiovascular Event subject profiles and a listing of reasons for considering an event as a SAE will also be produced.

The following analyses of adverse events will be included:

- An overview summary of AEs, including counts and percent of participants with:

  AE

  - any AE
  - AEs related to study intervention
  - AEs leading to study intervention discontinuation only
  - AEs leading to background therapy discontinuation only
  - AEs leading to discontinuation of both study intervention and background therapy
  - AEs leading to dose interruption/delay of study intervention
  - AEs leading to dose interruption/delay of background therapy
  - AEs leading to dose reduction of background therapy

  Serious Adverse event (SAE)

  - any SAE
  - SAEs related to study intervention
  - fatal SAEs
  - Fatal SAEs related to study intervention

  SAE excluding COVID-19 infections (categories as above)

- Incidence of AEs overall, and by study intervention relationship as assessed by the investigator, and intensity. AEs with missing intensity will be considered severe. Exposure adjusted event rates per 100 person-years will also be reported.

- Incidence of common AEs (≥ 5% or as defined, in either treatment group for this study).

- Incidence of all SAEs overall, drug-related SAEs, and fatal SAEs. Exposure adjusted event rates per 100 person-years for SAEs will also be reported.

- Incidence of AEs that led to study intervention discontinuation.

Further AE tables required for Plain Language Summary and public registers will be produced.

Event rates per 100 person-years of exposure

The event rate will be calculated as:

Event rate = 100 * number of events / total number of person-years of exposure,

where total person-years of exposure =

$$\frac{\sum_{\text{all subjects in population}} [\text{duration of exposure in days (excluding any treatment breaks)}]}{365.25}$$

Exposure is calculated as described in Section 4.5.1.

4.5.2.1. Adverse Events of Special Interest and Other Important AEs

Adverse events of special interest (AESI) for GSK3196165 and other important AEs will be derived using MedDRA and Common Terminology Criteria for Adverse Events 2017 v5.0 (CTCAE).

Overall summaries of the incidence of AESI and other important AEs will be tabulated. Rate of events per 100 person-years of exposure will also be reported. Further summaries of event characteristics will be produced.

The following will be considered an AESI or other important AEs for the purpose of analyses:

AESI

- serious infections – overall, and excluding COVID-19 infections
- opportunistic infections
- Latent TB, Active TB and TB reactivation
- neutropenia ≥ Grade 3 (< 1.0×10^9/L)
- pulmonary alveolar proteinosis
- serious hypersensitivity reactions, including anaphylaxis
- persistent (≥ 21 days) cough (CTCAE Grade ≥ 2)
- persistent (≥ 21 days) dyspnoea (dyspnoea scale Grade ≥ 2)
- injection site reactions

Other important AEs

- cardiovascular events
- adjudicated cardiovascular events include:
  - cardiovascular (CV) death
  - non-fatal myocardial infarction (MI)
  - hospitalisation for unstable angina
  - non-fatal stroke

hospitalisation for heart failure
deep vein thrombosis (DVT)
pulmonary embolism (PE)

- GI perforation and adjudicated GI perforation
- malignancies include:
  - any malignancy
    - solid, excluding non-melanoma skin cancer – overall and
      - by type including breast, lung
    - non-melanoma skin cancer
    - hematologic
    - lymphoma
  - any malignancy, excluding non-melanoma skin cancer
- herpes infection – overall, and by herpes zoster, herpes simplex and non-specific herpes infection
- all-cause mortality
- serious pulmonary infection – overall, and excluding COVID-19 infections
- pneumonia (serious and non-serious) - overall, and excluding COVID-19 infections
- hepatitis B and hepatitis B reactivation
- thromboembolic events
- COVID-19 infections (confirmed, suspected or probable cases)
- adjudicated serious COVID-19 infections (confirmed cases and probable cases)

Adjudicated CV events will be further summarised as follows:

- MACE (defined as: CV death, non-fatal MI, or non-fatal stroke). The subcategories of CV death, non-fatal MI and non-fatal stroke will also be summarised.
- Broad MACE (defined as: CV death, non-fatal MI, hospitalisation for unstable angina, non-fatal stroke, and hospitalisation for heart failure)
- VTE (defined as: DVT and/or PE). This category will include participants who had a DVT and/or PE, i.e., any participants that have both DVT and PE and any participants that have either DVT or PE
- DVT only
- PE only

Other subcategories of cardiovascular events may also be considered.

Note: Cardiovascular deaths include those with a definite cardiovascular cause (cardiogenic shock, heart failure, arrhythmia/sudden death, MI, cardiac rupture, ischemic stroke, PE, venous/arterial thrombotic events) and any other deaths for which an alternative cause has not been identified.

4.5.2.2. Medical Device Deficiencies

Medical device deficiencies will be requested from the Biopharm Device Engineering. These deficiencies and any serious adverse device effects will be summarised manually in the CSR.

4.5.2.3. COVID-19 Assessment and COVID-19 AEs

Additional safety outputs/details relating to COVID-19 will be produced as previously stated in Section 4.5.2.1.

COVID-19 assessments for participants with COVID-19 AEs will also be produced.

4.5.3. Additional Safety Assessments

Safety summaries will be based on observed data with no imputation for withdrawal. All safety summaries of change or shift from baseline will use the pre-dose baseline of GSK3196165 (see Section 4.1.2).

Data will be summarised at the scheduled visit, unless otherwise indicated.

4.5.3.1. Laboratory Data

Only central laboratory data will be summarised.

All laboratory data (including abnormal urine results) for participants with any value of potential clinical importance/outside normal range will be listed, see Section 6.2.1.2.

Laboratory Change from Baseline

Change from baseline in key laboratory parameters is one of the 3 primary endpoints for this study (Section 1.1).

Change from baseline of laboratory data will be summarised at every scheduled assessed visit of study 209564 using summary statistics. Separate displays will be presented for haematology and chemistry laboratory tests, and lipids. Liver function tests will be included with chemistry laboratory tests. Box plots over time will be produced for selected laboratory parameters.

For this study, the key laboratory parameters are shown below (see Protocol Section 8.2.5). The data for these parameters will be presented first in each laboratory panel.

- WBCs
- Haemoglobin
- Platelets
- Lymphocytes
- Neutrophils
- Lipids
- Liver function tests

Laboratory results by maximum grade increase from baseline

The proportion of participants with an NCI-CTCAE Grade ≥ 3 haematological/clinical chemistry abnormalities is one of the 3 primary endpoints for this study (Section 1.1).

Summaries of laboratory results by worst-case grade increase from baseline grade will be provided for all the laboratory tests that are gradable by CTCAE v5.0. Only a participant's worst grade shift during the on-intervention period of study 209565 will be summarised.

Data from both scheduled and unscheduled visits of study 209564 will be included.

A listing of neutrophils and associated infections for the subset of participants who experienced Grade ≥ 3 neutropenia will be produced.

Urinalysis laboratory results

Summaries of laboratory results by worst-case result (discrete or character values) increase from baseline result will be provided for urinalysis. Only a participant's worst result shift during the on-intervention period of study 209564 will be summarised.

Data from both scheduled and unscheduled visits of study 209564 will be included.

Hepatobiliary laboratory abnormalities

A summary of hepatobiliary laboratory abnormalities during the on-intervention period of study 209564 will be produced. Possible Hy's law cases defined as any elevated alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN (>35% direct bilirubin) or ALT ≥ 3 × ULN and INR > 1.5 will be presented in a scatter plot of maximum ALT vs. maximum total bilirubin.

A scatter plot of maximum ALT vs. pre-dose ALT value of GSK3196165 for each participant during the on-intervention period of study 209564, will also be created.

Liver monitoring/stopping events

A summary or listing of liver events will be produced depending upon the number of events. For participants with more than one liver stopping or liver monitoring event, only data related to the earliest most severe criteria event will be included in the summary.

4.5.3.2. Vital Signs

A listing of vital signs data for participants with any values of potential clinical importance will be produced (see Section 6.2.1.4).

4.5.3.3. ECG

ECG data will be listed only, as follows.

- All ECG findings for participants with a clinically significant abnormal ECG finding.
- All ECG values for participants with any value of potential clinical importance (see Section 6.2.1.3).

4.6. Other Analyses

Not applicable.

4.7. Interim Analyses

Not applicable.

4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 2.

Table 2 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Protocol Section 10.6.3 ACR and EULAR Remission Boolean criteria are defined as - Tender/Painful Joint Count (28) - Swollen Joint Count (28) - hsCRP - PtGA	Definition has been revised to - Tender/Painful Joint Count (68) - Swollen Joint Count (66) - hsCRP - PtGA	For consistency with the qualifying studies definition of this endpoint.
CCI [redacted]		
Protocol Section 3 Objectives and Endpoints: Secondary Endpoints Absolute values at Weeks 24, 48 and every 48 weeks thereafter for: van der Heijde mTSS score (participants from 201790 and 201791 only)	This endpoint has been removed.	Due to study termination (see Section 4.3.1.1.)
Protocol Section 9.5 Interim Analyses.	No interim analyses will be performed.	Due to study termination.

5. SAMPLE SIZE DETERMINATION

No formal sample size calculations were performed for study 209564 (see Protocol Section 9.2).

Enrolment is dependent on the number of participants who have completed the treatment phase of the qualifying studies, and who, in the investigator's judgment will benefit from extended treatment with GSK3196165. It is anticipated that approximately 3000 participants may be eligible to join.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the "Enrolled" or "Safety" population. A summary of the number of participants in each of the participant level analysis sets will be provided. Enrolment will be presented by country and site, overall.

6.1.1. Participant Disposition

Reasons for screen failures as per the eCRF will be summarised, see Protocol Section 5.4.

The number of participants, who entered and withdrew from study 209564, will be summarised. Because the study was terminated, no participants should have completed the study. Reasons for withdrawal from the study will be summarised, according to the categories in the eCRF. In addition, participants will be summarised according to the relationship to COVID-19.

Participants who permanently stopped study intervention for any reason will be considered as permanently discontinued both from the study intervention and the study at that time, see Protocol Section 7.2. Reasons for discontinuation of study intervention will be summarised. In addition, participants will be summarised according to the relationship to COVID-19.

A listing of screen failure, study intervention discontinuation and study withdrawal will be presented.

6.1.2. Demographic and Baseline Characteristics

Demographic and participant characteristics of participants at the start of study 209564 will be described.

The parameters include:

- Demographic (age, gender, race and ethnicity) and other study population characteristics at baseline (height, weight, BMI). Age will also be summarised according to categorised values: 18-49, 50-64, ≥ 65 years.
- Disease history (time since RA diagnosis/start of symptoms, RA functional class, anti-CCP status, Rheumatoid Factor)
- Smoking history – overall and by categorised values: < 50 or ≥ 50 years.

Descriptive statistics of selected efficacy parameters collected at the final study visit of the qualifying study will also be tabulated.

In addition, the number of participants enrolled from each qualifying study will be summarised.

Further summaries required for Plain Language Summary and public registers will be produced.

A listing of demographic characteristics will be produced.

6.1.3. Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO dictionaries. Summaries will be based on the GSK Drug dictionary only and will use the Safety population.

Concomitant medications will be summarised by ATC level 1 and ingredient. Concomitant medications are those 'ongoing' at baseline of study 209564 and/or started during the On-Intervention period (see Section 6.2.2).

A summary of concomitant COVID-19 vaccines will also be produced.

A listing of concomitant medications will be produced.

6.1.3.1. Prior and Baseline Rheumatoid Arthritis Medications

All ongoing rheumatoid arthritis medications at baseline will be summarised as follows:

- oral corticosteroid (prednisone or prednisone-equivalent), using frequency (%) and daily dose using summary statistics.
- methotrexate (MTX) (oral or injected), using frequency (%) and weekly dose using dose level categories: >0 to <10 and >= 10 mg/week.
- csDMARDs (not MTX) by preferred term, using frequency (%).
- participants on (exactly) two csDMARDs, using frequency (%).
- biological biosimilar (bs)/biological original (bo)/targeted synthetic (ts) DMARDs by preferred term, using frequency (%). Note: participants should not be receiving bs/bo/tsDMARDs at the time of starting study 209564.

Ongoing medications at baseline are those started before first dose date of study intervention in study 209564 and continued during the On-Intervention period as defined in Section 6.2.2.

Previous DMARD use by randomisation strata and prior failed medication by mechanism, prior to Day 1 of the qualifying study, will also be summarised.

Prior failed medication is defined as:

- Prior failed medication by randomisation strata
  csDMARD only
  1 bDMARD
  >1 bDMARD
  ≥1 JAK
  Note: per randomisation strata in the IRT for studies 201791 and 202018; since there is none in 201790, all patients are considered as csDMARD only.

- Prior failed medication by mechanism:
  - Prior Failed aTNF: exactly one aTNF agent
  - Prior Failed bDMARDs or tsDMARDs: exactly two b/tsDMARDs of interest.

6.1.4. Protocol Deviations

Important protocol deviations will be summarized and listed.

Protocol deviations will be tracked by IQVIA and overseen by the GSK study team throughout the conduct of the study in accordance with the latest version of the Protocol Deviation Management Plan maintained by IQVIA in their TMF system. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to [unblinding and] freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations SDTM dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

In addition, a summary of important protocol deviations related to COVID-19 will be produced.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be tabulated, and presented graphically over time.

A listing of participants excluded from any study population will be produced.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

6.2.1.1. Laboratory Grading

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) will be used to assign grades to the relevant laboratory parameters.

6.2.1.2. Laboratory Values of Potential Clinical Importance

The following criteria are measured in serum, plasma, or blood, and will be used to flag potential clinical importance:

Parameters	Unit	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (> x)
Hematocrit	Ratio of 1	Male	0.2	0.6
		Female	0.2	0.6
		Change from Baseline	↓ 0.075	
Hemoglobin	g/L	Male	80	180
		Female	80	180
		Change from Baseline	↓ 20	
Lymphocytes	$\times 10^9$ /L		0.75	
Neutrophil Count	$\times 10^9$ /L		1.0	16.0
Platelet Count	$\times 10^9$ /L		100	550
White Blood Cell Count (WBC)	$\times 10^9$ /L		2.0	20.0
Eosinophils	$\times 10^9$ /L			1
Albumin	g/L		30	55
Calcium	mmol/L		2	2.75
Creatinine	μmol/L			150
		Change from Baseline		↑ 44.2
Glucose	mmol/L		3	11
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	160
GFR from Creatinine Adjusted for BSA	mL/min/1.73m^2		60	

Parameters	Unit	Category	Clinical Concern Range	
Cholesterol	mmol/L			6.5
Triglycerides	mmol/L			2.3
Urea	mmol/L			10.5
ALT/SGPT	U/L			≥ 2× ULN
AST/SGOT	U/L			≥ 2× ULN
Alkaline Phosphate	U/L			≥ 2× ULN
Total Bilirubin	μmol/L			≥1.5× ULN
Creatinine Kinase	U/L			≥2× ULN
Gamma Glutamyl Transferase	U/L			≥2× ULN
Lactate Dehydrogenase	U/L			≥2× ULN

The following criteria are measured in urine, and will be used to flag potential clinical importance:

Parameters	Unit	Category	Clinical Concern Range
Bacteria			Moderate Many
Squamous Epithelial Cells			Moderate (6-20) Many (21 or greater)
Glucose			1+ OR 1/4 G/DL (%) 2+ OR 1/2 G/DL (%) 3+ OR 1 G/DL (%)
Protein			1+ 2+ 3+
Erythrocytes			10-15 15-25 25-50 50-100 >100
Leukocytes			10-15 15-25 25-50 50-100 >100
Yeast Cells			Moderate Many

6.2.1.3. ECG Values of Potential Clinical Importance

The following criteria will be used to flag potential clinical importance:

Parameters	Unit	PCI Range
Absolute QTc Interval	msec	>450 (H)
Absolute PR Interval	msec	<110 (L); >220 (H)
Absolute QRS Interval	msec	<75 (L); >110 (H)

6.2.1.4. Vital Sign Values of Potential Clinical Importance

The following criteria will be used to flag potential clinical importance:

Parameters	Unit	PCI Range
Systolic blood pressure	mmHg	<85 (L); >160 (H)
Diastolic blood pressure	mmHg	<45 (L); >100 (H)
Heart rate	bpm	<40 (L); >110 (H)

6.2.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention start date in study 209564.

Pre-Intervention is defined as time prior to the first dose of study intervention in study 209564.

On-Intervention is defined as time from first dose of study intervention in study 209564 up to the Safety follow up visit (8 weeks after last dose). If time of assessment of study intervention is not collected, the following assessments on the first dose date will be assumed to be taken prior to the first dose of study 209564 and therefore considered pre-intervention: ECG, Lab, and vital signs. The first dose date is considered on-intervention for AE and concomitant medication.

Post-Intervention is defined as any time post on-intervention window. Any data collected after the On-Intervention period, are considered post-study, and will not be summarised.

6.2.3. Study Day and Reference Dates

The reference date is the study intervention start date in study 209564 and will be used to calculate study day.

The study day is calculated as below:

Assessment Date = Missing	Study Day = Missing
Assessment Date < Reference Date	Study Day = Assessment Date – Ref Date
Assessment Date ≥ Reference Date	Study Day = Assessment Date – Ref Date + 1

6.2.4. Assessment Window

For data summaries by visit, the nominal visit description will be used. Unscheduled visit data, cardiovascular events, and early withdrawal visit data, will be slotted into a target visit based on the visit windows defined in the table below.

If there are multiple assessments within the same window, a scheduled visit will be prioritised over un-scheduled visits. If all assessments within the same window are from unscheduled visits, the closest one to the target day will be used in the slotting. If multiple assessments are equally close, the average of those assessments will be used. In case of laboratory data, central laboratory assessments will be prioritised over local laboratory assessments.

Analysis Set / Domain	Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
All (Lab change/shift from baseline)	Baseline	Baseline	Baseline	GSK3196165
All	Day 1	Day 1	Day 1	Week 0
All (efficacy)	Day 1	Day 2	Day 43	Week 0
All	Day 8	Day 2	Day 22	Week 1
All (participants from study 202018)	Day 29	Day 23	Day 43	Week 4
All (participants from study 202018)	Day 85	Day 44	Day 127	Week 12
All (participants from studies 201790 and 201791)	Day 85	Day 23	Day 127	Week 12
All (efficacy)	Day 85	Day 44	Day 127	Week 12
All	Day 169	Day 128	Day 211	Week 24
All	Day 253	Day 212	Day 295	Week 36
All	Day 337	Day 296	Day 379	Week 48
All	Day 421	Day 380	Day 463	Week 60
All	Day 505	Day 464	Day 547	Week 72
All	Day 589	Day 548	Day 631	Week 84
All	Day (1 + 7×Week Number)	Target Day -41	Target Day +42	+12 weeks
All (participants withdrawn early from study intervention)	56 days after last treatment	42 days after last treatment	70 days after last treatment	EW Safety Follow Up (8 Week Follow Up)

6.2.5. Multiple measurements at One Analysis Time Point

Multiple readings at one analysis time-point are expected for ECG assessments done in triplicate.

For triplicate ECG measures, numerical data taken at a single time point will be averaged for each participant and the average reading used for analysis; for categorical data, the worst result will be used.

6.2.6. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The Electronic Data Capture (EDC) allows partial dates to be entered for AE start and end dates (but month and year must be present). • Partial dates (day of month) for AE recorded in the CRF will be imputed using the following conventions: **Missing start day**: If month and year of start date = month and year of study intervention start date in study 209564, then day of AE will be imputed as day of first exposure in study 209564. Otherwise, use 1st of month. **Missing end day**: Last day of month will be used for day, unless this is after the stop date of study intervention, in this case study intervention stop date will be used. **Completely missing start/end date**: no imputation.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following conventions. o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. o If the partial date is a stop date, last day of the month will be used for the day and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
Age	• Only year of birth is collected in the CRF, and therefore, the date of birth will be derived as follows: Year of birth = YYYY → Date of birth = 30 June YYYY • Age in years will be calculated as integer part (randomisation date of study 209564 – date of birth). • Birth date will be presented in listings as "YYYY".

6.2.7. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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NONE

7. REFERENCES

Not applicable.