Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for A multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, pharmacokinetics, pharmacodynamics, and efficacy of GSK2982772 in subjects with moderate to severe rheumatoid arthritis.
Compound Number	:	GSK2982772
Effective Date	:	17-DEC-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2015N251670_03 and 2015 2015N251670_04 in Germany.
- This RAP is intended to describe the safety, tolerability, PK, PD, and efficacy analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2015N251670_00	01-APR-2016	Original
2015N251670_01	25-MAY-2016	Protocol Amendment 1 incorporates the addition of risk text for drug interaction with Pglycoprotein (Pgp) inhibitors and narrow therapeutic index (NTI) CYP3A4 substrates, an updated list of prohibited medications plus some minor protocol clarifications and administrative changes.
2015N251670_02	14-JUL-2016	Protocol Amendment 02 incorporates the addition of suicidal ideation and behaviour (SIB) withdrawal criteria plus other minor protocol clarifications and administrative changes.
2015N251670_03	20-APR-2017	Protocol Amendment 03 incorporates the change in dosing regimen from 60 mg BID to 60 mg TID, restrictions on JAK inhibitors, defined non-reproductive potential criteria in Exclusion 11, change to clinical laboratory criteria in Exclusion 23, change in Haematologic Stopping Criteria in Section 5.4.5, addition of evaluation of joint space narrowing with MRI, flexibility in scheduling with MRI and synovial biopsy, some minor protocol clarifications and administrative changes.
2015N251670_04	03-AUG-2017	Protocol Amendment 04 incorporates a country specific amendment for Germany which reinstates the clinical laboratory criteria in Exclusion 23 and Haematologic Stopping Criteria in Section 5.4.5 that was changed in Amendment 03.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	**Reporting & Analysis Plan**	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
A formal interim analysis will be conducted during the study. The timing of this analysis will either be on the recommendation of the data review group to assess futility	A formal interim analysis will no longer be conducted based on review of recruitment information and recommendation by the DRC	Quick recruitment towards the end of the study meant that timelines for the interim analysis would occur after all subjects had completed the treatment phase of the study, therefore leaving no ability to stop the

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
based on 6 weeks of treatment, or when an appropriate number have completed 12 weeks of treatment, whichever is earliest. The purpose of the Interim Analysis would be to assess whether to stop the study for futility. This interim analysis may also facilitate decision making regarding the subsequent clinical development of GSK2982772 for RA.		study for futility
Exploratory endpoint defined as change from baseline in RA symptom questionnaire score	An overall score will not be provided due no available rules for how to combine these questions together, instead each item will be summarised separately	Development of the questionnaire still in progress and no scoring system currently in place. Therefore no overall questionnaire score can be calculated.
Exploratory endpoints: Inflammatory biomarkers, pathway engagement and mRNA in synovial tissue.	These endpoints will not be analysed due to very small sample size and therefore lack of sufficient data to enable statistical analysis to be conducted.	Uptake from subjects in the study to provide the optional synovial tissue samples was very limited. Only 5 subjects consented with only three of these providing a baseline and end of treatment sample. The decision therefore was made by the team not to perform the lab analysis of these samples, therefore planned analysis cannot be conducted. Synovial tissue samples will still be used to explore PK concentration and Target engagement

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To investigate the safety and tolerability of 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature). • 12-Lead ECG monitoring.

Objectives	Endpoints
Secondary Objectives	**Secondary Endpoints**
• To investigate the plasma concentrations of GSK2982772 following 60 mg three times daily doses of GSK2982772 in subjects with moderate to severe Rheumatoid Arthritis.	• Pre-dose concentrations of GSK2982772 on Days 8, and 43 (Week 6). • Post-dose concentrations of GSK2982772 on Days 1, 8, and 43 (Week 6) at 1, 2, 4 and 6 hours. • Trough concentrations on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in blood subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in blood inflammatory markers (e.g., may include but not limited to CRP, IL6, MMP-1, MMP-3, MMP-13, TIMP-1, MCP-1, MIF, MRP8/14 and other markers encompassed by Vectra DA).

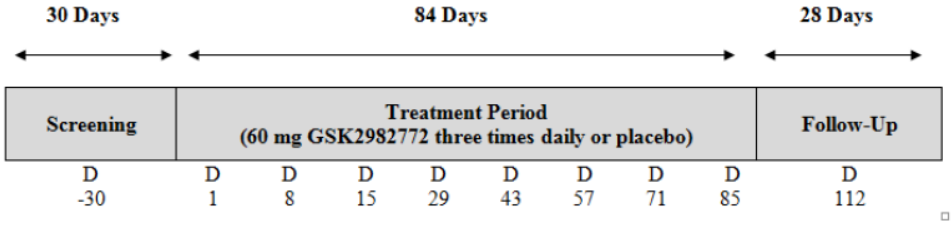
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on bone and synovial parameters as measured by MRI and DCE-MRI in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in MRI parameters in the most affected hand/wrist. MRI parameters may include assessment of bone erosions, synovitis, bone oedema and joint space narrowing as assessed in the OMERACT-RAMRIS (Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System) scoring system, the RAMRIQ (rheumatoid arthritis MRI quantitative) scoring system, the modified CARLOS (Cartilage Loss Scoring System) and additional exploratory endpoints as data permit.
	• Change from baseline in synovial inflammation as measured by dynamic contrast enhanced (DCE)-MRI in the most affected hand/wrist:
	  • Exchange rate (K^{trans})
	  • Interstitial volume (V_e)
	  • Plasma volume (V_p)
	  • Initial rate of enhancement (IRE)
	  • Maximal signal intensity enhancement (ME)
	  • Joint volume
	• Enhancing volume

• To investigate the effect of 60 mg three times daily doses of GSK2982772 on clinical disease activity in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Disease Activity Score (DAS) 28-CRP scores. • Proportion of subjects achieving categorical DAS28-CRP response (moderate/good EULAR response) at each assessment time points. • Proportion of subjects achieving categorical ACR20/50/70 response.
• To investigate the effect of 60 mg three times daily dosing of GSK2982772 on methotrexate (MTX) concentrations	• Plasma concentrations of MTX pre-dose GSK2982772 on Days 1, 8, and 43 (Week 6).

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on inflammatory biomarkers in synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in CD68+ macrophages, CD55+ fibroblast-like synoviocytes and a number of infiltrating CD3, CD22, CD138 inflammatory cells, and synovial inflammatory biomarkers including, but not limited to VEGF, IL-1β, IL-6, TNFα, and MMP-1.
• To investigate pathway and target engagement following 60 mg three times daily doses of GSK2982772 in blood and synovial tissue in subjects with moderate to severe Rheumatoid Arthritis.	• Pharmacology biomarker endpoints may include, but are not limited to the following, pre-dose at Days 1, 43 (Week 6) and trough on Day 85 (Week 12), as applicable and if evaluable samples and data permit: • Target Engagement Assay RIP1 (TEAR1) in blood and synovial tissue. • Total or phosphorylated RIP1, MLKL, and RIP3, cleaved and total caspase 3 and caspase 8 signatures in synovial tissue.
• To investigate the concentration of GSK2982772 and possible drug-related material, as well as specific distribution within tissue if feasible, in the synovial tissue after 60 mg three times daily doses of GSK2982772.	• Pre-dose GSK2982772 synovial tissue biopsies and possible drug-related material concentrations, as well as specific distribution within tissue if feasible, on Day 43 (Week 6), as evaluable samples and data permit
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on the quality of life of subjects with moderate to severe Rheumatoid Arthritis.	• Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). • Change from baseline in RA symptom questionnaire score. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in the blood of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from blood pre-dose on Days 1 and 43 (Week 6) and trough on Day 85 (Week 12).
• To investigate the effect of 60 mg three times daily doses of GSK2982772 on gene expression in synovium of subjects with moderate to severe Rheumatoid Arthritis.	• Transcriptomic analysis of mRNA isolated from synovial tissue pre-dose on Days 1 and 43 (Week 6).

2.3. Study Design

Overview of Study Design and Key Features



Key assessments:
Safety assessments, PK samples, DAS28, ACR20/50/70, FACIT-fatigue, Rheumatoid Arthritis Symptom Questionnaire Score, HAQ-DI assessments, MRI, PD samples

Design Features	This is a multicentre, randomised, double-blind (sponsor-unblinded), placebo-controlled study to investigate the safety and tolerability, PK, PD, and preliminary efficacy of GSK2982772 in subjects with moderate to severe RA.
Dosing	• 60mg GSK2982772 three times daily or placebo. Prior to protocol amendment 3 this was twice daily dosing.
Time & Events	• [Refer to Appendix 2: Schedule of Activities]
Treatment Assignment	• Subjects will be randomised across the two treatment arms, to receive either GSK2982772 or placebo in a 2:1 ratio. • 8 of the subjects were randomised to the BID dosing, all others randomised to TID
Interim Analysis	• Blinded safety, clinical and adverse event data will be reviewed at appropriate intervals by the GSK Safety Review Team (SRT). • Once an appropriate number of subjects have completed Day 43 (Week 6) the DAS28-CRP data will be reviewed in an unblinded manner and on an ongoing basis by the Data Review Committee. Additional inflammatory biomarkers, clinical and mechanistic endpoints (e.g. target engagement) may be reviewed if available. • No formal interim analysis will be conducted

2.4. Statistical Hypotheses / Statistical Analyses

The primary objective of the study is to investigate the safety and tolerability of GSK2982772 following 12 weeks of treatment. No formal statistical hypotheses will be conducted to assess this objective.

If appropriate, comparisons between the GSK2982772 and the placebo arm will be made to investigate the secondary pharmacodynamic, mechanistic and efficacy objectives. Trends over time will be investigated for both treatment arms along with associations between each of the pharmacodynamic, mechanistic and efficacy parameters.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analysis will be conducted. Details of decision to not conduct the planned interim analysis provided in Section 2.1.

Unblinded biomarker, efficacy and pharmacodynamic analyses will be conducted and delivered to the data review committee (DRC) according to the DRC charter. Safety will also be evaluated in the context of the pharmacodynamic, biomarkers and efficacy observed.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects	• Comprises of all subjects who were screened for the study	• Selected Accountability data
Randomised	• Comprises of all subjects who were randomised	• All listings unless specified
Safety	• Comprise of all subjects who receive at least one dose of study treatment. • This population will be based on the treatment the subject was randomised to.	• Demography • Safety • Efficacy • Exploratory • Biomarker
Pharmacokinetic GSK298772 (PK772)	• Subjects in the 'Safety' population who received an active dose and for whom a GSK2982772 pharmacokinetic sample was obtained and analysed.	• GSK2982772 PK
Pharmacokinetic Methotrexate (PKMeth)	• Subjects in the 'Safety' population who received an active dose and for whom a Methotrexate pharmacokinetic sample was obtained and analysed.	• Methotrexate PK
Per-Protocol (PP)	• Subjects in the 'Safety' population with those who had an important deviation with potential to	• DAS28-CRP

Population	Definition / Criteria	Analyses Evaluated
	impact the analysis excluded. Please see Section 12.1.1 for definition of deviations that lead to exclusion from this population.	
PP completers	• All subjects in the PP population who also complete the study. [1]	• DAS28-CRP

Refer to Appendix 12: List of Data Displays which details the population used for each display.
[1] Completion of the study as defined from the eCRF study conclusion page.

Note: "Subjects" is used to refer to "Participants" in all data displays to reflect GSK Display Standards and CDISC SDTM/ADaM standards

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [02OCT18 and Version 3].

- Data will be reviewed prior to freezing the database to ensure all important are captured and categorised on the protocol deviations dataset. This dataset will also be reviewed to ensure exclusions from any populations are documented appropriately.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions					
[RandAll NG / FSO Randomization System]		Data Displays for Reporting			
Code	Description	Description in tables/figures (TRTGRP)	Order in TF	Description in Listings (ATRTGRP)	Order in Outputs
A	GSK2982772 BID 60 mg	GSK2982772 60mg	2	GSK2982772 60mg BID	3
C	GSK2982772 60mg TID	GSK2982772 60mg	2	GSK2982772 60mg TID	4
P	Placebo	Placebo	1	Placebo BID	1
Q	Placebo TID	Placebo	1	Placebo TID	2

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. GSK2982772 60mg vs Placebo

If a subject is found to have received incorrect medication at all during their study duration all of their data will be analysed/summarised according to the treatment group, they were randomised to. A listing of planned and actual treatments will be provided identifying any subjects who did indeed receive incorrect medication.

A couple of the key efficacy endpoints will be summarised separately for the BID and TID treatment regimens, details are provided in Appendix 12: List of Data Displays.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment.

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Safety			
Vital Signs[1,2]	X	X	Day 1 (Pre-Dose)
12-Lead ECG[2]	X[3]	X	Day 1 (Pre-Dose)
Clinical Laboratory Values[2,4]	X	X	Day 1 (Pre-Dose)
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	Day 1 (Pre-Dose)

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Secondary			
Plasma concentrations of GSK2982772/MTX		X	Day 1 (Pre-Dose)
Inflammatory Biomarkers in Blood		X	Day 1 (Pre-Dose)
MRI/DCE-MRI		X	Day 1 (Pre-Dose)
DAS28(CRP)		X	Day 1 (Pre-Dose)
ACR20/50/70		X	Day 1 (Pre-Dose)
Exploratory			
Pharmacology Biomarkers in Blood		X	Day 1 (Pre-Dose)
Concentration of GSK2982772 and Possible Drug-Related Material in the Synovial Tissue		X	Day 1 (Pre-Dose)
HAQ-DI		X	Day 1 (Pre-Dose)
RA Symptom Questionnaire		X	Day 1 (Pre-Dose)
(FACIT)-Fatigue		X	Day 1 (Pre-Dose)
Physician Global Assessment		X	Day 1 (Pre-Dose)
Patient Global Assessment		X	Day 1 (Pre-Dose)
mRNA in Blood		X	Day 1 (Pre-Dose)

NOTES:

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- [1] Vital sign measurements include Blood Pressure, Heart Rate, Respiratory Rate, and Body Temperature.
- [2] Where both screening and pre-dose are available, the value closest to first dose will be used.
- [3] ECG recordings will be performed in triplicate at screening. Use the mean of the triplicate measurements.
- [4] Clinical Laboratory measurements include Clinical Chemistry, Haematology and Urinalysis.
- For Safety Data, If Day 1 pre-dose is missing then Screening will be used as baseline
- For Safety Data, If Day 1 is Post Dose, Screening will be used as baseline

5.2.1. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 5.2 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

5.3. Multicentre Studies

There are no planned adjustments for multiple centres or regions due to the size of the study. For all analyses all sites, countries and regions will be pooled.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

Category	Details
Strata	Not applicable for this study
Covariates	Baseline measure will be included as a covariate

5.4.2. Examination of Subgroups

There are no planned subgroup analyses to be conducted on this study.

5.5. Multiple Comparisons and Multiplicity

Unless specified no adjustments will be made for multiple comparisons or multiplicity.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Reporting Standards for Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

Note: "Subjects" is used to refer to "Participants" in all data displays to reflect GSK Display Standards and CDISC SDTM/ADaM standards

7. SAFETY ANALYSES

The safety analyses will be based on the safety population, unless otherwise specified.

7.1. Adverse Events Analyses

Adverse event analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 12: List of Data Displays.

7.4. Cardiovascular Events

If any of the following events are recorded in the eCRF as a CV event during the study further patient profiles will be generated according to IDSL and provided to the GCSP department: Arrhythmias, Congestive heart failure, Cerebrovascular events/stroke and Transient ischemic attack (TIA), Deep vein thrombosis (DVT)/Pulmonary embolism (PE), Myocardial Infarction/Unstable Angina, Peripheral arterial thromboembolism, Pulmonary Hypertension, Revascularisation, Valvulopathy.

8. EFFICACY ANALYSES

8.1. Efficacy Endpoints

Table 2 Overview of Planned Efficacy Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Efficacy														
FACIT-Fatigue				Y			Y	Y	Y	Y	Y			
HAQ-DI				Y			Y	Y	Y	Y	Y			
Patient Global assessment				Y			Y	Y	Y	Y	Y			
Physician Global Assessment				Y			Y	Y	Y	Y	Y			
DAS28-CRP				Y			Y	Y	Y	Y	Y			
DAS28-CRP EULAR response											Y			Y
ACR Response Rates											Y			Y
TJC28				Y			Y	Y	Y	Y	Y			
SJC28				Y			Y	Y	Y	Y	Y			
MRI parameters[2] in most affected wrist				Y			Y	Y	Y	Y	Y			
DCE-MRI [3]				Y			Y	Y	Y	Y	Y			
Patient assessment of joint Pain				Y			Y	Y	Y	Y	Y			
RA symptom questionnaire				Y			Y							
CRP				Y			Y	Y	Y	Y	Y			
CDAI [4]				Y			Y	Y	Y	Y	Y			
SDAI [4]				Y			Y	Y	Y	Y	Y			

1. **NOTES:**

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data
- 2: Bone erosions, synovitis, bone oedema, joint space narrowing (Based on RAMRIS/RAMRIQ and CARLOS)
- 3: Exchange rate, Interstitial volume, plasma volume, initial rate of enhancement, maximal signal intensity enhancement, joint volume, enhancing volume
- 4: Although not listed in the protocol as endpoints, these were added to aide decision making at the administrative review and the end of the study.

8.1.1. Population of Interest

The efficacy analyses will be based on the safety population, unless otherwise specified.

8.1.2. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.1.2.1. Statistical Methodology Specification

Statistical Analyses (cts endpoints with mmrm analysis)
Secondary/exploratory Endpoint(s)
• Change from baseline (pre-dose Day 1) in FACIT-Fatigue score at Days 43 (pre-dose), and 85. • Change from baseline (pre-dose Day 1) in HAQ-DI at days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in Patient Global Assessment at days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in Physician Global Assessment at days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in DAS28-CRP at days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in TJC28 at days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in SJC28 at days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in MRI parameters based on RAMRIS at days 43 (pre-dose) and 85. • Change from baseline (pre-dose Day 1) in MRI parameters based on RAMRIQ at days 43 (pre-dose) and 85. • Change from baseline (pre-dose Day 1) in MRI parameters based on CARLOS at days 43 (pre-dose) and 85. • Change from baseline (pre-dose Day 1) in MRI parameters based on DCE-MRI at days 43 (pre-dose) and 85. • Change from baseline (pre-dose Day 1) in patient assessment of pain at days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in CRP on days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in CDAI on days 15, 29, 43 (pre-dose), 57, 71, 85. • Change from baseline (pre-dose Day 1) in SDAI on days 15, 29, 43 (pre-dose), 57, 71, 85.
Model Specification
• Endpoints will be statistically analyzed using a mixed models repeated measures (MMRM) approach. • Terms fitted in the MMRM model will include: ○ Fixed Category : Treatment, Day, Treatment*Day

- Fixed Continuous Covariates : Baseline Score, baseline*Day
- Repeated Effect : Day

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line with a subject=SUBJID option.

Note: Other covariates maybe explored, if deemed appropriate for sensitivity analyses.

Model Checking & Diagnostics

- For the MMRM, model assumptions will be applied, but appropriate adjustments may be applied based on the data.
- In the unlikely circumstance that there are convergence problems with the MMRM analysis, this will be explored. For example the SCORING=4 option could be used in the MIXED statement, which makes SAS use Fisher scoring for the first 4 iterations. If the convergence problem cannot be resolved, the unstructured covariance matrix will be replaced by ANTE(1) covariance structure in combination with a random subject effect.
- In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

Model Results Presentation

- LS means and corresponding standard error of means (SEs) and 95% confidence intervals will be presented for each treatment by time interaction, together with estimated treatment differences (GSK2982772 – Placebo) and the corresponding 95% confidence intervals will be produced.
- Observed Margins will be specified to produce the LS means.
- Plots of LS means and standard errors from the model will be generated over time by treatment.

8.2. Exploratory Posterior Probabilities

Decision criteria for this study will be based on posterior probabilities of treatment differences (GSK2982772 vs Placebo) for the following endpoints; DAS28 (CRP), ACR20 and ACR50. Posterior probabilities will explore the likelihood that the treatment difference is greater than X based on the data observed.

A Bayesian approach will be employed to determine a 95% credible confidence interval and the posterior probabilities assuming a noninformative prior: Beta (1, 1) for ACR analyses and N [0, 1.E36).for the analysis of the DAS28-CRP. Any such analyses will be done by GSK II Clinical Statistics for both the administrative review and SAC.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Plasma Concentration data for GSK2982772 will be summarised and listed, no statistical analysis will be conducted. Summary statistics of GSK2982772 concentration by Day (1, 8, 43 and 85) and nominal blood sampling time (pre-dose, and 1, 2, 4 and 6 hours post-dose) will be determined.

Plasma concentration data for methotrexate will be summarised and listed, no statistical analysis will be conducted. Summary statistics of methotrexate pre-dose concentrations by Day (1, 8 and 43) will be determined.

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Standards for Pharmacokinetic).

9.1.2. Population of Interest

All PK statistical displays will be based on the ["PK772"] population, unless otherwise specified.

9.2. Population PK Analyses

GSK2982772 plasma concentrations from this study may be included in a cross-study population pharmacokinetic analysis after SAC. To support this analysis a NONMEM datafile will be generated. The details for the dataset specifications will be provided by CPMS after SAC, if needed.

9.3. PK/PD

Concentration data and blood/synovial fluid target engagement will be explored graphically.

Concentration data will also be presented graphically against change from baseline in DAS28 (CRP) by visit.

10. BIOMARKER ANALYSES

10.1. Biomarker

10.1.1. Endpoint / Variables

Overview of Planned Biomarker Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Secondary Biomarkers														
Inflammatory biomarkers in blood[1]				Y		Y	Y	Y	Y	Y	Y			

1. **NOTES:**

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data
    - 1: Markers including CRP, CHI3L1, EGF, IL6, Leptin, MCP-1, MIF, MMP-1, MMP-3, MMP-13, Resistin, SAA, S100A8/S100A9, TIMP-1, TNF-RI, VCAM-1, VEGFA and unadjusted Vectra DA

10.1.2. Population of Interest

The biomarker analyses will be based on the "Safety" population, unless otherwise specified.

10.1.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 10.1.1.will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10.1.3.1. Statistical Methodology Specification

Inflammatory Blood Biomarkers
Endpoint(s)
Change from baseline on log transformed inflammatory biomarkers in blood on Day 43 and 85 pre-dose: Log_e Change = Log_e (Visit) – log_e (Baseline) 1. Markers: CRP, CHI3L1, EGF, IL6, Leptin, MCP-1, MIF, MMP-1, MMP-3, MMP-13, Resistin, SAA, S100A8/S100A9, TIMP-1, TNF-RI, VCAM-1, VEGFA and unadjusted Vectra DA
Model Specification
• Endpoints will be statistically analyzed using a mixed models repeated measures (MMRM) approach.

- Terms fitted in the MMRM model will include:
  - Fixed Category : Treatment, Day, Treatment*Day
  - Fixed Continuous Covariates : Baseline Score, baseline*Day
  - Repeated Effect : Day

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line with a subject=SUBJID option.

Model Checking & Diagnostics

- For the MMRM, model assumptions will be applied, but appropriate adjustments may be applied based on the data.
- In the unlikely circumstance that there are convergence problems with the MMRM analysis, this will be explored. For example, the SCORING=4 option could be used in the MIXED statement, which makes SAS use Fisher scoring for the first 4 iterations. If the convergence problem cannot be resolved, the unstructured covariance matrix will be replaced by ANTE(1) covariance structure in combination with a random subject effect.
- In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

Presentation of results

- Adjusted geometric means for each treatment group at each timepoint and associated 95% confidence interval will be constructed by back transforming the LS means from the model.
- The treatment ratios and 95% CI will be calculated by back-transforming the difference in the LS means (GSK2982772 – Placebo) and associated 95% CI

Percentage change from baseline at each timepoint will be calculated using the formula:

100% x (exp(LS mean)- 1)

Plots of LS means and standard errors from the model will be generated over time by treatment.

10.2. Target Engagement

10.2.1. Endpoint / Variables

Table 3 Overview of Planned Target Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Target Engagement														
target engagement in blood[3]				Y		Y	Y	Y	Y	Y	Y			
target engagement in synovial tissue[3]							Y							

1. **NOTES:**

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data
- 3: TEAR1 in blood and synovial tissue, Free RIP1 and Total RIP1.

1.

10.2.2. Population of Interest

The target/pathway engagement analyses will be based on the "Safety" population, unless otherwise specified.

10.2.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 10.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10.2.3.1. Statistical Methodology Specification

Target Engagement
Endpoints
• Log Ratio = Log (free TEAR1) – log (total TEAR1) 1.
Model Specification
➢ A mixed effect model will be fitted with treatment, time (i.e. planned relative time) and treatment * time as a fixed effect and subject as a random effect. Baseline log ratio will be fitted as a continuous covariate along with Baseline log ratio* time. ➢ The Kenward and Roger method for approximating the denominator degrees of freedom and

Target Engagement
correcting for bias in the estimated variance-covariance of the fixed effects will be used. ➢ An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line with a subject=SUBJID option.
Model Checking
• For the MMRM, model assumptions will be applied, but appropriate adjustments may be applied based on the data. • In the unlikely circumstance that there are convergence problems with the MMRM analysis, this will be explored. For example, the SCORING=4 option could be used in the MIXED statement, which makes SAS use Fisher scoring for the first 4 iterations. If the convergence problem cannot be resolved, the unstructured covariance matrix will be replaced by ANTE(1) covariance structure in combination with a random subject effect. • In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS. Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. ➢ If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
Presentation of Results
➢ Engagement ratio relative to baseline and associated 95% confidence interval will be calculated for each post-baseline timepoint, using the formula $\exp(\ln(ratio_{post}/ratio_{baseline}) +1)$. ➢ Percentage target engagement at each timepoint will be calculated from the adjusted geometric means using the formula (1-engagment ratio)*100%. ➢ The treatment engagement ratios and 95% CI will be calculated by back-transforming the difference between the least square means and associated 95% CI ➢ The treatment difference percentage target engagement is (1 – treatment engagement ratio) * 100%

10.3. Transcriptomics Analyses- mRNA from Blood

RNA will be extracted and hybridised using a balanced batch design by Epistem. Microarray mRNA data will be normalised using gcRMA or RMA in Array Studio v5.0 or later. After normalisation, the data will be quality assessed and any samples deemed as QC fails will be excluded from any further analysis. This quality assessment will involve looking for outlying signals in both the normalised expression data and the MAS5 QC metrics generated from each sample. If any samples are excluded, the remaining data will be re-normalised. The output from the normalisation will be $\log_2$ transformed mRNA intensity data (measured in arbitrary units).

Microarray data consists of expression values ($\log_2$-transformed) derived from individual probesets designed against coding regions of individual genes. More than one probeset

can exist per gene. This analysis will be conducted at the probeset level. The probeset, gene or gene description will be included in the outputs.

In order to identify the most robustly expressed probesets, the data can be filtered to remove low intensity probesets, low quality and control probe sets prior to analysis. This could be done simply by excluding all probesets where all observations are <6 (on the $\log_2$ scale). Note it has been observed empirically that when you get below 100 (6.6 on the $\log_2$ scale) you are into the noise of the assay. Other more stringent methods of filtering the data could be used. In total there are 53,617 probesets that could be analysed.

mRNA data is available from blood samples only as described in Section 2.1. mRNA summaries and listings will be the responsibility of the GSK stats and programming team and will be delivered at an agreed date after SAC.

10.3.1. Endpoint / Variables

Overview of Planned Biomarker Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Transcriptomics														
mRNA from blood [4]				Y		Y	Y	Y	Y	Y	Y			

1. **NOTES:**

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data
- 4: Data to be provided by Epistem and analysed by the GSK stats and programming team

1.

10.3.2. Population of Interest

The transcriptomic analyses will be based on the "Safety" population, unless otherwise specified.

10.3.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 10.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. Note that probeset ID is required to be included in analyses and outputs if there is more than one probeset per gene.

Primary Statistical Analyses
Endpoint(s)
• Log2(intensity) mRNA expression of inflammatory gene transcripts • Percentage inhibition of inflammatory gene transcripts
Model Specification
• Endpoints will be statistically analyzed using a linear repeated measures mixed effects model. • Terms fitted in the linear repeated measures mixed effects model will include: o Fixed Category : Treatment, Visit, Treatment * Visit o Random Effect : Subject
Model Checking & Diagnostics
• For the MMRM, model assumptions will be applied, but appropriate adjustments may be applied based on the data. • In the unlikely circumstance that there are convergence problems with the MMRM analysis, this will be explored. For example, the SCORING=4 option could be used in the MIXED statement, which makes SAS use Fisher scoring for the first 4 iterations. If the convergence problem cannot be resolved, the unstructured covariance matrix will be replaced by ANTE(1) covariance structure in combination with a random subject effect. • In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS. Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. ➢ If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
Presentation of Results
• For each probeset analysed, adjusted means with corresponding 95% CI and fold changes (for Log2(intensity)) or difference in LS means (for Percentage inhibition) with corresponding 95% CI's can be outputted. The fold change is derived from the ratio of the back-transformed estimate of the difference between LS means. • Plots of LS means and standard errors from the model will be generated for each treatment by time.

10.3.3.1. Fold Change Analysis

The $\log_2$ normalised copy numbers (also referred to as log2(intensity)) received from the normalised process will be listed and summarised appropriately.

As the data will be $\log_2$ transformed prior to the analysis the treatment effects will be expressed as ratios after back transformation to the original scale. These ratios can be converted from treatment ratios to fold change values as follows:

- If ratio ≥ 1 then fold change = ratio
- If ratio < 1 then fold change = -1/ratio

To compare the expression value for each probeset, the following linear repeated measures mixed effects model will be fitted to each probeset that passes any pre-filtering, with $\log_2$ (intensity) as the response variable as outlined in Section 10.3.3. Where appropriate, particularly with microarray data, multiple testing will be taken into account using the Benjamini-Hochberg correction [Benjamini, 1995] to calculate FDR adjusted p-values. A summary may be generated, including probeset ID, gene ID, time point, adjusted means with corresponding 95% CI for each treatment group, Benjamini-Hochberg FDR adjusted p-value and fold changes corresponding 95% CI from each comparison for probesets found to be significant after the applying the Benjamini-Hochberg correction.

For each comparison, subsets of probesets will be identified based on an appropriate fold-change, for example, fold changes >1.5 or <-1.5. The proportion of probesets with fold changes >1.5 or <-1.5 will be summarised in a frequency table.

Exploratory graphical reporting on the back-transformed scale can include:

- Log_2 (intensity) plotted against time point separately for individual subjects, grouped by treatment group
- Adjusted mean intensity and 95 CI% plotted by treatment group and time point

10.3.3.2. Microarray: Percentage inhibition

Based on results from the fold change analyses, the selected probesets will be further explored through percentage inhibition. The $\log_2$ normalised data is back transformed and the percentage inhibition is derived on a subject level on the back transformed data for each probeset. The percentage inhibition will be determined for each probeset per subject, where it is defined as the reduction from baseline. For example:

Day X – baseline = -40% would be a 40% reduction (i.e. -40% change from baseline) which in turn is defined as a 40% inhibition.

So the percentage inhibition would be calculated as:

$$[\ (\text{Day x} - \text{Baseline}) / \text{Baseline}\ ] * -100 = \%\ \text{inhibition}$$

A subset of probesets may be identified and individual subject mRNA intensities and percentage inhibitions may be listed, summarised and plotted appropriately for each selected probeset. The selected probesets will be statistically analysed appropriately, and the output from the mixed effects model (outlined in Section 10.3.3) summarised.

11. REFERENCES

Benjamini Y and Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J Royal Stat Soc 1995;57:289-300

12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

12.1.1. Exclusions from Per Protocol Population

Criteria for exclusion from the per protocol population are detailed in the protocol deviation management plan (PDMP). The stats and programming team will use the information in the protocol deviations dataset to select subjects who have deviations that are flagged as important and that should be removed from the per protocol population.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Procedures	Screening (-30)	Treatment Period[17]													Early Withdrawal[18]	Follow Up (±3)[19]
		Day 1	Day 8 (±3)	Day 15 (±3)	Day 22 (±3)	Day 29 (±3)	Day 36 (±3)	Day 43 (±3) (week 6)	Day 50 (±3)	Day 57 (±3)	Day 64 (±3)	Day 71 (±3)	Day 78 (±3)	Day 85 (+2) (week 12)		
Site Visit	X	X	X	X		X		X		X		X		X	X	X
Phone call					X		X		X		X		X			
General/Safety Assessments and Procedures																
Informed Consent	X															
Subject Demography	X															
Full medical history[1]	X															
Inclusion/Exclusion Criteria	X															
Full physical exam[2]	X													X	X	X
Brief physical exam		X[4]		X		X		X[4]		X		X				
Vital signs (BP, HR, RR, temperature)	X	X[4]	X	X		X		X[4]		X		X		X	X	X
12-lead ECG	X[3]	X[4]	X	X		X		X[4]		X		X		X	X	X
Concomitant medication review & AE reporting/SAEs[5]	X----------X															
PROs/Questionnaires/Diaries/Disease Assessments and Procedures																
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X[4]						X[4]						X	X	
FACIT-fatigue; RA Symptom and Impact Diary[6]		X[4]						X[4]						X	X	
HAQ-DI; Patient Assessment of joint pain[6]		X[4]		X		X		X[4]		X		X		X	X	
Patient Global Assessment (PtGA)[6]	X	X[4]		X		X		X[4]		X		X		X	X	

Procedures	Screening (-30)	Treatment Period[17]													Early Withdrawal[18]	Follow Up (±3)[19]
		Day 1	Day 8 (±3)	Day 15 (±3)	Day 22 (±3)	Day 29 (±3)	Day 36 (±3)	Day 43 (±3) (week 6)	Day 50 (±3)	Day 57 (±3)	Day 64 (±3)	Day 71 (±3)	Day 78 (±3)	Day 85 (+2) (week 12)		
Tender (28) & Swollen (28) joint count	X	X[4]		X		X		X[4]		X		X		X	X	
Physician Global Assessment (PGA)		X[4]		X		X		X[4]		X		X		X	X	
MRI/DCE-MRI[7]		X[4, 20]						X[4,21]						X[22]	X[16]	
Study Treatment																
Randomisation		X														
Study medication (three times daily)[8]		X----------X														
Dispensing of study medication		X				X				X						
Dispensing of diary cards		X	X	X		X		X		X		X				
Collection and review of diary cards			X	X		X		X		X		X		X	X	
Laboratory (Safety) Assessments and Procedures																
TB, HIV, HepB, Hep C Ab, Anti-CCP, Anti-dsDNA, RF	X															
FSH & estradiol (if applicable)	X															
Serum pregnancy test (WCBP only)	X															
Urine pregnancy test (WCBP only)[9]		X[4]	X	X		X		X[4]		X		X		X	X	X
Haematology, chemistry, urinalysis	X	X[4]	X	X		X[10]		X[4]		X[10]		X[10]		X	X	X
CRP	X	X[4]		X		X		X[4]		X		X		X	X	
Blood sample for PD inflammatory biomarkers,		X[4]						X[4]						X	X	

Procedures	Screening (-30)	Treatment Period[17]													Early Withdrawal[18]	Follow Up (±3)[19]
		Day 1	Day 8 (±3)	Day 15 (±3)	Day 22 (±3)	Day 29 (±3)	Day 36 (±3)	Day 43 (±3) (week 6)	Day 50 (±3)	Day 57 (±3)	Day 64 (±3)	Day 71 (±3)	Day 78 (±3)	Day 85 (+2) (week 12)		
mRNA, and TE[11]																
PK blood samples GSK2982772[12]		X	X[4]					X[4]						X	X	
PK blood samples for MTX[13]		X[4]	X[4]					X[4]								
Pharmacogenetic sample (PGx)		X[14]														
Synovial biopsies for PK, inflammatory biomarkers, mRNA, target engagement & pathway engagement analysis[15]		X[4,20]						X[4,21]							X[16]	

Footnotes:

1. Full medical history (includes past and current conditions, medication history, substance usage, and family history of premature CV disease).
2. Full physical exam (includes height/weight at screening, height not measured at later time points).
3. Triplicate ECG to be performed at screening only.
4. Pre-dose.
5. Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up. AEs will be collected from the start of Study Treatment until the follow-up contact. On Days 22, 36, 50, 64, and 78, subjects will be questioned about their general health status via phone call.
6. All PRO assessments should be conducted on site before any tests, procedures, or assessments, to avoid influencing the subjects' perception.
7. DCE-MRI will be performed on all subjects, provided that sites have DCE-MRI capability and experience (e.g., hardware and software requirements). If sites do not have DCE-MRI capability or experience, a regular MRI will be performed of the affected hand/wrist. If the same joint is used for MRI and synovial biopsy, MRI should be performed before biopsy (if applicable).
8. Subjects must take study medication three times a day approximately 8 hours apart. Exact time of dosing to be recorded in diary cards. On Day 1, the first study dose will be administered at the site. On Days 8, 43 and 85 only, subjects must not take their medication at home in the morning. Subjects will complete pre-dose assessments and then will be administered their morning dose of medication at site on Days 8 and 43. On Day 85, subjects are no longer receiving study medication.
9. If urine pregnancy test is positive, a confirmatory serum pregnancy test must be performed.
10. Haematology and chemistry only. No urinalysis required on Days 29, 57 and 71. When clinical laboratory samples are taken on the same day as the MRI, the samples should be taken first prior to the administration of the contrast fluid with MRI. If this is not feasible (i.e. MRI is performed first), it is recommended that a separate IV catheter or straight venipuncture be performed in the *opposite* arm to where the MRI contrast fluid was administered.

11. Blood samples for inflammatory biomarkers, mRNA and target engagement. See laboratory manual for full details on sample collection, handling and shipment.
12. PK blood samples for GSK2982772 will be taken pre-dose on Days 8 and 43. Post-dose serial PK samples will be taken on Days 1, 8 and Day 43 at the following time points: 1, 2, 4, and 6 hours. A trough PK sample will be taken on Day 85 or at Early Withdrawal.
13. Only applicable if subjects are on MTX: PK blood samples for MTX will be taken pre-dose GSK2982772 on Day 1 (MTX alone), on Days 8 and 43 (MTX + GSK2982772). Subjects who are on MTX should ideally take their MTX dose on the same day of the week at approximately the same time of the day throughout the study. In addition, the Day 1, 8 and 43 visits should ideally be on the same day of the week.
14. A PGx blood sample is collected at the baseline visit, after the subject has been randomised and provided informed consent for genetic research. If the sample is not collected at the baseline visit, it can be collected at any time during the study after randomisation.
15. Synovial biopsies are optional.
16. Biopsy (if applicable) and MRI only are required at Early Withdrawal visit if subject withdraws after at least 14 days of treatment and prior to Day 43. If a subject withdraws between Days 43 and 57, an MRI is not required at the Early Withdrawal visit. If a subject withdraws on Day 57 or after, an MRI should be performed at the Early Withdrawal visit. A window allowance of $\pm$ 3 days of Early Withdrawal visit is allowed to perform the MRI.
17. Visit windows during the treatment period are relative to Day 1.
18. If a subject withdraws from the study, every effort will be made for the subject to complete an Early Withdrawal visit prior to the Follow Up visit.
19. Follow-up visit should be completed 28 days ($\pm$3 days) after the last dose of study medication.
20. MRI (and if applicable; a biopsy) may be performed during the screening window as an additional visit (if required) up to 7 days before Day 1 to allow sites flexibility in scheduling. The MRI must be completed prior to synovial biopsy (if performed on the same joint). The site should be reasonably confident that the subject has fully qualified for the study (e.g., screening clinical labs, vital signs, physical examination, etc.) before the MRI (and if applicable: a biopsy) is/are performed.
21. A biopsy (if applicable) and MRI may be performed on a separate day within the Day 43 window allowance ($\pm$3 days). A separate visit to perform the MRI followed by synovial biopsy (if applicable) is only allowed to accommodate scheduling. If biopsy is being performed, this visit must be scheduled after the Day 43 visit where the PK, clinical laboratory tests and other required Day 43 procedures are performed. Subjects must not take their study medication at home in the morning before the full Day 43 visit and also the morning before MRI and biopsy (if applicable) visit if being done on a separate day.
22. For MRI performed on day 85, a visit window of up to 2 days after is allowed in order to perform the MRI.

12.3. Appendix 3: Assessment Windows

12.3.1. Definitions of Assessment Windows for Analyses

No Assessment Windows will be defined for Analysis, and summaries and analyses will be based on nominal visits.

12.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

12.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment unless otherwise specified. Treatment phases are to be included on A&R datasets.

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date +1
Post-Treatment	Date > Study Treatment Stop Date +1

12.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior
Post-Treatment	Any medication that is started >= Study Treatment Stop Date +1

1. **NOTES:**

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

1.

12.4.2. Treatment Emergent Flag for Adverse Events

Treatment States for AE Data

Treatment State	Definition
AE = Pre-Treatment	AE Start Date < Study Treatment Start Date
AE = On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date +1. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date +1
AE = Post-Treatment	If AE onset date is after the treatment stop date+1. AE Start Date > Study Treatment Stop Date +1
AE Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date: **= AE Onset Date - Treatment Start Date** If Treatment Start Date ≤ AE Onset Date: **= AE Onset Date - Treatment Start Date +1** Missing otherwise.
AE Duration (Days)	**AE Resolution Date – AE Onset Date + 1**
AE = Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	UK1SALX00175
HARP Area	arenv \ arprod \ gsk2982772 \ mid203168 \ final
QC Spreadsheet	arenv \ arwork \ gsk2982772 \ mid203168 \ final \ documents
Analysis Datasets	
• Analysis datasets will be created according to Integrated Data Standards Library (IDSL) GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for all tables at the time of the SAC.	

12.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

• Subject level listings will not be provided in the main body of the GSK Clinical Study Report. All subject level listings will be located in the modular appendices as ICH or non-ICH listings
Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or figures, unless otherwise stated. • All unscheduled visits will be listed.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	

• Refer to IDSL Statistical Principals 7.01 to 7.13.
 	
Placebo in graphs to be shown in Blue and GSK2982772 in Red
 	
`style graphdata1/ color=BLUE contrastcolor=BLUE linestyle=1 markersymbol="circlefilled";`
`style graphdata2/ color=RED contrastcolor=RED linestyle=34 markersymbol="trianglefilled";`
 	
For outputs which are displayed for all 4 treatment groups (ie by regimen)
 	
`style graphdata1/ color=BLUE contrastcolor=BLUE linestyle=1 markersymbol="circlefilled";`
`style graphdata2/ color=BLACK contrastcolor=BLACK linestyle=1 markersymbol="circlefilled";`
`style graphdata3/ color=RED contrastcolor=RED linestyle=34 markersymbol="squarefilled";`
`style graphdata4/ color=DARKGREEN contrastcolor=DARKGREEN linestyle=2 markersymbol="trianglefilled";`	

12.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	Not applicable

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 12.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visit (including unscheduled visits) for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

12.6.2. Study Population

Demographics
Date of Birth
• Only the year of birth will be captured, and therefore the date of birth is then derived as follows: Year of birth = YYYY → Date of birth = PPD YYYY
Age
• Calculated as the integer part of (date of screening – date of birth) Age = integer part (date of screening – PPD YYYY) • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**
Race category
• White: 'White: Arabic/North African Heritage' and 'White: White/Caucasian/European Heritage', or both of these, but no other category checked • African descent: 'African American/African Heritage', and no other category checked • Asian: 'Asian – Central/South Asian Heritage', 'Asian – East Asian Heritage', 'Asian – Japanese Heritage', and 'Asian – South East Asian Heritage', or any combination of these, but no other category checked • Other: Any combination that has not been categorized above ('mixed race')
Disease **History**
Time since formal diagnosis= date of visit - date of formal diagnosis- Time since onset of first musculoskeletal symptoms= date of visit - date of first musculoskeletal symptoms-

Demographics
If date of visit is missing use screening date.

Treatment Compliance
• Subject compliance will be based on the number of expected tablets to be taken and the number actually taken and will depend on whether a subject was taking investigational product (two 30mg tablets) twice a day or three times according to the regimen they were randomized to: • **Total tablets taken is (Total number of Tablets Dispensed-Total Tablets Returned)** • **Duration of exposure is calculated as described in extent of exposure section below** • Total Tablets expected to be taken is duration of exposure*4 for BID subjects and *6 for TID subjects Note: if any of the tablets dispensed/returned contain missing number of tablets total tablets taken will be set to missing. • Treatment compliance will be calculated based on the formula: **Treatment Compliance = (Total tablets taken/total tablets expected to be taken)*100** **where** **Note compliance will only be calculated for subjects who took at least one dose (i.e.) number of tablets taken is >=1**
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Total Tablets taken*30 for GSK2982772 subjects** **Cumulative dose will be 0 for placebo subjects.** Note: If the total tablets taken is missing cumulative dose will be set to missing.

12.6.3. Efficacy

12.6.3.1. HAQ-DI

The functional status of the subject 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:

- dressing & grooming, rising, eating, walking, hygiene, reach, grip, and common daily activities.

Each functional area contains at least two questions. For each question, there is a four-level response set that is scored from 0 (without any difficulty) to 3 (unable to do). If aids or devices or physical assistance are used for a specific functional area and the maximum response of this functional area is 0 or 1 the according value is increased to a score of 2.

HAQ-DI Aids

Aid or equipment	**Will be associated with category score**
Walking stick/frame, crutches, wheelchair	Walking
Aids used for dressing	Dressing and grooming
Specially adapted utensils	Eating
Specially adapted chair	Rising
Raised toilet seat, bath rail, bath seat	Hygiene
Long-handled appliance in bathroom	Hygiene
Long-handled appliance for reaching	Reach
Jar opener	Grip
Other (1)	Dressing & grooming, rising, eating, walking
Other (2)	hygiene, reach, grip, common daily activities

If "other" is marked as an aid or equipment, then this can be assigned to a group of four functional areas and will be handled as an aid or equipment for each of the four functional areas. Therefore, if the maximum score of a functional area is 0 or 1 that value is increased to a score of 2 for each of the four functional areas.

Regarding these corrections, the highest response within each functional area determines the score of that specific functional area. If no questions within a given functional area were answered, no score will be provided for that category (even if answers on aids or equipment are available).

HAQ-DI is only calculated if there are at least 6 functional area scores available.

The average of these non-missing functional area scores defines the continuous HAQ-DI score ranging from 0 to 3. If there are less than 6 functional area scores available, no imputation will be done and the HAQ-DI will be set to missing for the according assessment.

12.6.3.2. Patient Global Assessment

The patient global assessment of arthritis disease activity (PtGA) is measured on a 10cm visual analogue scale (VAS) with values 0=very well to 10=very poor. More commonly this measurement is reported as measured off the 10cm VAS in mm. For reporting purposes, the VAS measurement from the eCRF will be converted from cm to mm by multiplying values by 10. All listings and summaries of the PtGA will be using mm.

12.6.3.3. Physician Global Assessment (PGA)

The physician global assessment of arthritis disease activity (PGA) is measured on a 10cm visual analogue scale (VAS) with values 0=none to 10=extremely active. More commonly this measurement is reported as measured off the 10cm VAS in mm. For reporting purposes, the VAS measurement from the eCRF will be converted from cm to mm by multiplying values by 10. All listings and summaries of the PGA will be using mm.

12.6.3.4. Disease Activity Score (DAS28):

Disease activity Score (DAS28 CRP) is a numeric outcome based on Tender joint count 28 (TJC28), swollen joint count 28 (SJC28), C-reactive protein (CRP) and patient global assessment (PtGA). CRP values will be taken from the clinical chemistry data within the lab dataset.

The joint counts will be based on 28 joints as follows (both left and right sides): Shoulder, elbow, wrist, metacarpophalangeal (first (thumb), second, third, fourth, fifth), proximal interphalangeal (thumb (interphalangeal), index, middle, ring, little) and knee.

The DAS28-CRP score will be calculated using the following formula:

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

- If one of the components is missing at an individual assessment point, the DAS28-CRP value for that assessment will be set to missing.
- Note PtGA must be measured in mm for this calculation as described in Section 12.6.3.2

Categorical DAS28 Response

DAS28-CRP scores will each be categorized using EULAR response criteria. Response at a given time point is defined based on the combination of current DAS28 score and the improvement in the current DAS28 score relative to baseline. The definition of no response, moderate response and good response is captured in the following table:

Table 4 EULAR Response Criteria

Current DAS28	DAS28 decrease from baseline value		
	>1.2	>0.6 to ≤1.2	≤ 0.6
≤ 3.2	Good response	Moderate response	No response
> 3.2 to ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

If the post-baseline DAS28-CRP score is missing, then the corresponding EULAR category will be missing. If the baseline DAS28-CRP is missing, then all post-baseline EULAR response values will be missing.

DAS28 Low Disease Activity (LDA)

DAS28-CRP Low Disease Activity is defined as a DAS28 score of <3.2.

DAS28 Remission

DAS28-CRP remission is achieved by a DAS28-CRP value <= 2.6.

12.6.3.5. ACR Response Rates

The American College of Rheumatology's (ACR) definition for calculating improvement in RA is calculated as a 20% improvement (ACR20) in both tender and swollen joint counts and 20% improvement in at least 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, patient's assessment of arthritis pain, disability (HAQ-DI), and an acute-phase reactant (i.e. CRP value). Similarly, ACR50 and ACR70 are calculated with the respective percent improvement. This efficacy measurement will be made at every post-baseline study assessment time point.

The specific components of the ACR Assessments that will be used in this study are as follows and can be grouped into three components:

- Tender/Painful Joint count (28)
- Swollen Joint Count (28)
- 5 Remaining ACR-Core Set Measures:
  - Patient Assessment of Joint Pain
  - PtGA

- PGA
- CRP
- HAQ-DI

For all visits, if any of the component scores are missing, meaning ACR20/50/70 responder definitions cannot be properly assessed, then those scores will be considered as not having met the criteria for improvement. Therefore, if TJC28 or SJC28 or 3 or more of the 5 remaining ACR-core set measures are missing, ACR20/ ACR50/ ACR70 will each be considered as "no response" in the DAS_ACR dataset.
For missing Baseline values or a Baseline value of 0, the percentage improvement can't be calculated and the ACR will be considered as not having met the criteria for improvement
e.g.

- if TJC28 or SJC28 is missing or 0 at baseline then ACR20/50/70 will be considered as 'no response'
- if TJC28 and SJC28 are non-missing and >0 at baseline but there are < 3 of the 5 remaining core set measures that are non-missing and >0 at baseline then ACR20/50/70 will be considered as 'no response'

Data from the screening visit will not be used to impute baseline.

12.6.3.6. Swollen and Tender/Painful Joint Count

Four different scores will be calculated to evaluate swelling and tenderness of joints. TJC28 and SJC28 will take 28 joints into account.

The assessment for swelling is the total number of joints with a present swelling and ranges from 0 to 28 for SJC28 .

The assessment for tenderness is the total number of joints with a present tenderness and ranges from 0 to 28 for TJC28.

The following 28 joints will be taken into account for TJC28 and SJC28: Shoulder (2 joints), Knee (2), Elbow (2), Wrist (2), Fingers (PIP, MCP: 20).

Artificial, ankylosed and missing joints are excluded from swelling and tenderness assessment.

If there are missing or excluded observations for tender or swollen joints then the remaining observations will be assessed and weighted by dividing the number presented by number of non-missing and by multiplying by 28 for the joint count. No imputations for individual joints will be done. If a joint is not evaluable at Baseline, then that joint is set to missing throughout the study.

If data for more than 50% of the joints are missing at the time of a given assessment, then the total count will be set to missing for that visit.

Observed joint states will be listed without any modification for every subject and visit.

12.6.3.7. FACIT-Fatigue

The FACT-G scoring guide identifies those items which must be reversed before being added to obtain subscale totals. Items are scored using a Likert scale from 0 to 4, to “0” (not at all) to“4” (very much).

In order to calculate a total score negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all FACIT scales and symptom indices, the higher the score the better the QOL.

Negatively stated items refer to all statements asked except (‘I have energy’ and ‘I am able to do my usual activities’)

Fatigue Score = [sum of Item Scores] x [13] / [number of items answered].

A Fatigue score will only be calculated if at least 7 responses have been provided.

12.6.3.8. DCE-MRI

Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) parameters are measured at each individual joint and consist of:

- Exchange Rate (K^{trans})
- Interstitial Volume (V_e)
- Plasma Volume (V_p)
- Initial Rate of Enhancement (IRE)
- Maximum signal intensity enhancement (ME).

All DCE-MRI parameters will be presented as a total measure over all joints at each time point.

DCI-MRI parameters will be calculated as:

$$\frac{\sum_{all\ joints}(Parameter)}{Number\ of\ Joints}$$

Parameters will also be presented normalized by the VEP.

Normalized DCE-MRI parameters will be calculated as:

$$\frac{\sum_{all\ joints}(VEP\ *\ Parameter)}{\sum_{all\ joints} VEP}$$

If parameters are missing for individual joints, these joints will be excluded from the numerator and denominator of the calculation.

If data for more than 50% of the joints are missing at the time of a given assessment, then the total count will be set to missing for that visit. This threshold might be altered after review of the actual raw data.

12.6.3.9. CDAI and SDAI

Although not specified in the protocol as endpoints both the Simple Disease Activity Index (SDAI) and clinical disease activity index (CDAI) will be calculated and summarised.

SDAI

SDAI is a composite score calculated using the formula:

SDAI= SJC28 + TJC28+ PtGA + PGA+ CRP

Where PtGA and PGA is measured 0-10 and CRP is measured in (mg/dl). Higher values represent higher disease activity.

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

SDAI Remission SDAI <= 3.3

SDAI Low Disease Activity 3.3 < SDAI <= 11

CDAI

CDAI is a composite score calculated using the following formula:

CDAI= SJC28+ TJC28 + PtGA+ PGA

Where PtGA and PGA are measured 0-10. CDAI ranges from 0 to 76 with higher values representing higher disease activity.

Remission is achieved for a non-missing CDAI value ≤2.8 and

Low Disease Activity 2.8 < CDAI <= 10

If one of the components is missing at an individual assessment point, no imputations will be done and the CDAI value for that assessment will be set to missing.

12.6.4. Safety

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

12.6.5. Biomarker

TEAR
Target Engagement
• Ratio = free / total • Target Engagement = 100 – (ratio $_{post}$/ratio $_{baseline}$) * 100)) • BIOMARK dataset: BICAT = TRIPK1 (total) or FRIPK1 (free) for the same smpty

12.6.6. PK

Synovial Tissue Pharmacokinetic Concentrations
Synovial Tissue PK Conc
• The density of human synovial tissue is 1.184 g/mL per Gastroplus V9.0. • The volume of solvent added to each tissue sample was 0.5 mL. • For actual tissue weights, please refer to the Excel spreadsheet
Synovial PK Concentration (ng/mL)

1. PK Conc in Weight of Tissue Sample = SMS PK Conc in Soln (ng/mL) X [0.5 mL + (Tissue Weight (g) / 1.184 g/mL)] 2. PK Conc in tissue as concentration (ng/g) = PK Conc in Weight of Tissue Sample / Tissue Weight 3. PK Conc in tissue as concentration (ng/mL) = PK Conc in tissue as concentration (ng/g) 1.184 g/mL
Example (fictitious) data: SMS tissue homogenate concentration = 2 ng/mL Tissue weight = 0.014 g SMS plasma concentration= 400 ng/mL Example Calculations: 1. Convert GSK2982772 concentration in the homogenate to GSK2982772 concentration in the tissue sample as follows: 2 ng/mL X [0.5 mL + (0.014 g/1.184 g/mL)] = 2ng/mL X 0.512 mL = 1.024 ng GSK2982772 in a 0.014 g tissue sample 2. Convert absolute amount of GSK2982772 in this skin tissue sample to a tissue concentration as follows: 1.024 ng / 0.014 g tissue = 73.1 ng GSK2982772/g tissue = 73.1 ng/g 3. Convert ng/g tissue to ng/mL tissue as follows: 73.1 ng/g X 1.184 g/mL = 86.5 ng GSK2982772/mL tissue = 86.5 ng/mL 4. Determine the ratio of GSK2982772 tissue concentration to GSK2982772 plasma concentration for a given patient as follows: 86.5 ng/mL / 400 ng/mL = 0.216

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion was defined as one who has completed all phases of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study at the discretion of the investigator. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. Withdrawal visits will not be summarised and will be listed only.

12.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

12.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

12.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450	< 480
		≥ 480	<500
		≥ 500	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec	> 30	≤ 59
	msec	≥ 60	

12.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	Bpm	< 40	> 110

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg	≥ 20	≥ 40	≥ 20	≥ 40
Diastolic Blood Pressure	mmHg	≥ 10	≥ 20	≥ 10	≥ 20
Heart Rate	Bpm	≥ 15	≥ 30	≥ 15	≥ 30

12.9. Appendix 11: Abbreviations & Trade Marks

12.9.1. Abbreviations

Abbreviation	Description
ACR	American College of Rheumatology
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
CARLOS	Cartilage Loss Scoring System
CDAI	Clinical Disease Activity Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CRP	C-reactive protein
CS	Compound symmetry
CSH	Heterogenous compound symmetry
CSR	Clinical Study Report
CV	Cardiovascular
CV_b	Coefficient of Variation (Between)
DAS 28-CRP	Disease Activity Score 28-CRP
DBF	Database Freeze
DBR	Database Release
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DOB	Date of Birth
DP	Decimal Places
DRC	Data Review Committee
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GCSP	Global Clinical Safety & Pharmacovigilence
GSK	GlaxoSmithKline
HAQ-DI	Disability Index of the Stanford Health Assessment Questionnaire
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
II	Immuno-Inflammation
IRE	Initial rate of enhancement
Ktrans	Exchange rate
LS	Least squared
ME	Maximal signal intensity enhancement
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
MTX	Methotrexate

Abbreviation	Description
OMERACT-RAMRIS	Outcome Measures in Rheumatology, Rheumatoid Arthritis Magnetic Resonance Image Scoring System
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PE	Pulmonary embolism
PGA	Physician Global Assessment
PK	Pharmacokinetic
PK772	Pharmacokinetic GSK298772
PKMeth	Pharmacokinetic Methotrexate
PP	Per Protocol
PopPK	Population PK
PtGA	Patient Global Assessment
QC	Quality Control
QOL	Quality of Life
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RA	Rheumatoid Arthritis
RAMOS	Randomization & Medication Ordering System
RAMRIQ	Rheumatoid Arthritis MRI Quantitative
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDAI	Simple Disease Activity Index
SDTM	Study Data Tabulation Model
SE	Standard Error
SJC28	Swollen Joint Count 28
SRT	Safety Review Team
TA	Therapeutic Area
TEAR1	Target Engagement Assay RIP1
TIA	Transient ischemic attack
TFL	Tables, Figures & Listings
TJC28	Tender Joint Count 28
VAS	Visual Analogue Scale
V_e	Interstitial volume
Vep	Volume of enhancing Pannus
V_p	Plasma volume

12.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ADVAIR

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

12.10. Appendix 12: List of Data Displays

12.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.18	NA
Efficacy	2.1 to 2.67	2.1 to 2.23
Safety	3.1 to 3.24	3.1 to 3.3
Pharmacokinetic	4.1 to 4.2	4.1 to 4.7
Pharmacokinetic / Pharmacodynamic	NA	5.1 to 5.3
Biomarker	6.1 to 6.14	6.1 to 6.7
Section	**Listings**	
ICH Listings	1 to 40, and 85	
Other Listings	41 to 84	

12.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

12.10.3. Deliverables

Delivery [Priority] [1]	Description
AR	Administrative review, delivered by the GSK stats and programming team
SAC [1]	Final Statistical Analysis Complete responsibility of Quanticate
SAC2 [1]	Post SAC and delivered by the GSK stats and programming team

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

12.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition for the Study Conclusion Record	ICH E3, FDAAA, EudraCT Add footnote: Note: "Subjects" is used to refer to "Participants" in all data displays to reflect GSK Display Standards and CDISC SDTM/ADaM standards.	AR SAC[1]
1.2.	Safety	SD1 / SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	AR SAC[1]
1.3.	All subjects	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC[1]
1.4.	Randomised	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations Please add footnote to say that randomised population=enrolled population	SAC[1]
Protocol Deviation					
1.5.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC[1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Population Analysed					
1.6.	All subjects	SP1	Summary of Study Populations	IDSL	SAC[1]
Demographic and Baseline Characteristics					
1.7.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include summary of time since formal diagnosis of RA and time since onset of first musculoskeletal symptoms	SAC[1]
1.8.	Randomised	DM11	Summary of Age Ranges	EudraCT Please add footnote to say that randomised population=enrolled population	SAC[1]
1.9.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC[1]
1.10.	Safety	SU1	Summary of Tobacco Use	IDSL	SAC[1]
Prior and Concomitant Medications					
1.11.	Safety	MH1	Summary of Past Medical Conditions	ICH E3	SAC[1]
1.12.	Safety	MH1	Summary of Current Medical Conditions	ICH E3	SAC[1]
1.13.	Safety	MH1	Summary of Past Cardiovascular Risk Factors	ICH E3 Include only pre-defined list	SAC[1]
1.14.	Safety	MH1	Summary of Current Cardiovascular Risk Factors	ICH E3 Include only pre-defined list	SAC[1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.15.	Safety	FH1	Summary of Family History: Cardiovascular Risk Factors	IDSL	SAC[1]
1.16.	Safety	CM1	Summary of Prior Medications	ICH E3	AR SAC[1]
1.17.	Safety	CM1	Summary of Concomitant Medications	ICH E3	AR SAC[1]
Exposure and Treatment Compliance					
1.18.	Safety	EX1 / EX5	Summary of Exposure to Study Treatment	ICH E3	SAC[1]

12.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Efficacy					
2.1.	Safety	EFF_T1	Summary of FACIT-Fatigue by Visit		AR SAC [1]
2.2.	Safety	EFF_T2	Summary of Change from Baseline in FACIT-Fatigue by Visit		AR SAC [1]
2.3.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in FACIT-Fatigue		AR SAC [1]
2.4.	Safety	EFF_T1	Summary of HAQ-DI by Visit		AR SAC [1]
2.5.	Safety	EFF_T2	Summary of Change from Baseline in HAQ-DI by Visit		AR SAC [1]
2.6.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in HAQ-DI		AR SAC [1]
2.7.	Safety	EFF_T1	Summary of Patient Global Assessment by Visit		SAC [1]
2.8.	Safety	EFF_T2	Summary of Change from Baseline in Patient Global Assessment by Visit		SAC [1]
2.9.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in Patient Global Assessment		SAC [1]
2.10.	Safety	EFF_T1	Summary of Physician Global Assessment by Visit		SAC [1]
2.11.	Safety	EFF_T2	Summary of Change from Baseline in Physician Global Assessment by Visit		SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in Physician Global Assessment		SAC [1]
2.13.	Safety	EFF_T1	Summary of DAS28(CRP) by Visit		AR SAC [1]
2.14.	Safety	EFF_T2	Summary of Change from Baseline in DAS28(CRP) by Visit		AR SAC [1]
2.15.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in DAS28(CRP)		AR SAC [1]
2.16.	Safety	EFF_T1	Summary of DAS28(CRP) by Visit and Dosing Regimen	Separate page for BID and TID	AR SAC [1]
2.17.	Safety	EFF_T2	Summary of Change from Baseline in DAS28(CRP) by Visit and Dosing Regimen	Separate page for BID and TID	AR SAC [1]
2.18.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in DAS28(CRP) and Dosing Regimen	Separate page for BID and TID	AR SAC [1]
2.19.	Safety	EFF_T4	DAS28-CRP EULAR Response Categories		AR SAC [1]
2.20.	Safety	EFF_T4	DAS28-CRP Remission and Low Disease Activity	Update column for EULAR response to be summarise number and percent of subjects meeting remission and LDA criteria by visit	AR SAC [1]
2.21.	Safety	EFF_T5	ACR Response Rates by Visit		AR SAC [1]
2.22.	Safety	EFF_T4	DAS28-CRP EULAR Response Categories and Dosing Regimen	Separate page for BID and TID	AR SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	Safety	EFF_T4	DAS28-CRP Remission and Low Disease Activity and Dosing Regimen	Separate page for BID and TID Update column for EULAR response to be summarise number and percent of subjects meeting remission and LDA criteria by visit	AR SAC [1]
2.24.	Safety	EFF_T5	ACR Response Rates by Visit and Dosing Regimen	Separate page for BID and TID	AR SAC [1]
2.25.	Safety	EFF_T1	Summary of Tender Joint Count (28 Joints) by Visit		AR SAC [1]
2.26.	Safety	EFF_T2	Summary of Change from Baseline in Tender Joint Count (28 Joints) by Visit		AR SAC [1]
2.27.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in Tender Joint Count (28 Joints)		AR SAC [1]
2.28.	Safety	EFF_T1	Summary of Swollen Joint Count (28 Joints) by Visit		AR SAC [1]
2.29.	Safety	EFF_T2	Summary of Change from Baseline in Swollen Joint Count (28 Joints) by Visit		AR SAC [1]
2.30.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in Swollen Joint Count (28 Joints)		AR SAC [1]
2.31.	Safety	EFF_T1	Summary of MRI parameters: RAMRIS scoring system	Separate page for each parameter	SAC [1]
2.32.	Safety	EFF_T2	Summary of Change from Baseline in MRI parameters: RAMRIS scoring system	Separate page for each parameter	SAC [1]
2.33.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in MRI parameters: RAMRIS scoring system	Separate page for each parameter	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34.	Safety	EFF_T1	Summary of MRI parameters: RAMRIQ scoring system	Separate page for each parameter	SAC [1]
2.35.	Safety	EFF_T2	Summary of Change from Baseline in MRI parameters: RAMRIQ scoring system	Separate page for each parameter	SAC [1]
2.36.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in MRI parameters: RAMRIQ scoring system	Separate page for each parameter	SAC [1]
2.37.	Safety	EFF_T1	Summary of MRI parameters: CARLOS scoring system	Separate page for each parameter	SAC [1]
2.38.	Safety	EFF_T2	Summary of Change from Baseline in MRI parameters: CARLOS scoring system	Separate page for each parameter	SAC [1]
2.39.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in MRI parameters: CARLOS scoring system	Separate page for each parameter	SAC [1]
2.40.	Safety	EFF_T1	Summary of synovial inflammation DCE-MRI	Separate page for each parameter	SAC [1]
2.41.	Safety	EFF_T2	Summary of Change from Baseline in synovial inflammation DCE-MRI	Separate page for each parameter	SAC [1]
2.42.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in synovial inflammation DCE-MRI	Separate page for each parameter	SAC [1]
2.43.	Safety	EFF_T1	Summary of synovial inflammation DCE-MRI by Dosing Regimen	Separate page for each parameter/Dosing regimen	SAC [1]
2.44.	Safety	EFF_T2	Summary of Change from Baseline in synovial inflammation DCE-MRI by Dosing Regimen	Separate page for each parameter/Dosing regimen	SAC [1]
2.45.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in synovial inflammation DCE-MRI by Dosing Regimen	Separate page for each parameter/Dosing regimen	SAC [1]
2.46.	Safety	EFF_T1	Summary of Patient Assessment of joint Pain by Visit		AR SAC [1]
2.47.	Safety	EFF_T2	Summary of Change from Baseline in Patient Assessment of joint pain by Visit		AR SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.48.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in Patient Assessment of joint pain		AR SAC [1]
2.49.	Safety	DM1	Summary of RA symptom Questionnaire	Add column for visit Summary statistics for numeric responses and number (%) in each category for each other question	SAC [1]
2.50.	Safety	EFF_T1	Summary of CRP by Visit		SAC [1]
2.51.	Safety	EFF_T2	Summary of Change from Baseline in CRP by Visit		SAC [1]
2.52.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in CRP		SAC [1]
2.53.	PP	EFF_T1	Summary of DAS28(CRP) by Visit		SAC [1]
2.54.	PP	EFF_T2	Summary of Change from Baseline in DAS28(CRP) by Visit		SAC [1]
2.55.	PP	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in DAS28(CRP)		SAC [1]
2.56.	PP-completer	EFF_T1	Summary of DAS28(CRP) by Visit-Per protocol Completers	Include subjects who completed the study and are in PP population	SAC [1]
2.57.	PP-completer	EFF_T2	Summary of Change from Baseline in DAS28(CRP) by Visit--Per protocol Completers	Include subjects who completed the study and are in PP population	SAC [1]
2.58.	PP-completer	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in DAS28(CRP)- -Per protocol Completers	Include subjects who completed the study and are in PP population	SAC [1]
2.59.	Safety	EFF_T1	Summary of Clinical Disease Activity Index by Visit		AR SAC [1]
2.60.	Safety	EFF_T2	Summary of Change from Baseline in Clinical Disease Activity Index by Visit		AR SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.61.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in Clinical Disease Activity Index		AR SAC [1]
2.62.	Safety	EFF_T1	Summary of Simple Disease Activity Index by Visit		AR SAC [1]
2.63.	Safety	EFF_T2	Summary of Change from Baseline in Simple Disease Activity Index by Visit		AR SAC [1]
2.64.	Safety	EFF_T3	Summary of Statistical Analysis Results for Change from Baseline in Simple Disease Activity Index		AR SAC [1]
2.65.	Safety	EFF_T6	Summary of Bayesian Analysis of Change from Baseline in DAS28-CRP at day 85	GSK Responsibility seed=5235 thin=50 nbi=1000 nmc=500000	AR SAC [1]
2.66.	Safety	EFF_T7	Summary of Bayesian Analysis of ACR20 at day 85	GSK Responsibility Seed=240, nbi=1000 nmc=100000 thin=10	AR SAC [1]
2.67.	Safety	EFF_T7	Summary of Bayesian Analysis of ACR50 at day 85	GSK Responsibility Seed=241, nbi=1000 nmc=100000 thin=10	AR SAC [1]

Note for MRI parameters, a list of expected bones/joints for DCE and RAMRIS can be provided in an excel file on request.

12.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Efficacy					
2.1.	Safety	EFF_F1	FACIT-Fatigue, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]
2.2.	Safety	EFF_F1	HAQ-DI, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]
2.3.	Safety	EFF_F1	Patient Global Assessment, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		SAC [1]
2.4.	Safety	EFF_F1	Physician Global Assessment, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		SAC [1]
2.5.	Safety	EFF_F1	DAS28-CRP, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]
2.6.	Safety	EFF_F2	Individual Subject Profiles for DAS28-CRP		SAC [1]
2.7.	Safety	EFF_F1	DAS28-CRP, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment and Dosing regimen over Time	Separate page for each dosing regimen	AR SAC [1]
2.8.	Safety	EFF_F3	Proportion (± SE) of subjects in each DAS28-CRP EULAR Response Category	Separate page for each EULAR response category	AR SAC [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.9.	Safety	EFF_F4	Proportion (±SE) of subjects achieving ACR20/50/70	Separate page for AC20/50 and 70	AR SAC [1]
2.10.	Safety	EFF_F1	Tender Joint Count (28), Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]
2.11.	Safety	EFF_F1	Swollen Joint Count (28), Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]
2.12.	Safety	EFF_F1	MRI parameters: RAMRIS scoring, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time	Separate page for each parameter	SAC [1]
2.13.	Safety	EFF_F1	MRI parameters: RAMRIQ scoring, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time	Separate page for each parameter	SAC [1]
2.14.	Safety	EFF_F1	MRI parameters: CARLOS scoring, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time	Separate page for each parameter	SAC [1]
2.15.	Safety	EFF_F1	DCE-MRI, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time	Separate page for each parameter	SAC [1]
2.16.	Safety	EFF_F2	Individual Subject Profiles for DCE-MRI	Separate page for each parameter	SAC [1]
2.17.	Safety	EFF_F1	DCE-MRI, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment and Dosing Regimen over Time	Separate page for each parameter/dosing regimen	SAC [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18.	Safety	EFF_F1	Patient Assessment of Joint Pain, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time	Separate page for each parameter	AR SAC [1]
2.19.	Safety	EFF_F1	CRP, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]
2.20.	PP	EFF_F1	DAS28-CRP, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		SAC [1]
2.21.	PP-Completer	EFF_F1	DAS28-CRP, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time	Include subjects who completed the study and are in PP population	SAC [1]
2.22.	Safety	EFF_F1	Clinical Disease Activity Index, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]
2.23.	Safety	EFF_F1	Simple Disease Activity Index, Adjusted Mean (±SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		AR SAC [1]

12.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	[Safety]	AE1	Summary of Adverse Events by System Organ Class and Preferred Term	IDSL	SAC [1]
3.2.	[Safety]	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.3.	[Safety]	AE3	Summary of Common (≥10%) Adverse Events by Overall Frequency	ICH E3 Common defined as >= 10% within either treatment group	SAC [1]
3.4.	[Safety]	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	ICH E3	SAC [1]
3.5.	[Safety]	AE15	Summary of Common (≥10%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC [1]
3.6.	[Safety]	AE3	Summary of Common (≥10%) Drug-Related Adverse Events by Overall Frequency	ICH E3	SAC [1]
Serious and Other Significant Adverse Events					
3.7.	[Safety]	AE1	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC [1]
3.8.	[Safety]	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term /by Overall Frequency	IDSL	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.	Safety	AE16	Summary of Subjects and Number of Occurrences of Serious, Drug-Related Serious, Fatal Serious, and Drug-Related Fatal Serious Adverse Events	FDAAA, EudraCT	SAC [1]
Laboratory: Chemistry					
3.10.	[Safety]	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC [1]
3.11.	[Safety]	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline	ICH E3	SAC [1]
3.12.	[Safety]	LB17	Summary of Worst Case Lipids Results by NR Criteria Post-Baseline Relative to Baseline by Randomised Treatment	ICH E3 (i.e. treatment emergent) Lipids parameters = LDL, HDL Recommended for larger studies, could be covered by listings for smaller studies. The specific criteria to be defined by the study/project team. Values could be categorized by: [1] Above/below reference range (e.g., normal range, clinical concern range). [2] Graded toxicity scales. [3] Changes from baseline to reference range category. Or [1] On-treatment. [2] Post-baseline (i.e., anything after first dose and not necessarily while On-treatment). [3] Through IP end + X days, etc.	SAC [1]
Laboratory: Hematology					

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.13.	[Safety]	LB1	Summary of Hematology Changes from Baseline	ICH E3	SAC[1]
3.14.	[Safety]	LB17	Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline	ICH E3	SAC[1]
Laboratory: Urinalysis					
3.15.	[Safety]	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3	SAC[1]
3.16.	[Safety]	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	SAC[1]
Laboratory: Hepatobiliary (Liver)					
3.17.	[Safety]	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC[1]
3.18.	[Safety]	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC[1]
ECG					
3.19.	[Safety]	EG1	Summary of ECG Findings	IDSL	SAC[1]
3.20.	[Safety]	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC[1]
3.21.	[Safety]	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC[1]
3.22.	[Safety]	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC[1]
Vital Signs					
3.23.	[Safety]	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC[1]
3.24.	[Safety]	VS7	Summary of Worst Case Vital Signs by PCI Criteria Post-Baseline Relative to Baseline	IDSL	SAC[1]

12.10.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	[Safety]	AE10	Plot of Common (≥10%) Adverse Events and Relative Risk	IDSL	SAC[1]
Laboratory					
3.2.	[Safety]	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT	IDSL	SAC[1]
3.3.	[Safety]	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC[1]

12.10.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK772	PK01	Summary of Plasma GSK2982772 Concentration-Time Data (ng/mL) by Dosing Regimen	Pre-dose, Day 1, 8, 43 and 85. Day 1, 8 and 43 at 1, 2, 4 and 6 h post dose	AR SAC [1]
4.2.	PKMeth	PK01	Summary of Plasma Methotrexate Concentration Data (ng/mL) by Dosing Regimen	Pre-dose Day 1, 8 and 43	SAC[1]

12.10.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK772	PK_F1	Spaghetti plot of GSK2982772 Individual Plasma Concentration Data by Study Day	Spaghetti plot of individual trough concentrations vs day (8, 43 and 85). Separate panels for each per regimen (bid and tid)	SAC [1]
4.2.	PK772	PK_F2	GSK2982772 Trough Plasma Concentration Data by Study Day	Plot of individual trough concentrations vs day (8, 43 and 85) and overlaid with box and whisker plot. Separate panels for each regimen (bid and tid)	AR SAC [1]
4.3.	PK772	PK_F3	GSK2982772 Plasma Concentration Data by time relative to dose	Spaghetti plot of observed plasma concentration versus time (pre-dose =0, 1, 2, 4, and 6 hours post dose). One panel for each regimen and separate pages for each day (1, 8, and 43)	AR SAC [1]
4.4.	PK772	PK_F4	Mean (±SE) GSK2982772 Plasma Concentration Data by time Relative to Dose by Study Day	Mean concentration vs time (pre-dose =0, 1, 2, 4, and 6 hours post dose) for Day 1, 8 and 43. One plot/panel per regimen (bid and tid)	SAC [1]
4.5.	PK772	PK_F5	Mean (±SE) GSK2982772 Plasma Concentration Data by Time relative to Dose, by Dosing Regimen	Mean concentration vs time for bid and tid regimen on one plot. One panel per day (1, 8 and 43)	AR SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.6.	PK772	PK_F1	GSK2982772 Trough Concentrations in Plasma and Synovial Fluid by Study Day	Spaghetti Plot of observed trough concentrations by body fluid (plasma and synovial fluid) on Day 43 and D85. One panel each for BID and TID Just present subjects who have both plasma and synovia concentrations and update x-axis label to say concentration use legend to distinguish between synovial and plasma concentration	SAC [1]
4.7.	PK772	PK_F6	GSK2982772 Trough Concentrations Plasma vs Synovial Fluid	Scatter plot of GSK2982772 Trough Plasma Concentration on X-axis and synovial fluid concentration on Y-Axis. All data, one symbol each for bid and tid Only include subjects who have both plasma and synovial concentration data	AR SAC [1]

12.10.11. Pharmacokinetic/Pharmacodynamic Figures

PK/PD Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	PK772	PK_F6	GSK2982772 Plasma Trough Concentration vs Blood TEAR1% Target engagement by Study Day	Scatter plot of GSK2982772 Trough Plasma Concentration vs Blood TEAR1. All data on one plot, one symbol each for bid and tid	SAC [1]
5.2.	PK772	PK_F6	GSK2982772 Synovial Fluid Trough Concentration vs Synovial Fluid TEAR1% Target engagement	Scatter plot of GSK2982772 Trough Synovial Fluid Trough Concentration vs Synovial Fluid TEAR1. All data on one plot, one symbol each for bid and tid	SAC [1]
5.3.	PK772	PK_F6	GSK2982772 Plasma Trough Concentration vs DAS28 (CRP) Change from baseline	Scatter plot of GSK2982772 Trough Plasma Concentration vs DAS28 change from baseline. All data on one plot, one symbol each for bid and tid, separate page for each relevant visit	SAC [1]

12.10.12. Biomarker Tables

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Inflammatory Biomarkers in blood					
6.1.	Safety	PD_T1	Summary of Blood Inflammatory Biomarkers	One page for each cell type/measure by visit/time and treatment	SAC [1]
6.2.	Safety	PD_T2	Summary of Percentage Change from Baseline in Blood Inflammatory Biomarkers	One page for each cell type/measure by visit/time and treatment	SAC [1]
6.3.	Safety	PD_T3	Adjusted Mean (95% CI) Percentage Change in Blood Inflammatory Biomarkers	Present %CVb instead of SE	SAC [1]
6.4.	Safety	PD_T1	Summary of Blood Inflammatory Biomarkers by Dosing Regimen	One page for each cell type/measure by visit/time and treatment/dosing regimen	SAC [1]
6.5.	Safety	PD_T2	Summary of Percentage Change from Baseline in Blood Inflammatory Biomarkers by Dosing Regimen	One page for each cell type/measure by visit/time and treatment/dosing regimen	SAC [1]
6.6.	Safety	PD_T3	Adjusted Mean (95% CI) Percentage Change in Blood Inflammatory Biomarkers by Dosing Regimen	Present %CVb instead of SE Separate page for each dosing regimen	SAC [1]
Pathway and Target engagement					
6.7.	Safety	EFF_T1	Summary of TEAR1 % Target Engagement in Blood		SAC [1]
6.8.	Safety	PD_T4	Adjusted Mean (95% CI) TEAR1 % Target Engagement in Blood		SAC [1]
6.9.	Safety	EFF_T1	Summary of Pathway Engagement in Blood	No longer being produced due to limited sample size	SAC [1]

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
mRNA					
6.10.	Safety	PD_T2	Summary of mRNA Intensity of Inflammatory Gene Transcripts in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values.	SAC2 [1]
6.11.	Safety	PD_T5	Frequency Table Summarising the Number of Probe Sets with Various Fold Change in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values. Use cut-offs 1.5 and -1.5 initially. Change to -1.25 and 1.5 if no one achieves the initial cut-offs	SAC2 [1]
6.12.	Safety	PD_T6	Summary of Analysis for Microaray mRNA Intensity Data in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values. If Adj Mean FC lies between -1 and 1 then do not include on table	SAC2 [1]
6.13.	Safety	PD_T2	Summary of mRNA Percentage Inhibition of Inflammatory Gene Transcripts in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values.	SAC2 [1]
6.14.	Safety	PD_T6	Summary of Analysis for Microaray mRNA Percentage Inhibition Data in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values. If Adj Mean FC lies between -1 and 1 then do not include on table	SAC2 [1]

12.10.13. Biomarker Figures

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.1.	Safety	EFF_F1	Inflammatory Blood Biomarkers, Adjusted Mean (±SE) Change from Baseline in and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time	One page for each cell type/measure by visit/time and treatment	SAC [1]
6.2.	Safety	EFF_F2	Individual Subject Profiles of Inflammatory Biomarkers	Separate page for each cell type/measure	SAC [1]
6.3.	Safety	EFF_F1	Inflammatory Blood Biomarkers, Adjusted Mean (±SE) Change from Baseline in and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment and Dosing regimen over Time	One page for each cell type/measure by visit/time and treatment/dosing regimen	SAC [1]
6.4.	Safety	EFF_F1	TEAR1 % Target Engagement in Blood, Adjusted Mean (±SE) Change from Baseline in and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time		SAC [1]
6.5.	Safety	PD_F1	Individual Subject Profiles for mRNA Expression of Inflammatory Gene Transcripts in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values. Line plot by subjid coloured by treatment group for each probeset / gene.	SAC2 [1]
6.6.	Safety	PD_F2	Adjusted Mean Intensities for mRNA Expression of Inflammatory Gene Transcripts in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values. Y xais – log2 scale	SAC2 [1]

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.7.	Safety	PD_F3	Adjusted Mean (±SE) Fold Change in mRNA Expression of Inflammatory Gene Transcripts in Blood	GSK to produce Only to be produced for significant probsets based on adjusted p-values. If Adj Mean FC lies between -1 and 1 then do not include on table Include band from FC -1 to 1, transparency 0.5	SAC2 [1]

12.10.14. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC[1]
2.	Randomised	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC[1]
3.	Randomised	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC[1]
4.	Randomised	TA1	Listing of Planned and Actual Treatments	IDSL	SAC[1]
Protocol Deviations					
5.	Randomised	DV2	Listing of Important Protocol Deviations	ICH E3	SAC[1]
6.	Randomised	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC[1]
Populations Analysed					
7.	All Subjects	SP3/SP3a	Listing of Subjects Excluded from Any Population	ICH E3	SAC[1]
Demographic and Baseline Characteristics					
8.	Randomised	DM2	Listing of Demographic Characteristics	ICH E3	SAC[1]
9.	Randomised	POP_L1	Listing of Rheumatoid Arthritis Disease History	Include time since formal diagnosis of RA and time since onset of first musculoskeletal symptoms	SAC[1]
10.	Randomised	DM9	Listing of Race	ICH E3	SAC[1]
11.	Randomised	MH2	Listing of Medical History (including CV risk factors)	IDSL	SAC[1]
Prior and Concomitant Medications					
12.	Randomised	CP_CM3	Listing of Concomitant Medications	IDSL	SAC[1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
13.	Randomised	EX3	Listing of Exposure Data	ICH E3 Please add a column for study treatment to differentiate between dates/times for IP and Methotrexate	SAC[1]
14.	Randomised	POP_L2	Listing of Dispensing Data	Listing of container number, number of tablets dispensed, returned and then %compliance	SAC[1]
Adverse Events					
15.	Randomised	AE8	Listing of All Adverse Events	ICH E3	SAC[1]
16.	Randomised	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC[1]
17.	Randomised	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC[1]
Serious and Other Significant Adverse Events					
18.	Randomised	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC[1]
19.	Randomised	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC[1]
20.	Randomised	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC[1]
21.	Randomised	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC[1]
22.	Randomised	PSRAE1	Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1- Section 2)	IDSL	SAC [1]
23.	Randomised	PSRAE3	Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)	IDSL	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
24.	Randomised	PSRAE4	Listing of Possible Suicidality-Related Adverse Event Data (Section 4)	IDSL	SAC [1]
25.	Randomised	PSRAE5	Listing of Possible Suicidality-Related Adverse Event Data (Section 5- Section 8)	IDSL	SAC [1]
Hepatobiliary (Liver)					
26.	Randomised	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC[1]
27.	Randomised	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC[1]
All Laboratory					
28.	Randomised	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC[1]
29.	Randomised	LB5	Listing of Laboratory Values of Potential Clinical Importance		SAC[1]
30.	Randomised	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC[1]
31.	Randomised	UR2A	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC[1]
32.	Randomised	LB5	Listing of Lipids Outside of the Normal Range	Include fasted status.	IA [1], SAC[1]
ECG					
33.	Randomised	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	IDSL Include absolute PCI subjects. Footnote: H=High absolute, L= Low absolute	SAC[1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
34.	Randomised	EG3	Listing of All ECG Changes for Subjects with a Value of Potential Clinical Importance	Include change from baseline PCI subjects. Footnote: H=High change from baseline value, L= Low change from baseline value	SAC[1]
35.	Randomised	EG3	Listing of ECG Values of Potential Clinical Importance	"Include absolute PCIs. Footnote: H=High absolute, L= Low absolute."	SAC[1]
36.	Randomised	EG3	Listing of ECG Changes of Potential Clinical Importance	"Include change from baseline PCIs. Footnote: H=High change, L= Low change."	
37.	Randomised	EG5	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding	IDSL	SAC[1]
38.	Randomised	EG5	Listing of Abnormal ECG Findings	IDSL	SAC[1]
Vital Signs					
39.	Randomised	VS4	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	IDSL	SAC[1]
40.	Randomised	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC[1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
85	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	**ICH E3**	SAC[1]

12.10.15. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
CSSRS					
41.	Randomised	ECSSRS4	Listing of C-SSRS suicidal Ideation and Behaviour Data		SAC[1]
42.	Randomised	ECSSRS5	Listing of C-SSRS Suicidal Behaviour Details		SAC[1]
PK					
43.	PK772	PK07	Listing of GSK2982772 Pharmacokinetic Concentration-Time Data		SAC[1]
44.	PKMeth	PK07	Listing of Methotrexate Pharmacokinetic Concentration-Time Data		SAC[1]
Efficacy					
45.	Randomised	EFF_L11	Listing of FACIT-Fatigue		SAC[1]
46.	Randomised	EFF_L8	Listing of HAQ-DI		SAC[1]
47.	Randomised	EFF_L10	Listing of Patient and Physician Global Assessment		SAC[1]
48.	Randomised	EFF_L6	Listing of DAS28-CRP, EULAR response and Joint Counts		SAC[1]
49.	Randomised	EFF_L7	Listing of ACR Response Rates and ACR Components		SAC[1]
50.	Randomised	EFF_L1	Listing of MRI Data, Inflammatory Structural Joint Damage: RAMRIS		SAC[1]
51.	Randomised	EFF_L2	Listing of MRI, Inflammatory Structural Joint Damage: RAMRIQ		SAC[1]
52.	Randomised	EFF_L3	Listing of MRI, Inflammatory Structural Joint Damage: CARLOS		SAC[1]
53.	Randomised	EFF_L4	Listing of Joint Inflammation: DCE-MRI		SAC[1]
54.	Randomised	EFF_L5	Listing of Swollen and Tender Joint States		SAC[1]
55.	Randomised	EFF_L12	Listing of Patient Assessment of Joint Pain		SAC[1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
56.	Randomised	EFF_L9	Listing of RA Symptom and Impact Diary		SAC[1]
57.	Safety	n/a	Raw SAS Output of Statistical Analysis of FACIT-Fatigue		SAC[1]
58.	Safety	n/a	Raw SAS Output of Statistical Analysis of HAQ-DI		SAC[1]
59.	Safety	n/a	Raw SAS Output of Statistical Analysis of Patient Global Assessment		SAC[1]
60.	Safety	n/a	Raw SAS Output of Statistical Analysis of Physician Global Assessment		SAC[1]
61.	Safety	n/a	Raw SAS Output of Statistical Analysis of DAS28(CRP)		SAC[1]
62.	Safety	n/a	Raw SAS Output of Statistical Analysis of DAS28(CRP) by dosing regimen		SAC[1]
63.	Safety	n/a	Raw SAS Output of Statistical Analysis of TJC(28)		SAC[1]
64.	Safety	n/a	Raw SAS Output of Statistical Analysis of SJC(28)		SAC[1]
65.	Safety	n/a	Raw SAS Output of Statistical Analysis of MRI:RAMRIS		SAC[1]
66.	Safety	n/a	Raw SAS Output of Statistical Analysis of MRI:RAMRIQ		SAC[1]
67.	Safety	n/a	Raw SAS Output of Statistical Analysis of MRI:CARLOS		SAC[1]
68.	Safety	n/a	Raw SAS Output of Statistical Analysis of DCE-MRI		SAC[1]
69.	Safety	n/a	Raw SAS Output of Statistical Analysis of DCE-MRI by Dosing Regimen		SAC[1]
70.	Safety	n/a	Raw SAS Output of Statistical Analysis of Patient Assessment of joint pain		SAC[1]
71.	Safety	n/a	Raw SAS Output of Statistical Analysis of CRP		SAC[1]
72.	PP	n/a	Raw SAS Output of Statistical Analysis of DAS28(CRP)		SAC[1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
73.	PP-completers	n/a	Raw SAS Output of Statistical Analysis of DAS28(CRP)-PP completers	Include subjects that complete the study and are in the PP population	SAC[1]
74.	Safety	n/a	Raw SAS Output of Statistical Analysis of CDAI		AR, SAC[1]
75.	Safety	n/a	Raw SAS Output of Statistical Analysis of SDAI		AR, SAC[1]
Biomarker					
76.	Randomised	PD_L1	Listing of Inflammatory Biomarkers in Blood		SAC[1]
77.	Randomised	PD_L3	Listing of TEAR1 % Target Engagement in Blood		SAC[1]
78.	Randomised	PD_L3	Listing of TEAR1 % Target Engagement in Synovial Tissue		SAC[1]
79.	Randomised		Listing of Pathway Engagement in Blood	No longer being produced due to limited sample size	SAC[1]
80.	Randomised	PD_L2	Listing of mRNA Expression of Inflammatory Gene Transcripts in Blood	Only to be produced for significant probsets based on adjusted p-values. GSK To produce	SAC2[1]
81.	Safety	n/a	Raw SAS Output of Statistical Analysis of Blood Inflammatory Biomarkers		SAC[1]
82.	Safety	n/a	Raw SAS Output of Statistical Analysis of Blood Inflammatory Biomarkers by Dosing Regimen		SAC[1]
83.	Safety	n/a	Raw SAS Output of Statistical Analysis of TEAR1 Target Engagement in Blood		SAC[1]
84.	Safety	n/a	Raw SAS Output of Statistical Analysis of mRNA in Blood	GSK To produce	SAC2[1]

12.11. Appendix 13: Example Mock Shells for Data Displays

Example:
POP_L1
Protocol: 203168
Population: Randomised

Listing of RA Disease History

Treatment Group	Site ID/ Unique Subject ID	Date of formal diagnosis	Time since formal diagnosis (years)	Date of onset of first musculoskeletal symptoms	Time since onset of first musculoskeletal symptoms (years)
GSK2982772	XX/XXXXX	DDMMMYYY	xx.x	DDMMMYYY	xx.x
	XX/XXXXX	DDMMMYYY	xx.x	DDMMMYYY	xx.x
	XX/XXXXX	DDMMMYYY	xx.x	DDMMMYYY	xx.x
…	…	…	…	…	…

PPD

Example:POP_L2

Protocol: 203168

Population: Randomised

Listing of Dispensing Data

Treatment Group	Site ID/ Unique Subject ID	Visit	Container number	Number of tablets dispensed	Number of tablets returned	Treatment Compliance (%)[1]
GSK2928772	XX/XXXXX	Day 1	XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
		Day 29	XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	
		Day 57	XXXXXX	xx	xx	
			XXXXXX	xx	xx	
			XXXXXX	xx	xx	

		XXXXXX	xx	xx		
		XXXXXX	xx	xx		
		XXXXXX	xx	xx	xx.x	
XX/XXXXX	Day 1	XXXXXX	xx	xx		
		….	….	….		

PPD

[1] Compliance = (Total tablets taken/total tablets expected to be taken)*100.

Note: Compliance will only be calculated for subjects who took at least one dose.

Example EFF_T1
Protocol: 203168
Population: Safety

Table XX: Summary Statistics for [*Continuous Parameter*] by Treatment and Visit

Treatment	N	Visit	n	Mean	{95% CI (Lower,Upper)}	SD	Median	Min.	Max.
Placebo	18	Day X	18	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Y	18	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Z	18	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		...							
GSK2982772	6	Day X	6	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Y	6	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Z	6	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		...							

PPD

Example EFF_T2
Protocol: 203168
Population: Safety

Table XX: Summary Statistics for Change from Baseline in [*Continuous Parameter*] by Treatment and Visit

Treatment	N	Visit	n	Mean	{95% CI (Lower,Upper)}	SD	Median	Min.	Max.
Placebo	18	Day X	18	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Y	18	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Z	18	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		...							
GSK2982772	6	Day X	6	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Y	6	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		Day Z	6	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xxxx.xx	xxxx.x	xxxx.x
		...							

PPD

Example: EFF_T3
Protocol: 203168
Population: Safety

Table x.x:
Repeated Measures Analysis of the Change from Baseline in [*Continuous Parameter*]

Visit	Treatment Group	N	n	LSMean[1]	Standard Error	95% CI for LSMean (Lower, Upper)	Difference from Placebo	95% CI for Difference (Lower,Upper)
Day XX	Placebo	xx	x	x.xx	x.xxx	(x.xx, x.xx)		
	GSK2982772	xx	x	x.xx	x.xxx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)
Day XX	Placebo	xx	x	x.xx	x.xxx	(x.xx, x.xx)		
	GSK2982772	xx	x	x.xx	x.xxx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)

...

Repeated Measures Analysis adjusted for Baseline Score, Treatment Group, Visit, Baseline Score by Visit and Treatment Group
by Visit Interaction
[1] LSMean is least squares adjusted mean.

Example: EFF_T4
Protocol: 203168
Population: Safety

Summary of DAS28(CRP) EULAR Response Categories

Visit	EULAR Category [1]	Treatment AN=xx		Treatment B N=xx	
		n	% (SE)	n	% (SE)
Day X	n	XX		xx	
	No response	Xx	xx (xx)	xx	xx (xx)
	Moderate Response	xx	xx (xx)	xx	xx (xx)
	Good Response	xx	xx(xx)	xx	xx (xx)
…					

[1] Response at a given time point is defined based on the combination of current DAS28 score and the improvement in the current DAS28 score relative to baseline.

PPD

Example: EFF_T5
Protocol: 203168 Page 1 of x
Population: Safety

Summary of ACR Response Rates [1]

ACR20

Visit		Treatment A N=xx		Treatment B N=xx	
		n	% (SE)	n	% (SE)
Day X	n	XX			
	No Response	xx	xx (xx)	XX xx	xx (xx)
	Response	xx	xx (xx)	xx	xx (xx)
DAY Y	n	xx		xx	
	No Response	xx	xx (xx)	xx	xx (xx)
	Response	xx	xx (xx)	xx	xx (xx)

[1] The American College of Rheumatology's (ACR) definition for calculating improvement in RA is calculated as a 20% improvement (ACR20) in both tender and swollen joint counts and 20% improvement in at least 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, patient's assessment of arthritis pain, disability (HAQ-DI), and an acute-phase reactant (i.e. CRP value). Similarly, ACR50 and ACR70 are calculated with the respective percent improvement.

PPD

Example: EFF_T6
Protocol: 203168 Page 1 of x

Population: Safety

Table XX
Summary of Bayesian Analysis of Change from Baseline in DAS28-CRP at day 85

Treatment Difference	SD of Treatment Difference	95% Credible Interval [1]	Probability (treatment difference > x), where x = 0	0.3	0.5	0.7	1
x.xx	x.xx	(x.xx, x.xx)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

A non-informative prior for the change in DAS28-CRP score from baseline in each treatment group was used, thus maximising the information provided by the observed data; the prior follows a Normal(0,10^36) distribution.
Note: A reduction in score on the DAS28-CRP scale is associated with disease improvement. The probability statements above are shown on the positive scale, representing a difference in decline, therefore the larger the difference in decline the greater the improvement over placebo.
[1] Interval is defined as the 2.5th and 97.5th percentiles of the posterior distribution.

PPD

Example: EFF_T7
Protocol: 203168
Population: Safety

Table XX
Summary of Bayesian Analysis of ACR20 at day 85

Treatment Difference	SD of Treatment Difference	95% Credible Interval [1]	Probability (treatment difference > x), where x = 0	5	10	20	30
xx.x	xx.xx	(xx.xx, xx.xx)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

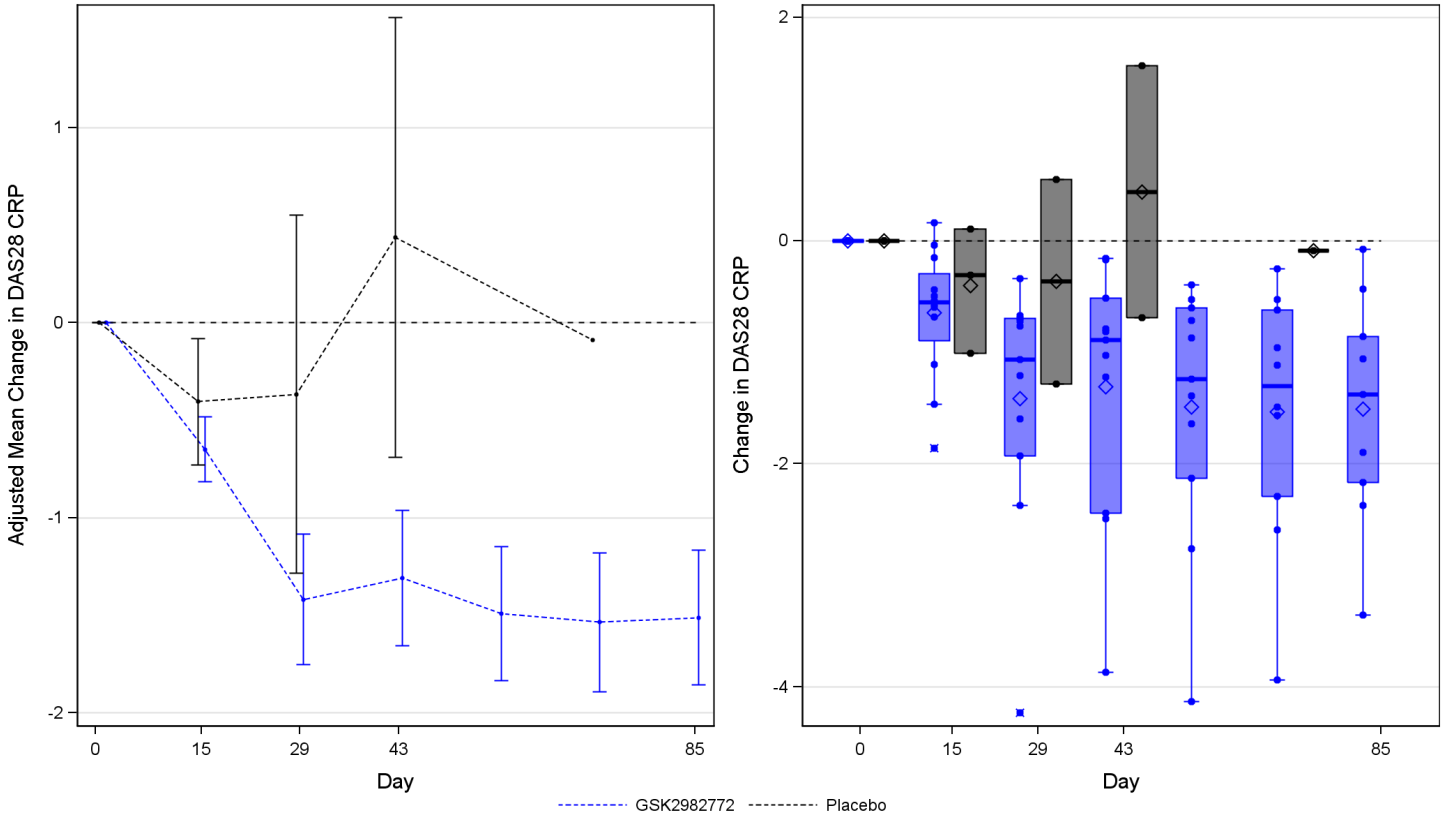
An non-informative prior for the probability of acheiving ACR 20 in each treatment group was used, thus maximising the information provided by the observed data; the prior follows a Beta(1,1) distribution.

[1] Credible Interval is defined as the 2.5th and 97.5th percentiles of the posterior distribution.

PPD

Example: EFF_F1
Protocol: 203168
Population: Safety

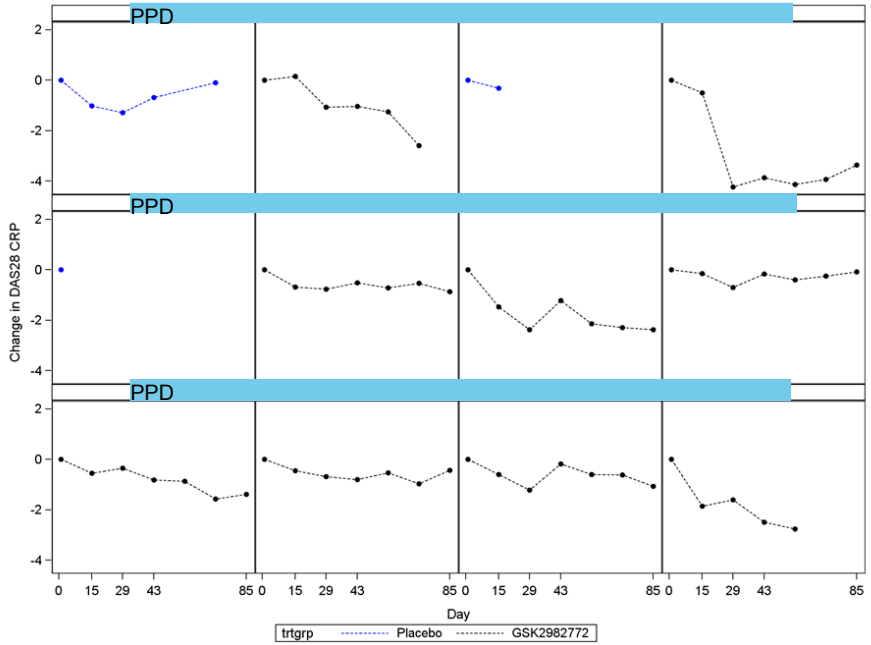
[*Continuous Parameter,*] Adjusted Mean (+/-SE) Change from Baseline and Box and Whisker Plot of Unadjusted Change from Baseline by Treatment over Time



PPD

Example: EFF_F2
Protocol: 203168
Population: Safety

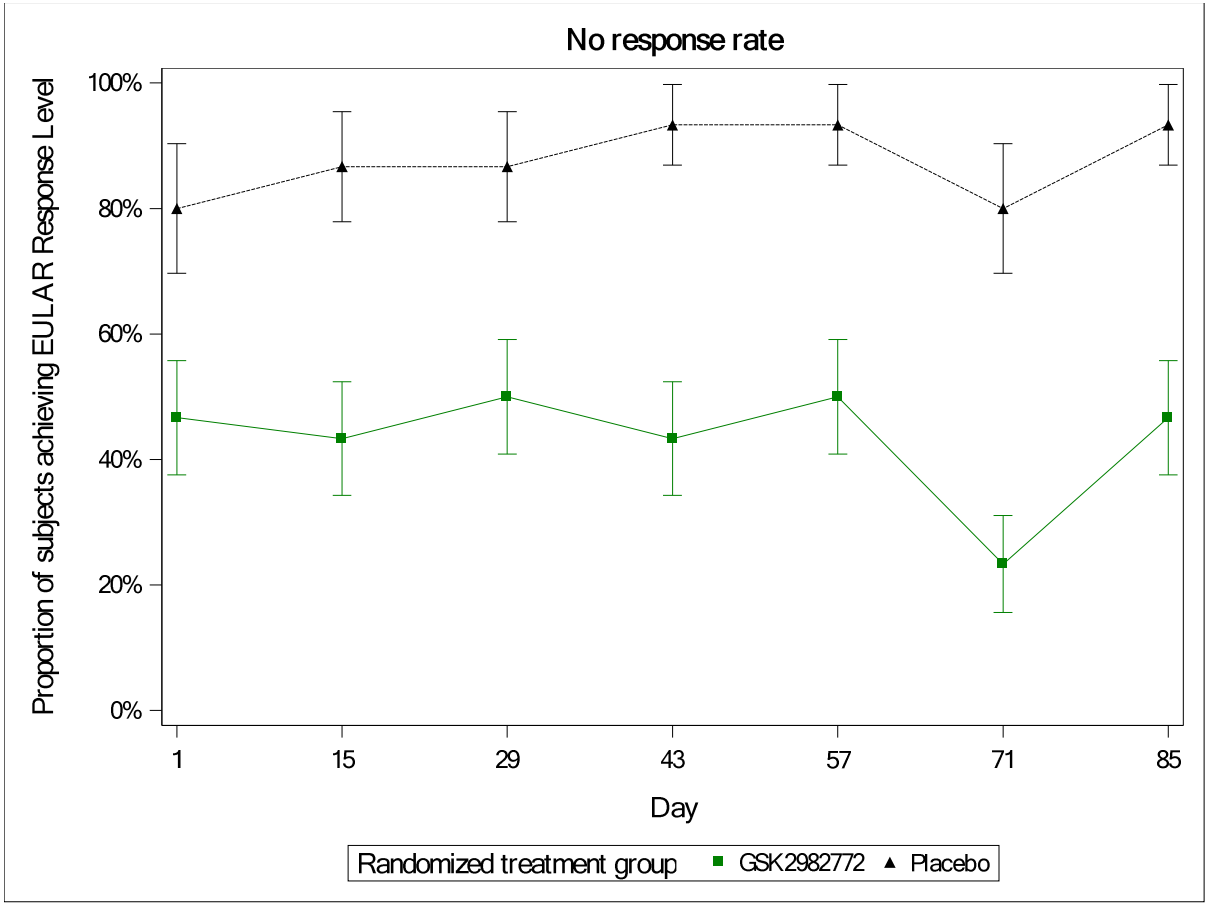
Individual Subject Profiles for DAS28-CRP



PPD

Example: EFF_F3
Protocol: 203168
Population: Safety

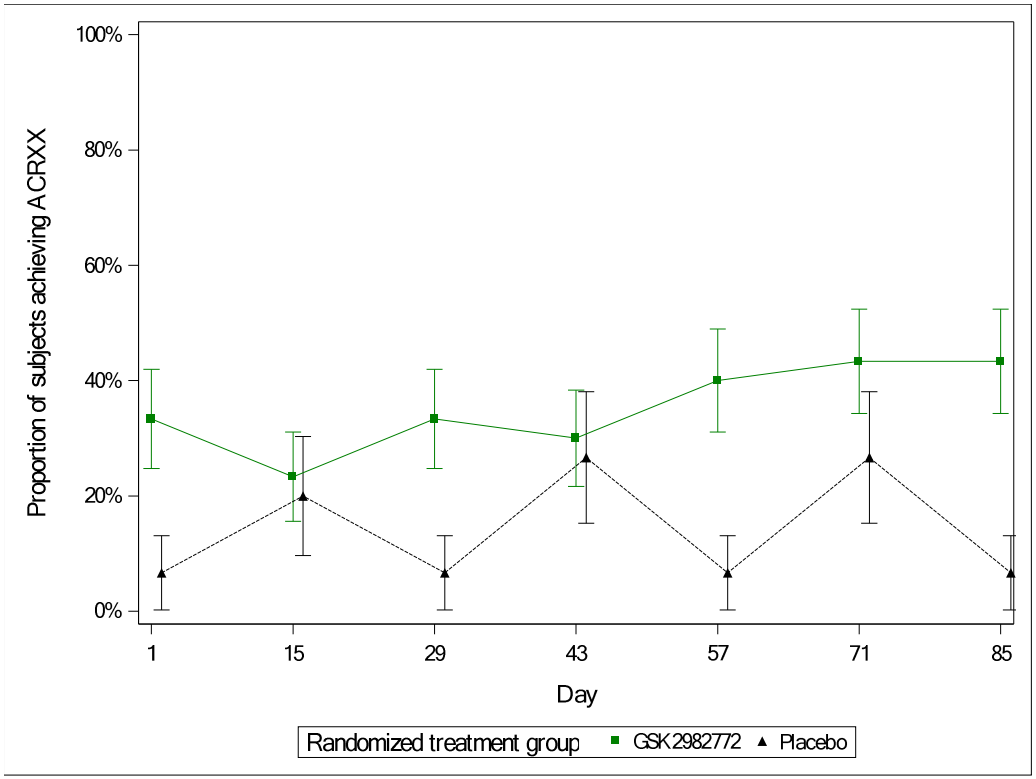
Proportion of subjects in each DAS28-CRP EULAR Response Category



PPD

Example: EFF_F4
Protocol: 203168
Population: Safety

Proportion of subjects achieving ACR20/50/70



PPD

Example: PD_T1
Protocol: 203167
Population: Safety

Table X.X
Summary Statistics of Blood Inflammatory Biomarkers

Parameter: X (Units)

Treatment	N	Visit	Planned Relative Time	n	Mean	{95% CI (Lower,Upper)}	SD	Median	Min.	Max.
Placebo	XX	DAY 1	PRE-DOSE	XX	X.XX	(X.XX, X.XX)	X.XXX	X.XX	X.X	XX.X
		DAY 43	PRE-DOSE	XX	X.XX	(X.XX, X.XX)	X.XXX	X.XX	X.X	XX.X
		DAY 85	DAY 85	XX	X.XX	(X.XX, X.XX)	X.XXX	X.XX	X.X	XX.X
GSK2982772	XX	DAY 1	PRE-DOSE	XX	X.XX	(X.XX, X.XX)	X.XXX	X.XX	X.X	XX.X
		DAY 43	PRE-DOSE	XX	X.XX	(X.XX, X.XX)	X.XXX	X.XX	X.X	XX.X
		DAY 85	DAY 85	XX	X.XX	(X.XX, X.XX)	X.XXX	X.XX	X.X	XX.X

Example: PD_T2
Protocol: 203168
Population: Safety

Table X.X
Summary of Percentage Change in Blood Inflammatory Biomarkers

Parameter: X (Units)

Treatment	N	Visit	Mean Baseline [1]	Planned Relative Time	n	Mean	{95% CI (Lower,Upper)}	SD	Median	Min.	Max.
Placebo	XX	DAY 43	X.XXX	PRE-DOSE	XX	XX.XXX	(XX.XXX,XX.XXX)	XXX.XXXX	X.XXX	XX.XX	XX.XX
		DAY 85	X.XXX	DAY 85	XX	XX.XXX	(XX.XXX,XX.XXX)	XXX.XXXX	X.XXX	XX.XX	XX.XX
GSK2982772	XX	DAY 43	X.XXX	PRE-DOSE	XX	XX.XXX	(XX.XXX,XX.XXX)	XXX.XXXX	X.XXX	XX.XX	XX.XX
		DAY 85	X.XXX	DAY 85	XX	XX.XXX	(XX.XXX,XX.XXX)	XXX.XXXX	X.XXX	XX.XX	XX.XX

[1] Baseline is taken as the mean of the planned pre-dose measurements.

Example: PD_T3
Protocol: 203163
Population: Safety

Table X.X
Adjusted Mean (95% CI) Percentage Change in Blood Inflammatory Biomarkers

Parameter: X (Units)

Visit	N	Treatment	n	Geometric LSMean	%CVb	95% CI for LSMean	Difference From Placebo	95% CI for Difference Lower, Upper)
DAY 43	XX	Placebo	XX	XX.XX	XX.XXX	(XX.XX, XX.XX)		
	XX	GSK2982772	XX	XX.XX	XX.XXX	(XX.XX, XX.XX)	XX.XX	(XX.XX, XX.XX)
DAY 85	XX	Placebo	XX	XX.XX	XX.XXX	(XX.XX, XX.XX)		
	XX	GSK2982772	XX	XX.XX	XX.XXX	(XX.XX, XX.XX)	XX.XX	(XX.XX, XX.XX)

Note: Baseline is defined as the latest pre-dose assessment.
Note: Analysis performed using a MMRM model, adjusting for the following covariates: treatment, baseline, Visit, baseline by visit and an interaction between treatment and visit.

Example: PD_T4
Protocol: 203168
Population: Safety

Table x.x:
Adjusted Mean (95% CI) TEAR1 % Target Engagement in Blood

Visit	Comparison	GSK LSMean Engagement Ratio	GSK LSMean Engagement %	Placebo LSMean Engagement Ratio	Placebo LSMean Engagement %	Treatment Ratio (95% CI)	Diff % Engagement (95% CI)
DAY 43	GSK2982772 vs Placebo	X.XX	X	X.XX	X	X.XX (X.XX, X.XX)	X.X (X.X, X.X)
DAY 85	GSK2982772 vs Placebo	X.XX	X	X.XX	X	X.XX (X.XX, X.XX)	X.X (X.X, X.X)

Note: Baseline is defined as the latest pre-dose assessment.
Note: Percentage target engagement = (1 - engagement ratio) * 100.
Repeated Measures Analysis adjusted for log baseline, Treatment Group, Visit, log baseline by Visit and Treatment Group by Visit Interaction

Example: PD_T5
Protocol: 203168
Population: Safety

Table XX.XX :
Frequency table summarising the number of probe sets in various fold change

Probeset	Gene	Visit	N	n	Treatment	Fold Change in Blood < 1.5	Fold Change in Blood >1.5
XXXXXX	XXXXXX	Baseline	XX	XX	Placebo	xx (xx.xx)	xx (xx.xx)
					GSKXXXXXX XXmg	xx (xx.xx)	xx (xx.xx)
		WEEK xx	XX	XX	Placebo	xx (xx.xx)	xx (xx.xx)
					GSKXXXXXX XXmg	xx (xx.xx)	xx (xx.xx)
		WEEK xx	XX	XX	Placebo	xx (xx.xx)	xx (xx.xx)
					GSKXXXXXX XXmg	xx (xx.xx)	xx (xx.xx)

Example: PD_T6
Protocol: 203168

Table XX.XX :
Summary of Analysis for Microarray mRNA Data from xxxx

Probeset	Gene	Visit	N	n	Treatment	Adjusted mean	95% CI	Fold Change	Adjusted p-value
XXXXXX	XXXXXX	Baseline	XX	XX	Placebo	XX.X	(XX.X, XX.X)		
					GSKXXXXXX XXmg	XX.X	(XX.X, XX.X)	XX.X	X.XXX
		WEEK xx	XX	XX	Placebo	XX.X	(XX.X, XX.X)		
					GSKXXXXXX XXmg	XX.X	(XX.X, XX.X)	XX.X	X.XXX
		WEEK xx	XX	XX	Placebo	XX.X	(XX.X, XX.X)		
					GSKXXXXXX XXmg	XX.X	(XX.X, XX.X)	XX.X	X.XXX

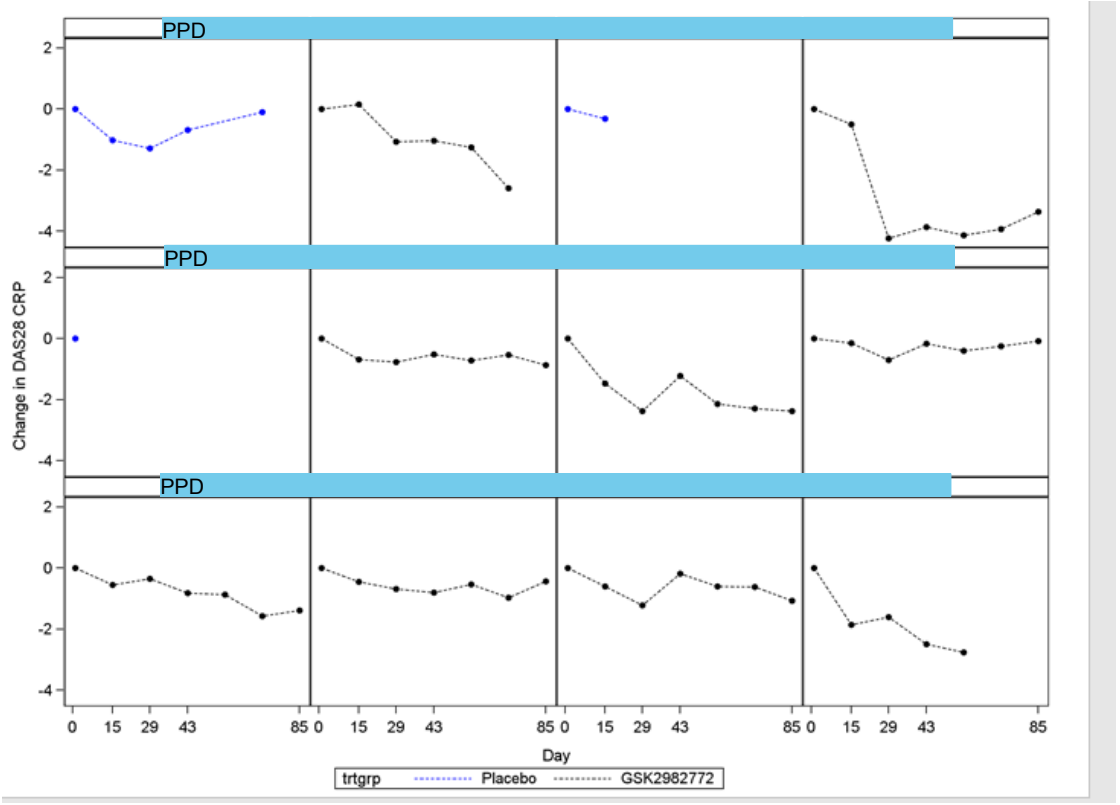
Note: Fold change in relative to the baseline value

Note: Fold change from baseline is defined as ratio to baseline if the ratio is >= 1, otherwise it is defined as -1/ratio to baseline.

Programming note: Please present SE not 95% CI

Example: PD_F1
Protocol: 203168
Population: Safety

Figure X
Individual [*Continuous Parameter*] Scores over Time by Treatment



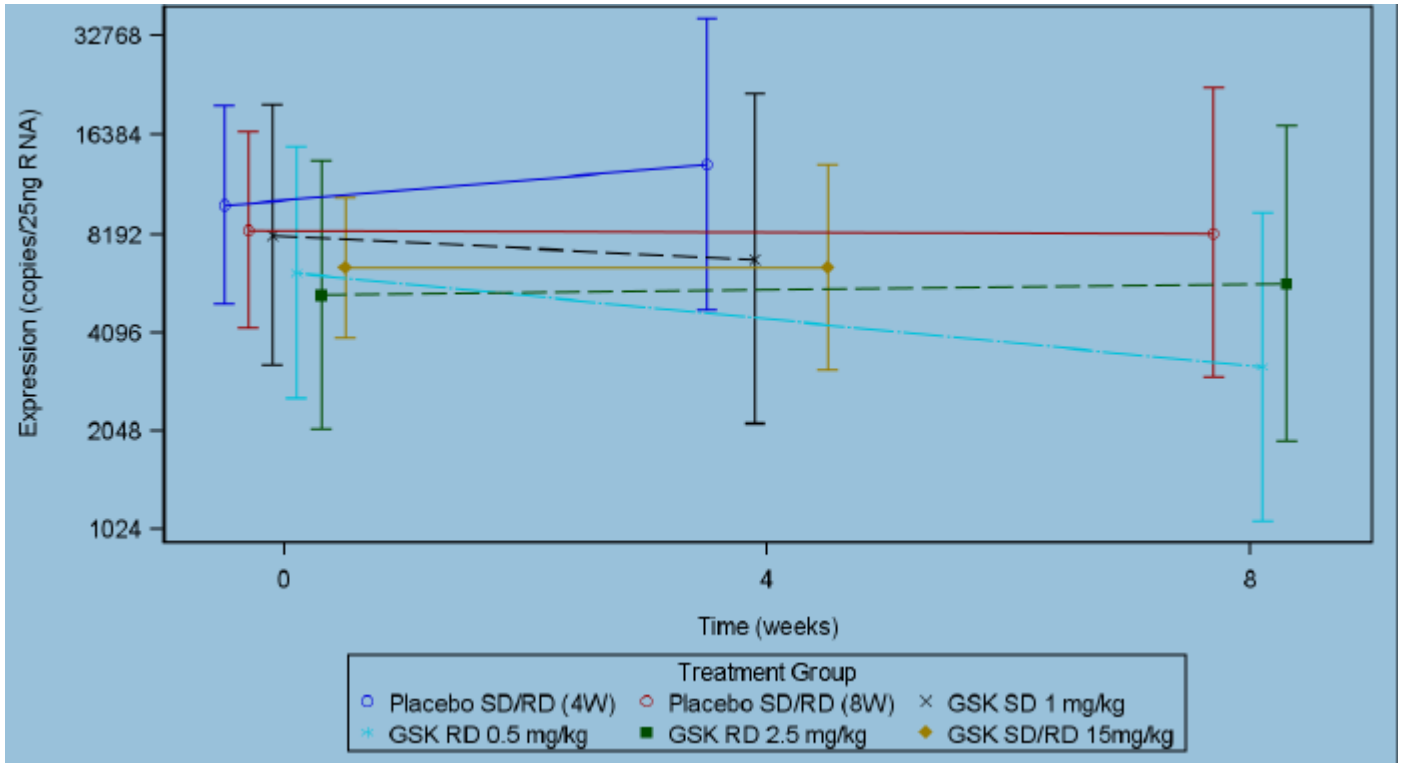
PPD

Example: PD_F2

Protocol: 203168
Population: Safety

Figure XX.XX:
Adjusted mean probe set intensity values (+/- SE) by time from xxxx

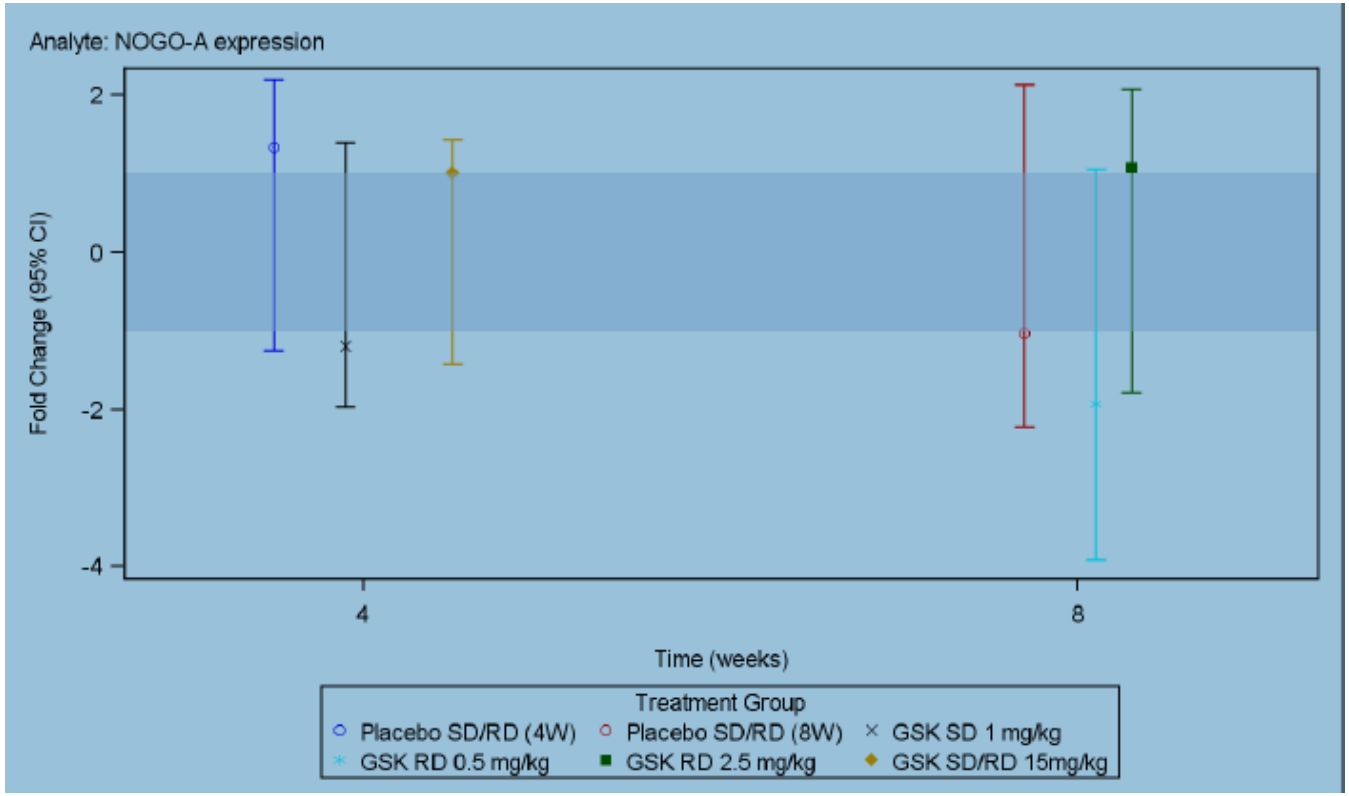
Gene ID: XXXX



Example: PD_F3
Protocol: 203168
Population: Safety

Figure XX.XX:
Adjusted Fold Change in mRNA Expression

Gene ID: XXXX



Programming note to present SE's not 95% CI

Example: EFF_L1
Protocol: 203168
Population: Safety

Listing of MRI Data, Inflammatory Structural Joint Damage: RAMRIS

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Number of Available Joints	Synovitis	Bone Erosion	Bone Edema/Osteitis	Cartilage Loss
XXXX/ XXXXX	Baseline	xx	xxx	xxx	Xxx	xxx
	Week X	xx	xxx	xxx	Xxx	xxx
	Etc.					
XXXX/ XXXXX	Baseline	xx	xxx	xxx	Xxx	xxx
	Week X	xx	xxx	xxx	Xxx	xxx
	Etc.					

PPD

Example: EFF_L2
Protocol: 203168
Population: Safety

Listing xx
Listing of MRI Data, Inflammatory Structural Joint Damage: RAMRIQ

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Synovitis	Synovitis Normalized	Erosive Damage (Normalized)	Cartilage Space Loss	Bone Marrow Lesions
XXXX/ XXXXX	Baseline					
	Week X					
	Etc.					
XXXX/ XXXXX	Baseline					
	Week X					
	Etc.					

PPD

Example: EFF_L3
Protocol: 203168
Population: Safety

Listing xx
Listing of MRI Data, Inflammatory Structural Joint Damage: CARLOS

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Result
XXXX/ XXXXX	Baseline	Complete cartilage denuding or diffuse bone-on-bone contact
	Week X	Complete ankylosis
	Etc.	
XXXX/ XXXXX	Baseline	
	Week X	
	Etc.	

PPD

Example: EFF_L4
Protocol: 203168
Population: Safety

Listing of Joint Inflammation: DCE-MRI

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Exchange Rate	Interstitial Volume	Plasma Volume	Joint Volume	Enhancing Volumne	Initial Rate of Enhancement	Maximum signal intensity enhancement
XXXX/ XXXXX	Baseline							
	Week X							
	Etc.							
XXXX/ XXXXX	Baseline							
	Week X							
	Etc.							

PPD

Example: EFF_L5
Protocol: 203168
Population: Safety

Listing of Observed Swollen and Tender Joint States

Treatment Group: Treatment A
Site ID/Unique Subject ID: <Site ID/Subject ID>

Visit		Joints of Left Extremities	Joints of Right Extremities	
Baseline	Tender	Shoulder, Wrist, MCP3, PIP5	Elbow, Sternoclavicular, Hip, DIP3	PIP5
	Swollen			
	Not available			
Week X		…	…	
Etc.				
Baseline				
Week X				
Etc.				

PPD

Example: EFF_L6 Page 1 of n
Protocol: 203168
Population: Safety

Listing of DAS28-CRP, EULAR response and Joint Counts

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Remission?	Low disease Activity?	TJC28/ TJC68	SJC28/ SJC66
XXXX/ XXXXX		Yes		xx.x/ xx.xx	xx.x/ xx.xx
	Baseline			xx.x/ xx.xx	xx.x/ xx.xx
	Week X			Etc.	Etc.
	Etc.				
XXXX/ XXXXX		No		xx.x/ xx.xx	xx.x/ xx.xx
	Baseline			xx.x/ xx.xx	xx.x/ xx.xx
	Week X			Etc.	Etc.
	Etc.				

Note: DAS28(CRP) remission is achieved by a DAS28(CRP) value lower than 2.6 and DAS28(CRP) Low Disease Activity is defined as a DAS28 score of <3.2.

PPD

Example: EFF_L7 Page 1 of n
Protocol: 203168
Population: Safety

Listing of ACR Response Rates and ACR Components

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	TJC68	SJC66	PtGA	PhGA	Pt Pain	CRP Value	HAQ-DI	ACR 20/50/70 Response
XXXX/ XXXXX	Week 1	Xx	xx	xx	xx	xx	xx	xx	ACR 50
	Week 2	Xx	xx	xx	xx	Xx	xx	xx	
	Etc.	Xx	xx	xx	xx	Xx	xx	xx	ACR 20
						Xx			
XXXX/ XXXXX	Week 1	Xx	xx	xx	xx	Xx	xx	xx	
	Week 2	Xx	xx	xx	xx	Xx	xx	xx	
	Etc.								

Note: Listing shows percentage change from Baseline. For all components, negative values represent improvement.
Note: ACR20 is achieved for a 20% improvement in both TJC68 and SJC66 and 20% improvement in 3 of the 5 remaining components. ACR50 and ACR70 are defined accordingly.

PPD

Example: EFF_L8 Page
1 of n
Protocol: 203168
Population: Safety

Listing of HAQ-DI

Treatment Group: Treatment A
Site ID/Unique Subject ID: <Site ID/Subject ID>

Visit	Dress & Groom Dress/ Wash hair	Rising Stand up/ Get in Bed	Eating Cut meat/ Lift Cup/ Open Milk	Walking Walk/ Climb stairs	Hygiene Wash Body/ Have Bath/ Toilet	Reach Reach/ Bend	Grip Open Car/ Open Jar/ Turn Tap	Activity. Shop/ Car/ Chores	Aids or Equipment	Help from another Person	HAQ-DI SCore
Baseline	1/3	0/2	0/2/2	1/3	0/2/2	2/2	0/2/1	0/2/2	Crutches	Eating, Rising	XX
Week X	x/x	x/x	x/x/x	x/x	x/x/x	x/x	x/x/x	x/x/x	XXXXX	XXXXX, XXXXX	
Etc.	…	…	…	…	…	…	…	…	…	…	

Note: 0 = Without any difficulty. 1 = With some difficulty. 2 = With much difficulty. 3 = Unable to do.
Note: HAQ-DI Pain Sore can be found in Listing 20.
Note: Functional areas in order of the columns are: Dress & Groom, Rising, Eating, Walking, Hygiene, Reach, Grip, Activity

PPD

Example: EFF_L9
Protocol: 203168
Population: Safety

Listing of RA Symptom and Impact Diary [1]

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Joint Pain Sitting/ Lying/ Moving	Joint Pain Walking/ Standing/ Lifting	Joint Paint at its Worst	Energy/ Tired	Stiffness/ Morning Stiffness	Morning Stiffness Duration	Joint Stiffness Severity	Had to Rest	Sleep Quality/ Affection
XX/XXXXX	Day X	2/ 5/ 5	4/ 3/ 4	3	No Energy/ A little of the time	All of the time/ Mild	Less than 30 Minutes	Mild	All of the time	Bad/ A little
XX/XXXXX	Day Y	0/ 4/ 10	2/ 5/ 5	10	Some Energy/ All of the time	None of the time/ Very severe	No morning stiffness	Severe	Most of the time	Very Good/ Somewhat
XX/XXXXX	Day Z						2-4 Hours			
XX/XXXXX										

[1] Symptoms rated relative to the last 24 hours

PPD

Example: EFF_L10 Page 1 of n
Protocol: 203168
Population: Safety

Listing of Patient and Physician Global Assessment [1]

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Actual Date	Study Day	Physician Assessment [1]	Patient Assessment [2]
XX/XXXXX	Day X			XX	XX
XX/XXXXX	Day Y				
XX/XXXXX	Day Z				
XX/XXXXX					

[1] Physician assessment of disease activity using the visual analogue scale with anchor's "0" (none) to "10" (extremely active).

[2] Patients assessment of how they feel today, using the visual analogue scale with anchor's "0" (Very good)" to "10" (very poor).

PPD

Example: EFF_L11 Page 1 of n
Protocol: 203168
Population: Safety

Listing of Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale [1]

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Actual Date	Study Day	Category	Response	Total Score
XX/XXXXX	Day X			I feel fatigued	Not at all	XX
				I feel weak all over	A little bit	
				I feel listless ("washed out")	Somewhat	
				I feel tired	Quite a bit	
				I have trouble starting things because I am tired	Very much	
				I have trouble finishing things because I am tired	A little bit Somewhat	
				I have energy	Not at all	
				I am able to do my usual activities	A little bit	
				I need to sleep during the day	A little bit	
				I am too tired to eat	Somewhat	
				I need help doing my usual activities	Quite a bit	
				I am frustrated by being too tired to do the things I want to do	Not at all	
				I have to limit my social activity because I am tired	Somewhat	
XX/XXXXX						
XX/XXXXX	Day Z					
XX/XXXXX						

[1] A global assessment of disease activity using the a visual analogue scale with anchor's "0" (none) to "10" (extremely active).

PPD

Example: EFF_L12 Page 1 of n
Protocol: 203168
Population: Safety

Listing of Patient Assessment of Joint Pain [1]

Treatment Group: Treatment A

Site ID/ Unique Subject ID	Visit	Actual Date	Study Day	Patient Assessment
XX/XXXXX	Day X			XX
XX/XXXXX	Day Y			
XX/XXXXX	Day Z			
XX/XXXXX				

[1] RA pain on average over the past 24 hours: using a visual analogue scale with anchor's "0" (no pain) to "10" (most severe pain).

PPD

Example : PD_L1
Protocol : 203168
Population : Safety

Listing XX:
Listing of Raw, Change from baseline and Percent Change in [variable}

Treatment	Subject	Visit	Visit date	Study day	Histopatholgical Scoring	Raw	Change	Percent Change
Placebo	XXX	XXX	XX/XX/XX	Day 1	K16	XXX.X		
					CD3/CD11c	XXX.X		
					CD161	XXX.X		
					Elactase +ve cels	XXX.X		
					epidermal thickness	XXX.X		
		XXX	XX/XX/XX	Day 43	K16	XXX.X	XXX.X	XXX.X
					CD3/CD11c	XXX.X	XXX.X	XXX.X
					CD161	XXX.X	XXX.X	XXX.X
					Elactase +ve cels	XXX.X	XXX.X	XXX.X
					epidermal thickness	XXX.X	XXX.X	XXX.X

Example : PD_L2
Protocol : 203168
Population : Safety

Listing XX:
Listing of Absolute, Percentage Inhibition and Maximum Percentage Inhibition in mRNA Expression

Gene	Treatment	Subject	Visit	CT1/CT2/ CTAVG/ Copy Number	Value	Percentage Inhibition [1]	Maximum Percentage Inhibition [2]
XXXXGENE	GSKXXXXXX XXmg	XXXX	Screening	CT1	XX.XXX		
				CT2	XX.XXX		
				CTAVG	XX.XXX		
				NORMALISED	XX.XXX		
			Baseline	CT1	XX.XXX		
				CT2	XX.XXX		
				CTAVG	XX.XXX		
				NORMALISED	XX.XXX	x.xxx	
			Week X	CT1	XX.XXX		
				CT2	XX.XXX		
				CTAVG	XX.XXX		
				NORMALISED	XX.XXX	x.xxx	

Example PD_L3
Protocol: 203168
Population: All Subjects

Listing 79
Listing of TEAR1 Concentrations and % Target Engagement: Part B

Treatment: Treatment A

Inv./ Subj.	Date	Actual Time	Visit	Planned Relative Time		Conc (pg/mL)	Ratio[1]	% Target Engagement [2]
PPD	PPD	9:42	DAY 1	PRE-DOSE	Free	9.31504	0.4670	
					Total	19.94849		
		11:51	DAY 1	1.5 HR	Free	5.11583	0.3894	16.605
					Total	13.13721		
		18:20	DAY 1	8 HR	Free	8.01224	0.3926	15.929
					Total	20.40949		
		10:09	DAY 1	24 HR	Free	7.82238	0.3761	19.456
					Total	20.79845		
		9:11	DAY 14	PRE-DOSE	Free	8.06836	0.3705	20.666
					Total	21.77966		
		10:50	DAY 14	1.5 HR	Free	8.44182	0.4155	11.012
					Total	20.31552		
		17:21	DAY XX	8 HR	Free	7.80388	0.3734	20.033
					Total	20.89901		

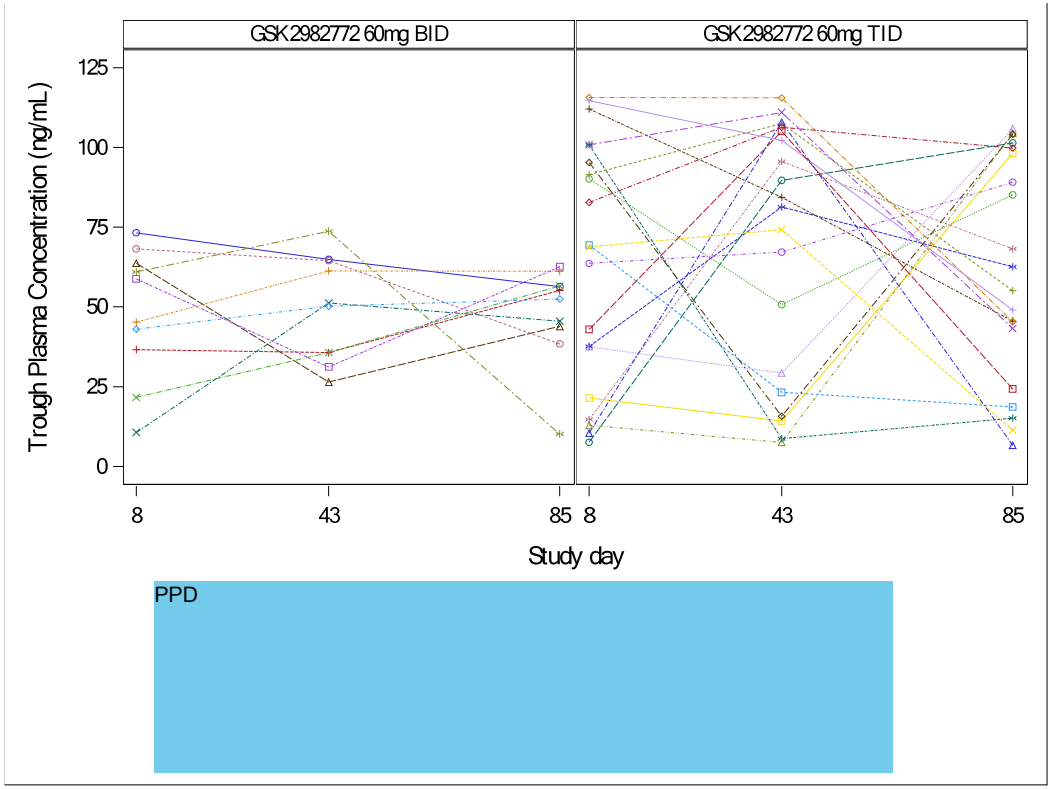
Note: Only Tru Culture results are included.
[1] Ratio=Free/Total
[2] %Target Engagement = 100 - ((ratio post/ ratio pre-dose)* 100).

PPD

Example: PK_F1

Protocol: 203168
Population: PK772

Figure XX.XX: GSK2982772 Trough Plasma Concentration by Study Day

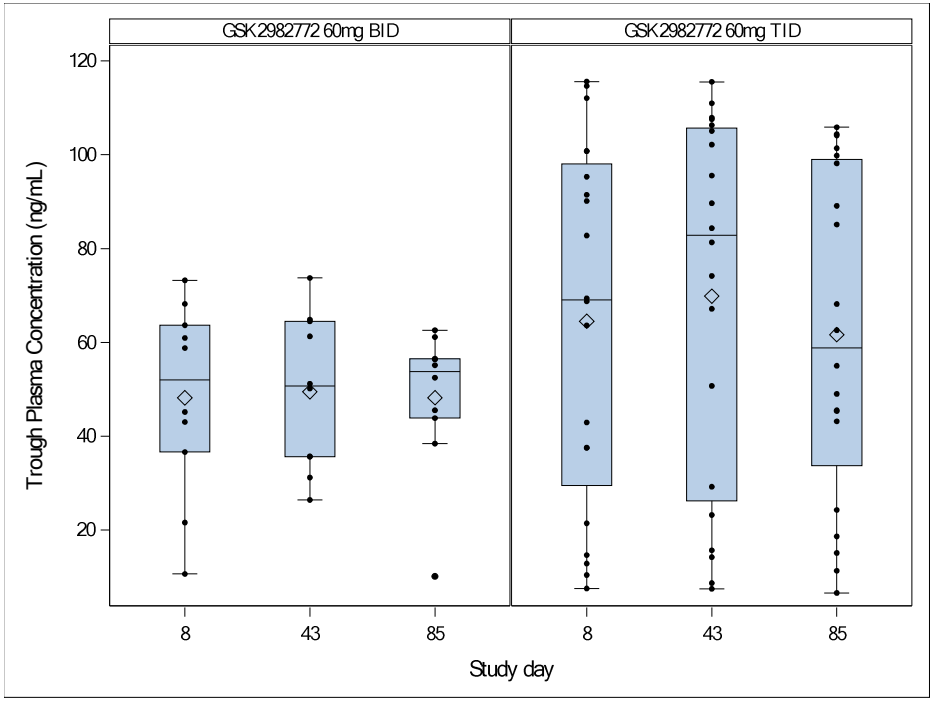


USE THIS SHELL FOR FIG. 4.6 AS WELL.

Example: PK_F2

Protocol: 203168
Population: PK772

Figure XX.XX: GSK2982772 Trough Plasma Concentration by Study Day

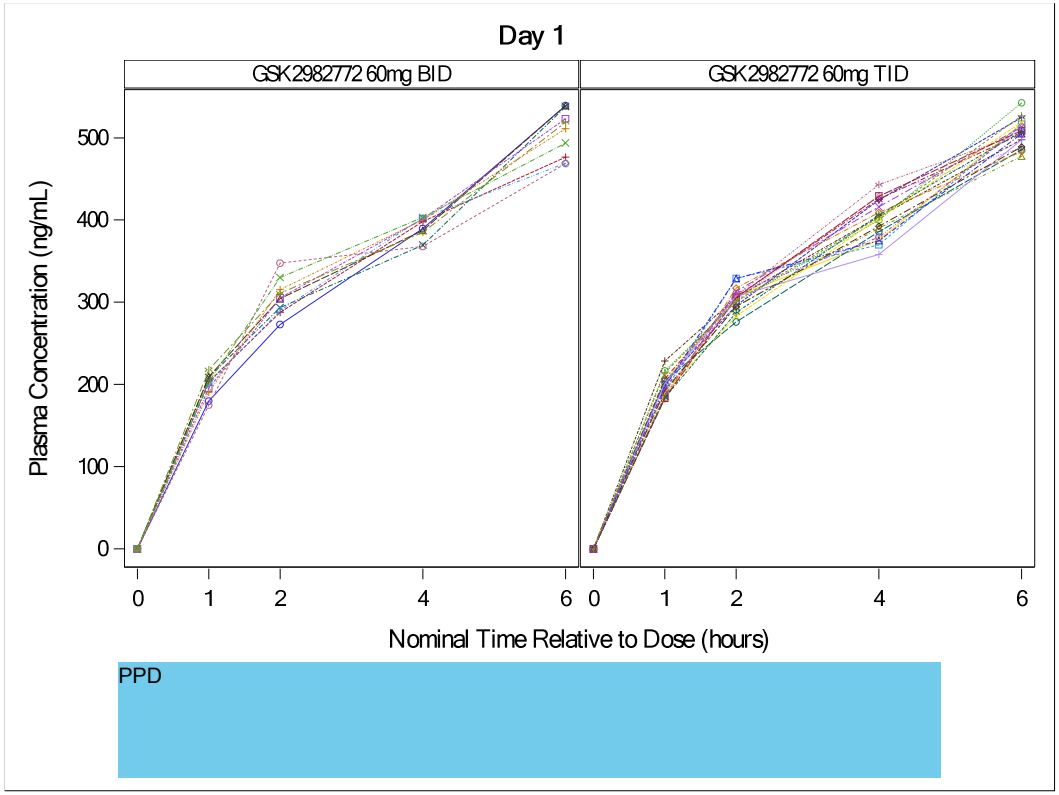


PPD

Example: PK_F3

Protocol: 203168
Population: PK772

Figure XX.XX: GSK2982772 Plasma Concentration by Time relative to Dose

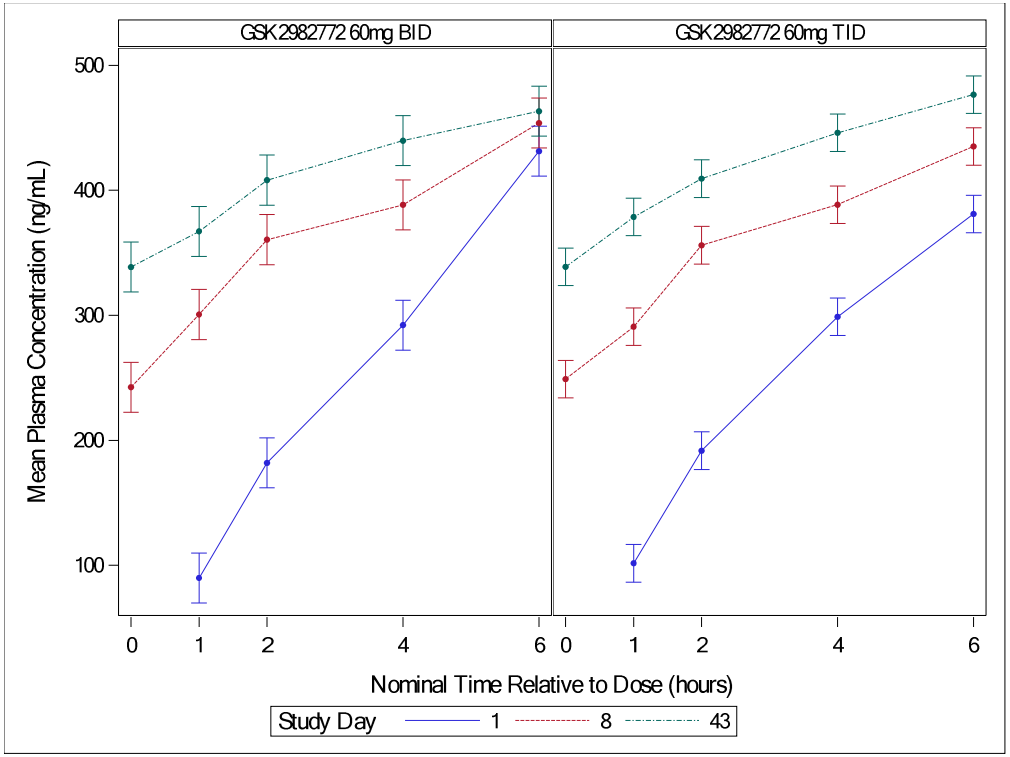


PPD

Include Day1, 8 and 43 as separate pages

Example: PK_F4

Figure XX.XX: Mean GSK2982772 Plasma Concentration Data by Time Relative to Dose by Study Day



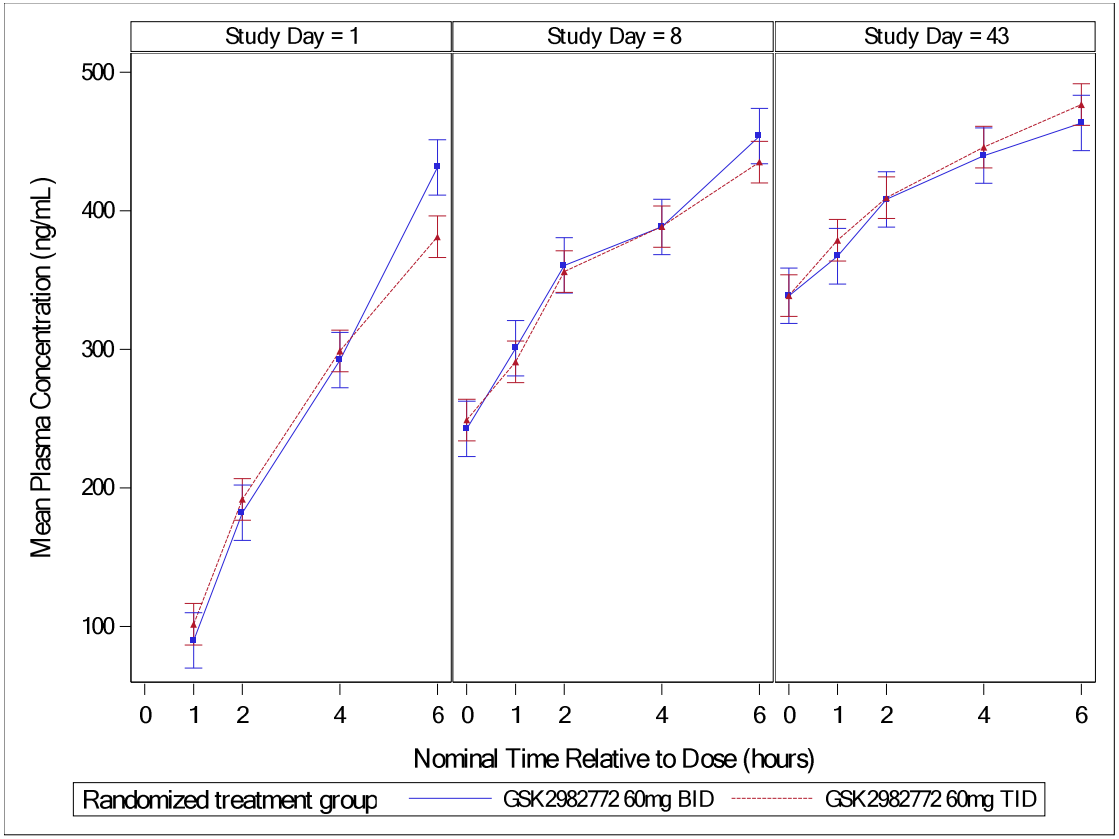
PPD

Example: PK_F5

Protocol: 203168

Population: PK772

Figure XX.XX: Mean GSK2982772 Plasma Concentration Data by Time Relative to Dose by Randomized Regimen



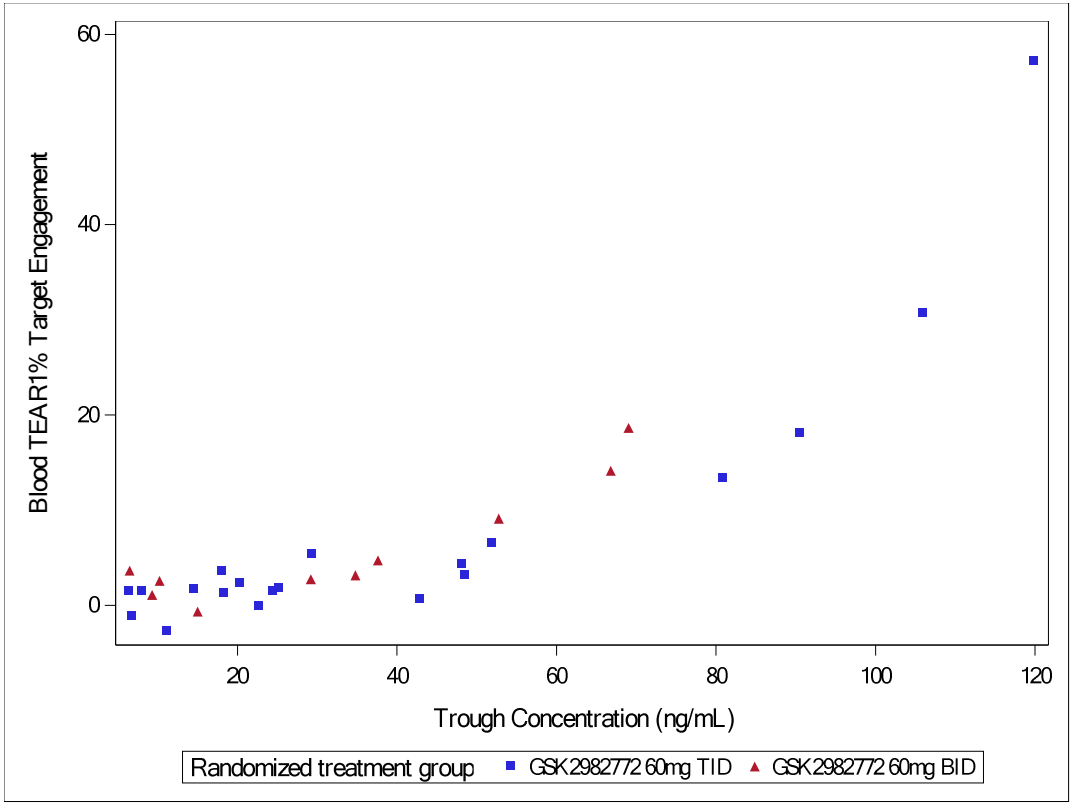
PPD

Example: PK_F6

Protocol: 203168

Population: PK772

Figure XX.XX: GSK2982772 Plasma Trough Concentration vs Blood TEAR1% Target engagement



PPD