CONFIDENTIAL

The GlaxoSmithKline group of companies 207546

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

Title	:	Reporting and Analysis Plan for GSK3358699 First time in human study 207546: A randomised, double-blind (sponsor open), placebo-controlled, three part study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single (in both fed and fasted states) or repeat doses of GSK3358699 in healthy male participants.
Compound Number	:	GSK3358699
Study Number	:	207546
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol GlaxoSmithKline Document Number 2017N332348_05.
- This RAP is intended to describe the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK3358699 (and GSK3206944 where applicable), in single (in both fed and fasted states) and repeat oral doses in healthy participants.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables.

RAP Author:

Approver	Date	Approval Method
PPD Statistician	NA	NA

RAP Team Review Confirmation:

Reviewer	Date	Confirmation Method
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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:		
2017N332348_01	30-NOV-2017	Original
2017N332348_02	25-JAN-2018	Amendment 1
2017N332348_03	21-MAR-2018	Amendment 2
2017N332348_04	29-MAY-2018	Amendment 3
2017N332348_05	11-DEC-2018	Amendment 4

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The following changes were made from the originally planned statistical analysis specified in protocol GlaxoSmithKline Document Number 2017N332348_05 [(Dated: 11-DEC-2018)]:

Protocol	**Reporting & Analysis Plan**	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Section 10.3: the populations described are Enrolled, Randomised, Evaluable, Safety, PK, PK/PD.	• Section 4: the populations described are Enrolled, Screened, Safety, PK.	• Randomised and Evaluable population not needed in any table, figure or listing. • PK/PD population and Safety population coincide. • Enrolled population needed for Tables of Age Ranges.

Due to the early termination of the study, the planned exploratory analysis detailed in the protocol will not be included in the main SAC delivery. Exploratory analysis will be performed separately in cases where it is deemed clinically or scientifically relevant. The study was terminated prior to any subjects being dosed with study treatment in Part B and therefore only minimal listings of screening data will be produced for this part.

2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• **[P1]** To evaluate the safety and tolerability of single and repeat oral doses of GSK3358699 in healthy male participants.	• AE reporting. • Laboratory safety data (clinical chemistry, haematology, urinalysis). • Vital signs (blood pressure, heart rate, body temperature). • 12 lead ECGs.
Secondary	
• **[S1]** To evaluate the systemic pharmacokinetic (PK) profile following single and repeat oral doses of GSK3358699 in healthy male participants.	• Plasma concentrations of GSK3358699 plus derived PK parameters.
• **[S2]** To evaluate the systemic PK profile of the acid metabolite, GSK3206944 following single and repeat oral doses of GSK3358699 in healthy male participants.	• Plasma concentrations of GSK3206944 plus derived PK parameters.
• **[S3]** To evaluate the intracellular PK profile of GSK3206944 in target cells following single and repeat oral doses of GSK3358699 in healthy male participants.	• Monocyte intracellular quantification of GSK3206944.
• **[S4]** To understand the extent of target engagement (TE) after *ex vivo* LPS challenge following single and repeat oral doses of GSK3358699 in healthy male participants.	• Plasma concentrations of monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6 and tumour necrosis factor (TNF) in blood stimulated *ex vivo* with LPS over time.

P1: Primary Objective 1 – Safety
S1: Secondary Objective 1 – GSK3358699 systemic PK
S2: Secondary Objective 2 - GSK3206944 systemic PK
S3: Secondary Objective 3 - GSK3206944 intracellular PK
S4: Secondary Objective 4 - TE

2.3. Study Design

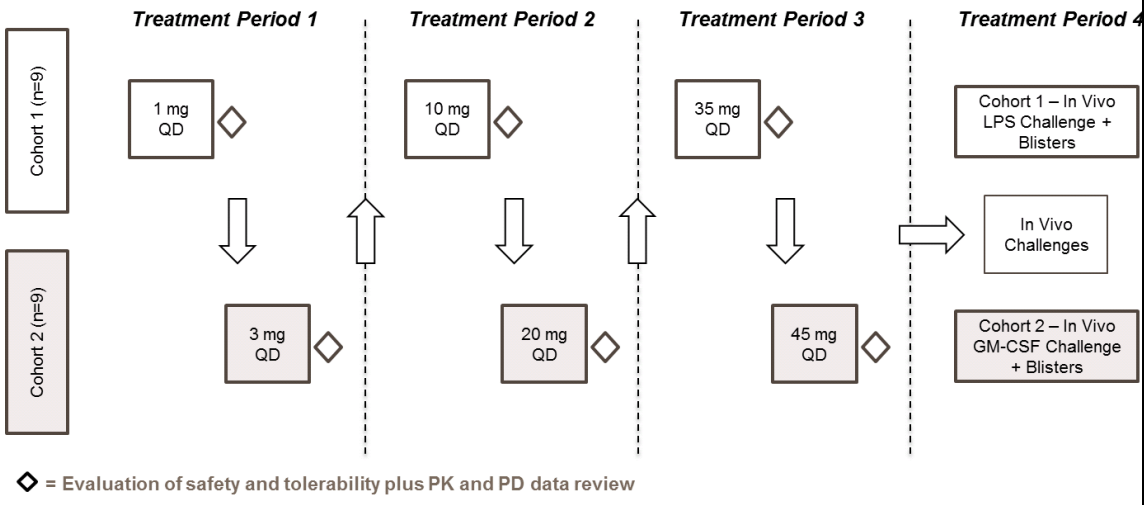
This study will be a randomised, double-blind (sponsor open), placebo-controlled, three part study of oral administration of GSK3358699 in healthy male participants. Part A will be a single ascending dose crossover design in two interlocking cohorts of participants (Cohorts 1 and 2). Part B will be a single dose, open-label two-way crossover study with GSK3358699 administered under fed and fasted conditions in a further cohort of participants (Cohort 3). Part C is planned to be a repeat dose design in 5 sequential cohorts of participants (Cohorts 4-8).

All participants in Part A, Part B and Part C of the study will attend a screening visit within 35 days prior to their first dose (with the exception of Cohort 8 where the screening visit will be within 45 days prior to their first dose) and a follow up visit within 7-14 days of their last dose. A second follow up visit will also be conducted approximately 5 weeks after the last dose for those participants in cohorts where challenges and blisters are being administered. If warranted, additional follow-up visits may be scheduled.

Note: Due to early termination of the study Parts B and C were not completed as planned. No subjects were randomised or dosed in Part B and subjects were only dosed in Cohorts 4 and 5 of Part C.

The table below provides an overview of the study design and the key features.

Part A: Single Ascending Doses and LPS / GM-CSF challenges



Part A Design features	• Participants who are randomised into Part A can be enrolled in another part of the study if they still fulfil all eligibility criteria (which means that participants having received LPS challenge in Part A will not be eligible to participate in another part of the study). • In the Part A dose escalation phase (treatment periods 1-3), there will be two interlocking cohorts (Cohorts 1 and 2) each with up to 9 healthy participants. Each participant will receive a maximum of 2 single ascending oral doses of GSK3358699 and 1 placebo dose. • At each dose level, GSK3358699 and placebo will be administered in a 2:1 ratio, within each period, according to the randomisation schedule, in a blinded manner. Up to a maximum of 6 dose levels will be studied in total in Part A. Participants who are enrolled in the dose escalation treatment Periods of Part A may choose to only take part in the dose escalation treatment Periods 1-3, or may choose to also take part in the challenge treatment period (Period 4). If a participant chooses to participate in the dose escalation treatment Periods 1-3 only, or does not (at screening) meet the eligibility criteria specific to challenges (treatment Period 4), a new participant

Part A: Single Ascending Doses and LPS / GM-CSF challenges	
	will be recruited for treatment Period 4 only and will be regarded as a replacement participant. If a subject prematurely discontinues the study during Part A, additional replacement participants will be recruited and assigned to the same treatment sequence, starting from the next planned dosing Period following the premature discontinuation. • Staggering of the first two participants (sentinel dosing) will be implemented in each cohort in each treatment period for this single dose phase. No participant will be a sentinel participant more than once. On Day 1, one of the two participants will receive the active dose and the other will receive placebo. Assuming adequate safety from these two participants over the first 48 hrs post-dose, the remaining participants in the cohort can then be dosed. • Data, and hence dose level, will be reviewed between each period. There will be a minimum 14 days between the start of dosing (i.e. dosing of sentinel participants) in Cohort 1 and Cohort 2 in each treatment period. • The decision to proceed to the next dose level of GSK3358699 will be made at a Dose Escalation Committee (DEC) meeting • Upon conclusion of the dose escalation phase of Part A, an additional dosing period (treatment period 4) will be included. Participants in both cohorts will attend the clinic for outpatient visits, on Day -10 (± 3 days) to have control blisters induced on the forearm (0.2% cantharidin), and will have a blister sample taken at a timepoint between approximately 48hrs post-blister induction. • Participants in Cohort 1 will be administered an IV *in vivo* LPS challenge at a dose of 0.75 ng/kg following treatment with GSK3358699 or placebo and will then have blisters induced on the forearm (0.2% cantharidin) approximately 20 minutes after the challenge. The final selection of LPS dose will take into account all available pre-clinical and clinical safety and PD data at the time of study initiation. • Participants in Cohort 2 will be administered 60 μg/m^2 *in vivo* GM-CSF challenge as an IV infusion following treatment with GSK3358699 or placebo and will then have blisters induced on the forearm (using 0.2% cantharidin) approximately 20 minutes after the end of the GM-CSF infusion. • Of the nine participants within each cohort, six will receive GSK3358699 and three will receive placebo in treatment period 4, as per the randomisation schedule.
Part A Time & Events	• Refer to Appendix 1: Schedule of Activities

Part A: Single Ascending Doses and LPS / GM-CSF challenges

Part A Treatment sequences

- Illustration of actual treatments after dose escalation in Part A.

		Period 1		Period 2		Period 3	
Cohort 1	N=3	P		10mg		40mg	
	N=3	1mg		P		40mg	
	N=3	1mg		10mg		P	
Cohort 2	N=3		P		20mg		30mg
	N=3		3mg		P		30mg
	N=3		3mg		20mg		P

P= Placebo; 1-40mg = GSK3358699

- The GSK3358699 dose for the challenge agent treatment Period 4 will be confirmed following completion of the dose escalation treatment periods 1-3.
- The GSK3358699 dose for Part B, and the first cohort in Part C will be confirmed by the DEC following completion of the dose escalation and challenge treatment periods in Part A. Doses for subsequent cohorts in Part C will be confirmed following completion of the previous Part C cohort at the prior dose level.
- Within each cohort, participants will be assigned to one of six dosing sequences for the dose escalation phase, where participants will be randomised to:

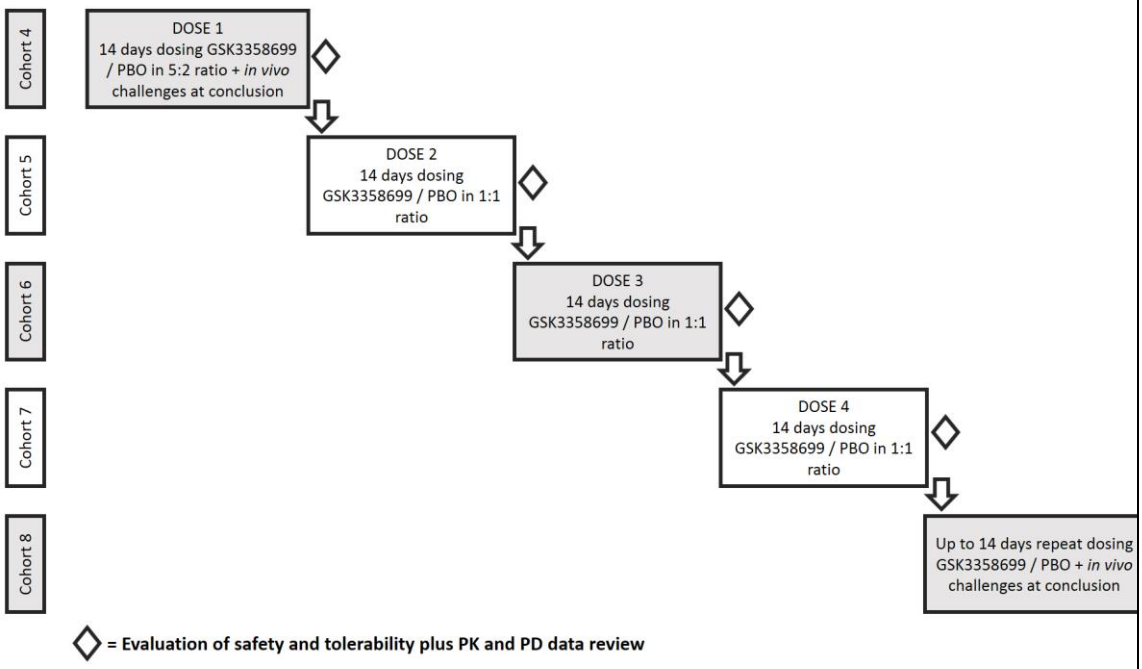
	Cohort 1	**Cohort 2**
Sequence	PCER APER ACPR PCEP APEP ACPP	PDFR BPFR BDPR PDFP BPFP BDPP

Where the treatment codes are as follows:

Treatment code	**Treatment Description**
A	1 mg GSK3358699 SD
B	3 mg GSK3358699 SD
C	10 mg GSK3358699 SD
D	20 mg GSK3358699 SD
E	40 mg GSK3358699 SD
F	30 mg GSK3358699 SD
P	Placebo SD
R	25 mg GSK3358699 SD

- Treatments E, F and R in the table above contain the description of the actual doses following DEC decisions, not the dose descriptions as given by RandAll (see Section 5.2).

Part A: Single Ascending Doses and LPS / GM-CSF challenges	
	• Of the nine participants within each Cohort, six will then receive GSK3358699 and three will receive placebo in treatment Period 4, as per the randomisation schedule.

Part C: Multiple Ascending Doses and LPS or GM-CSF challenge with cantharidin-induced blisters	
	
Part C Design features	• Participants who are randomised into Part C can be enrolled in Part B of the study, as well as be enrolled in a later cohort of Part C, if they still fulfil all eligibility criteria (which means that participants having received LPS challenge in Part A or Part C cohort 4 will not be eligible to participate in another cohort of the study). • Will consist of five cohorts of healthy participants: 14 participants in Cohort 4, 18 in each of Cohorts 5-7, 20 in Cohort 8. Note: Due to the early termination of the study subjects were only dosed in Cohorts 4 and 5. • Cohorts 5-7 will be dosed sequentially (i.e., Cohort 6 starts after dosing in Cohort 5 is completed). The decision to proceed to the next cohort and the associated dose level of GSK3358699 will be made at a DEC meeting. • Each cohort will take part in one repeat dose treatment period with 14 days of once-daily dosing. • In Cohort 4, participants will be randomised in a 5:2 ratio to receive either GSK3358699 or placebo, according to the randomisation schedule, once daily from Day 1 to Day 14 inclusive.

<table>
<tr><th colspan="2">Part C: Multiple Ascending Doses and LPS or GM-CSF challenge with cantharidin-induced blisters</th></tr>
<tr><td></td><td>• In Cohort 5-8, participants will be randomised in a 1:1 ratio to receive either GSK3358699 or placebo, according to the randomisation schedule, once daily from Day 1 to Day 14 inclusive.
• On Day 14 of Cohorts 4 and 8, an IV in vivo LPS challenge at a dose of 0.75 ng/kg or a 60 μg/m^2 GM-CSF challenge as an IV infusion will be administered, followed by blister induction.
• LPS / GM-CSF administration may be performed at low systemic concentrations of GSK3358699 when intracellular concentrations of the acid GSK3206944 are high; The decision on the timepoint for administration will be based on emerging data and will be no more than 24 h after dosing with GSK3358699 or placebo on Day 14.
• In Cohort 4, of the 14 randomised participants, 7 will receive LPS challenge and 7 GM-CSF challenge. Of the 7 participants receiving each challenge, 5 will be randomised to receive GSK3358699 and 2 to receive placebo at the start of the cohort.
• In Cohort 8, of the 20 randomised participants, 10 will receive LPS challenge and 10 GM-CSF challenge. Of the 10 participants receiving each challenge, it is planned that 5 will be randomised to receive GSK3358699 and 5 to receive placebo.</td></tr>
<tr><td>Part C Time & Events</td><td>• Refer to Appendix 1: Schedule of Activities</td></tr>
<tr><td>Part C Treatment Sequences</td><td>• Within each cohort participants will be assigned to either GSK3358699 or placebo in a 5:2 ratio (Cohort 4) or a 1:1 ratio (Cohorts 5-8). The treatments will be determined following the completion of Part A. The treatment codes will be:
<table>
<tr><th>Treatment code</th><th>Treatment Description</th></tr>
<tr><td>I</td><td>10 mg GSK3358699 RD</td></tr>
<tr><td>J</td><td>10 mg GSK3358699 RD</td></tr>
<tr><td>P</td><td>Placebo</td></tr>
</table></td></tr>
</table>

2.4. Statistical Analyses

The primary objective is to determine the safety and tolerability of single and repeat oral doses of up to 14 days with GSK3358699 in healthy participants.

There are no formal hypotheses being tested in the study.

An estimation approach will be used to quantify the single dose PK for each dose level studied and also to assess PK parameters following 14 days repeat dosing relative to single dosing.

3. PLANNED ANALYSES

3.1. Final Analyses

The final planned analyses (Parts A, B and C) will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol (Section 5.3 of the protocol): The end of the study is defined as the date of the last visit (including follow-up) of the last participant in the study (Parts A, B and Part C).

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 randomisation codes have been met.

4. Randomisation codes have been distributed according to RandAll NG procedures.

Due to the early termination of the study, the planned exploratory analysis will not be included in the main SAC delivery. Exploratory analysis will be performed separately in cases where it is deemed clinically or scientifically relevant. The study was terminated prior to any subjects being dosed with study treatment in Part B and therefore only minimal listings of screening data will be produced for this part.

4. ANALYSIS POPULATIONS

Population	Description	Outputs
Enrolled	• All participants who sign the ICF	• Study Population (specific only)
Screened	• All participants who were screened for eligibility	• Study Population (specific only)
Safety	• All screened participants who received at least one dose of study treatment. • This population will be based on the actual treatment the participant received.	• Study Population (all others) • Safety • PD
PK	• All participants in the Safety population who receive an active dose and for whom a PK sample was obtained and analysed. • This population will be based on the actual treatment the participant received. Note: Non-quantifiable [NQ] values will be considered as non-missing values for the purposes of deriving the PK population.	• PK

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.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.

- This dataset will be the basis for the listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This output 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. General

Separate outputs will be generated for each of Parts A, B and C. The presence of participants taking part in multiple parts/cohorts of the study will be appropriately notified in the relevant Safety outputs.

5.2. Study Treatment Display Descriptors

In the Tables, Listings and Figures (TLF), treatment should be presented with placebo first, then in order of increasing dose within each part.

Part A: Treatment group descriptions				
RandAll NG		**Data displays for reporting**		
Code	**RandAll description**	**Table/Figure Label**	**Listing Label**	**Order in TLF**
A	1 mg GSK3358699 SD	1 mg SD	1 mg SD – A	2
B	3 mg GSK3358699 SD	3 mg SD	3 mg SD – B	3
C	10 mg GSK3358699 SD	10 mg SD	10 mg SD – C	4
D	20 mg GSK3358699 SD	20 mg SD	20 mg SD – D	5
E	35 mg GSK3358699 SD	40 mg SD	40 mg SD – E	8
F	45 mg GSK3358699 SD	30 mg SD	30 mg SD – F	7
R	Dose X GSK3358699 SD	25 mg SD	25 mg SD – R	6
P	Placebo SD	Placebo SD	Placebo SD – P	1
Note: doses in RandAll descriptions and display descriptions differ for treatments E, F, R due to DEC decisions.				

Part C: Treatment group descriptions				
RandAll NG		**Data displays for reporting**		
Code	**Description**	**Table/Figure Label**	**Listing Label**	**Order in TLF**
I	Dose 1 GSK3358699 RD	10 mg RD	10 mg RD - I	2
J	Dose 2 GSK3358699 RD	10 mg RD	10 mg RD - I	2
Q	Placebo RD	Placebo RD	Placebo RD - Q	1
Note: the same dose level was administered in both Cohorts 4 and 5 due to the early termination of Cohort 4. Subjects in the active treatment group from both cohorts will be summarised and listed under the same treatment label.				

5.3. Baseline Definitions

5.3.1. Part A single dose (cross-over)

- Baseline definitions are applied to each period.
  - The baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits unless otherwise stated below: For ECGs and Vitals, baseline is defined as the mean of triplicate measurement at the latest pre-dose assessment.

  - For PD S4 assay, MCP-1, IL-6 and TNF, baseline is defined as an average of the day -1 1pm and day 1 pre-dose samples.
- If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.
- Replicate assessments at a timepoint will be averaged, and the mean value will be used.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3.2. Part C repeat dose (parallel)

- The baseline value will be the latest assessment prior to any dosing with a non-missing value, including those from unscheduled visits unless otherwise stated below:
  - For ECGs and Vitals, baseline is defined as the mean of triplicate measurement at the latest pre-dose assessment.

- For PD S4 assay, MCP-1, IL-6 and TNF, baseline is defined as an average of the Day -1 1pm and Day 1 pre-dose samples. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.
  - Replicate assessments at a timepoint will be averaged, and the mean value will be used.

- Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.4. Re-enrolled Participants

The protocol allows participants to take part in more than one cohort in this study. Instances where this occurred were as follows:

Subject Number			
Cohort 1	Cohort 2	Cohort 4	Cohort 5
PPD		PPD	
	PPD		PPD
		PPD	PPD

Participants who take part in more than one cohort are to be considered distinct participants for the purposes of the reporting of all the data in this study. However relevant displays will be footnoted.

5.5. 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
13.2	Appendix 2: Assessment Windows
13.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
13.4	Appendix 4: Data Display Standards & Handling Conventions
13.5	Appendix 5: Derived and Transformed Data
13.6	Appendix 6: Reporting Standards for Missing Data
13.7	Appendix 7: Values of Potential Clinical Importance and Normal Ranges

6. STUDY POPULATION ANALYSES

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

Study population analyses including analyses of participant's disposition, protocol deviations, demographic characteristics, prior and concomitant medications, and exposure will be based on GSK Core Data Standards.

Details of the planned displays are presented in Appendix 9: List of Data Displays.

7. EFFICACY ANALYSES

There are no efficacy analyses to be included in this FTIH study.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

The definition of an AE is detailed in Appendix 4 of the protocol.

Analyses of AEs will include all events, classified as in Section 13.3.

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards.

Details of the planned displays are presented in Appendix 9: List of Data Displays.

8.2. Clinical Laboratory Analyses

Laboratory evaluations will be based on GSK Core Data Standards and will include:

- Hematology laboratory tests
- Chemistry laboratory tests
- Urinalysis
- Liver function tests
- Other screening tests

Clinical laboratory analyses will include all assessments post-baseline. Unscheduled visits will not be included in summary tables and figures, but will be included in listings – see Section 13.4.2.

Details of the planned displays are presented in Appendix 9: List of Data Displays.

The laboratory assessments for each category are displayed below (Table 6 of the protocol):

Laboratory Assessments	**Parameters**			
Haematology				
Clotting parameters: APTT PT times Fibrinogen	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]				
CRP	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
Albumin	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
Glucose (fasting during Part C[2])	Calcium	Alkaline phosphatase	Cholesterol[2,3]	Low Density Lipoprotein[2,3]
High Density Lipoprotein[2,3]	Triglycerides[2,3]	Gamma-glutamyl	Creatine kinase (CK)[4]	

Laboratory Assessments	Parameters			
		transferase (GGT)[4]		
Routine Urinalysis				
• Microscopic examination (if blood or protein is abnormal)				

1. NOTES:
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 of the protocol. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. In Part C at certain time points as per the SoA lipids and glucose samples are required to be taken fasted.
3. Screening samples are required to be taken fasted.
4. To be analysed at screening, Day-1 and follow up only
   1.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results will be based on GSK Core Data Standards, unless otherwise specified.

The non-laboratory safety test results include:

- ECGs
- Vital signs
- Telemetry and Holter monitoring

Details of the planned displays are presented in Appendix 9: List of Data Displays.

9. PHARMACOKINETIC ANALYSES

The PK analyses described below will be carried out for GSK3358699 and GSK3206944 (acid metabolite) if the latter is quantifiable.

9.1. Endpoint / Variables

9.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Standards for Pharmacokinetic) to generate the plasma GSK3358699 and GSK3206944 concentration-time data, and the intracellular GSK3206944 concentration-time data, after single and repeat doses (Parts A and C), under fasted conditions.

In addition to the intracellular GSK3206944 raw concentration which is measured as ng per mL in reagent, the molar concentration within the monocytes will also be derived (see Appendix 5, Section 13.5.3).

9.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times.

Pharmacokinetic parameters listed below will be determined from the plasma GSK3358699 and GSK3206944 concentration-time data for Parts A and C, as data permits. Additional parameters may be included as required.

Parameter	Parameter description
AUC(0-t)	• Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) • Calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	• Area under the concentration-time curve extrapolated to infinity • Calculated as: AUC(0-∞) = AUC(0-t) + C(t) / lambda_z • This parameter is calculated for Part A only
AUC(0-24)	• Area under the concentration-time curve from time zero to 24 hours post-dose • Using the same method as for AUC(0-t)
AUC(0-tau)	• Area under the concentration-time curve from time zero to the end of the dosing period (dosing interval of duration tau)
Cmax	• Maximum observed concentration • Determined directly from the concentration-time data.
tmax	• Time to reach Cmax • Determined directly from the concentration-time data.
t1/2(terminal)	• Terminal half-life [The time it takes for the concentration levels to fall to 50% of their value in the terminal phase]. • Calculated as: t1/2 = ln(2) / lambda_z • Lambda_z is the terminal phase rate constant estimated by linear regression analysis of the log transformed concentration-time data
t1/2(initial)	• Actual initial half-life [The time it takes for the concentration levels to fall to 50% of their value in the initial phase]. • Calculated as: t1/2 = ln(2) / lambda_ini • Lambda_ini is the initial phase rate constant estimated by linear regression analysis of the log transformed concentration-time data

9.1.3. Summary Measure

In addition to the parameters mentioned above, the following will also be calculated:

Part C (repeat dose)	
R_0	• Accumulation between 1 single dose (Day 1) and repeat dose (Day 14) • Calculated as R0 =AUC(0-tau) Day 14/AUC(0-tau) Day 1
Rs	• Steady state ratio (time invariance kinetics) • Calculated as Rs=AUC(0-tau) Day 14/AUC(0-inf) Day 1

9.1.4. Population of Interest

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

9.1.5. Statistical Analyses / Methods

Details of the planned displays are presented in Appendix 9: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9.1.5.1. Dose proportionality (Part A)

Dose proportionality will be assessed for GSK3358699 by visual inspection of:

- Part A (single dose - fasted state): dose normalised AUC(0-∞) [or if not available AUC(0-t)] and Cmax values versus dose.

If data permits, dose proportionality may also be assessed for GSK3358699 using the power model described below.

Dose proportionality (Parts A and C)
Endpoints
• Part A (single dose - fasted state): AUC(0-t), AUC(0-∞) and Cmax
Model specification
• Power model (log-log linear model): $$y = \alpha \times dose^{\beta} \iff \log_e(y) = \log_e(\alpha) + \beta \times \log_e(dose)$$ Where ○ y = endpoint of interest ○ dose = actual dose received under fasted condition ○ β = parameter associated to dose (slope) ○ α = participant-specific random effect (intercept) • Terms fitted in the power model: ○ Response: log transformation of the endpoint of interest $\log_e(y)$

○ Fixed continuous covariates: $\log_e(dose)$ ○ Random: participant • 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 on the random effects terms (SAS: G matrix, random statement) will be used.
Model checking & diagnostics
• Normality 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
Table of the estimated slopes and 90% CI (slope close to 1 implies dose proportionality). The following will be derived: • Fold-increase for doubling dose: 2^{β}, where β is the slope • 90% CI for fold-increase: $(2^{b_l}, 2^{b_u})$, where (b_l, b_u) is the 90% CI for the slope

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

10.1. Primary Pharmacodynamic and Biomarker Analyses

The PD parameters collected during the study will be listed for each participant and treatment and summarised descriptively by treatment.

10.1.1. Endpoint / Variables

See Appendix 5: Derived and Transformed Data for the full list of biomarkers and the related displays planned for final SAC.

10.1.2. Summary Measure

Continuous summaries of absolute values, percentage inhibition and predicted percentage inhibition will be presented for each biomarker detailed in Appendix 5, Section 13.5.4.

10.1.3. Population of Interest

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

10.1.4. Statistical Analyses / Methods

Details of the planned displays are presented in Appendix 9: 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.

11. EXPLORATORY ANALYSES

Exploratory analysis detailed in the protocol will be covered outside of this RAP and reported separately from the main study reporting.

12. REFERENCES

GlaxoSmithKline Document Number 2017N332348_05. Study ID 207546: A randomised, double-blind (sponsor open), placebo-controlled, three part study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single (in both fed and fasted states) or repeat doses of GSK3358699 in healthy male participants. 11-DEC-2018.

13. APPENDICES

13.1. Appendix 1: Schedule of Activities

13.1.1. Part A General Schedule of Activities

Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period 1-3												Treatment Period 4	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
		Day -1	Day 1										Day 2	Day 3			
			Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6 h	8 h	12 h	24 h	48 h			
General																	
Informed consent	X														See separate Period 4 Schedule of Activities			
Inclusion and exclusion criteria	X	X															Day -1 assessment is to recheck eligibility against medical conditions, prior therapy etc, but not against Day -1 clinical chemistry and haematology results (see Section 9.4.7 of Protocol GlaxoSmithKline Document Number 2017N332348_05).
Demography	X																
Medical/medication/drug/ alcohol history	X	X															Includes substance usage and family history of premature cardiovascular (CV) disease and current medical conditions.
Admission to unit for in-patient stay		X															

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period 1-3													Treatment Period 4	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
		Day -1	Day 1										Day 2	Day 3				
			Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6 h	8 h	12 h	24 h	48 h				The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced i.e. treatment period 4
Discharge from Unit following in-patient stay														X				
Outpatient visit	X															X	X	
Safety Assessments including laboratory tests																		
Full Physical Exam	X														See separate Period 4 Schedule of Activities			
Brief Physical Exam		X												X		X		
Vital Signs	X	X	X					X	X		X	X	X	X		X	X	Blood pressure (BP), heart rate (HR), temperature, respiratory rate. See Section 9.4.4 of Protocol GlaxoSmithKline Document Number 2017N332348_05 for details on triplicate and single measurement timepoints.
12-Lead ECGs	X	X	X					X	X		X	X	X	X		X		12 Lead ECGs will be performed in triplicate at screening, Day-1, Day 1 pre-dose, Day 2 and Day 3. Single ECGs will be performed at other time points and if any cardiac symptoms are experienced. ECGs to be performed prior to blood draws and dosing where these fall at the same nominal time.

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period 1-3												Treatment Period 4	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
		Day -1	Day 1										Day 2	Day 3			
			Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6 h	8 h	12 h	24 h	48 h				The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced i.e. treatment period 4
Telemetry			<==========											======>				from 1 h pre-dose to 24 h post-dose
Holter monitoring (24 hours)	X																	If a participant is rescreened the Holter will not need to be repeated.
HIV, Hep B, Hep C	X																	
Haematology	X	X									X		X	X		X		Fasted screening samples. 24 and 48 hour samples will be taken prior to participants receiving breakfast
Coagulation	X										X		X	X		X		Fasted screening samples. 24 and 48 hour samples will be taken prior to participants receiving breakfast
Clinical Chemistry	X	X									X		X	X		X		Fasted screening samples. 24 and 48 hour samples will be taken prior to participants
Urinalysis	X	X									X		X	X		X		Fasted screening samples. 24 and 48 hour samples will be taken prior to participants receiving breakfast
Drug / Alcohol Test	X	X																
Urine Cotinine	X	X																
Visual forearm check (cosmetic assessment or blister healing where appropriate)	X	X														X	X	Visual forearm checks are only required if participant is scheduled to take part in treatment period 4. Details of checks:

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period 1-3												Treatment Period 4	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
		Day -1	Day 1										Day 2	Day 3			
			Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6 h	8 h	12 h	24 h	48 h			The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced i.e. treatment period 4
																	• Screening check prior to first treatment period (cosmetic assessment) • Day -1 check in treatment Period 3 only. Between Day -1 and Day 2 (ie 48 hour window) (cosmetic assessment) • Period 4 (cosmetic assessment and blister healing). For further detail on time points in Period 4 see Section 13.1.1.1. • Follow-up visits 1 and 2 (blister healing)
AE / SAE review	SAEs collected from signing of informed consent form until the final follow up visit; AEs collected continuously from time of first dose until the final follow up visit																
Concomitant Medication Review			Monitored from first dose until the end of the final treatment Period														

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period 1-3													Treatment Period 4	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
		Day -1	Day 1										Day 2	Day 3				The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced i.e. treatment period 4
			Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6 h	8 h	12 h	24 h	48 h				
Treatment Administration																		
Study Drug / Placebo Administration				X											See Period 4 SoA			
Pharmacokinetics, Pharmacodynamics and Genetics Samples																		
Blood sampling for systemic PK **[S1]** and **[S2]**			X		X	X	X	X	X	X	X	X	X	X	See separate Period 4 Schedule of Activities			
Blood sampling for intracellular PK **[S3]**							X		X		X		X	X				
Blood sample for ex vivo PD assay **[S4]**		X	X				X		X		X	X	X	X				Six samples (3 LPS and 3 null) are required on Day -1: to be taken (LPS and null) at approximately 13:00, 17:00 and 20:00. Day 1: Two pre-dose samples (LPS and null) to be taken at approximately 08:00.
Blood sample for circulating proteins **[E1a]**			X					X	X		X		X					
Blood sample for gene panel **[E1b]**			X					X	X		X		X					
Blood sample for companion diagnostic development		X																Sample to be taken on Day -1 in treatment Period 1 only.

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period 1-3												Treatment Period 4	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
		Day -1	Day 1										Day 2	Day 3			
			Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6 h	8 h	12 h	24 h	48 h			The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced i.e. treatment period 4
Genetics sample for *CES* genotyping and optional genetic research **[E5]**		X															Sample to be taken on Day -1 in treatment Period 1 only.
Urine sample for metabolite analysis **[E4]**			X	<==========										====>			Pre-dose sample, immediately prior to dosing participants will be instructed to void their bladder into a collection container. Following dosing participants will be instructed to collect all urine voided for a 0-24 hour collection.

13.1.1.1. Part A Period 4 Schedule of Activities

Procedure	Treatment Period 4																Notes
	Day -10 (±3	24-48h following Day -10 visit	Day -1	Day 1											Day 2	Day 3	If participants only take part in treatment Period 4 they will undergo screening assessments prior to this treatment Period as detailed in Section 13.1.1.
				Pre-dose	0 h	15 mins	30 mins	1 h	2 h	3 h	4 h	6h	8 h	12 h	24 h	48 h	
General																	
Admission to unit for in-patient stay			X														
Discharge from Unit following in-patient stay																X	
Outpatient visit	X	X															For baseline blister induction and sampling; see Section 13.1.1.2 and Section 13.1.1.3. The baseline blister samples collected will be repeated if > 4 months elapses between the baseline blister and the challenge treatment Period (eg if a reserve in the study is not dosed and is subsequently rescreened for a later cohort).
Safety Assessments including laboratory tests																	
Brief Physical Exam			X													X	
Vital signs			X	X	See Section 13.1.1.2 and Section 13.1.1.3 for vital signs measurements in relation to challenges												BP, HR, temperature, respiratory rate.
Body weight			X														Body weight will be measured on Day -1 to calculate doses for challenges.
12-Lead ECGs			X	X					X		X		X	X	X	X	12 lead ECGs will be performed in triplicate at Day -1, pre-dose Day 1, Day 2 and Day 3. Single ECGs will

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Procedure	Treatment Period 4															Notes
	Day -10 (±3	24-48h following Day -10 visit	Day -1	Day 1											Day 2	Day 3	If participants only take part in treatment Period 4 they will undergo screening assessments prior to this treatment Period as detailed in Section 13.1.1.
				Pre-dose	0 h	15 mins	30 mins	1 h	2 h	3 h	4 h	6h	8 h	12 h	24 h	48 h	
																	be performed at other time points and if any cardiac symptoms are experienced. ECGs to be performed prior to any blood draws or dosing scheduled for the same nominal time point.
Telemetry				<==========>													From 1 h pre-dose to 24 h post-dose. For participants receiving the LPS-challenge, telemetry must be performed for a minimum of 12 hours post-LPS or until their telemetry shows no clinically significant findings for 4 hours (whichever is longer).
Haematology			X									X			X	X	24 and 48 hour samples will be taken prior to participants receiving breakfast
Coagulation												X			X	X	24 and 48 hour samples will be taken prior to participants receiving breakfast
Clinical Chemistry			X									X			X	X	24 and 48 hour samples will be taken prior to participants receiving breakfast
Urinalysis			X									X			X	X	24 and 48 hour samples will be taken prior to participants receiving breakfast
Drug / Alcohol Test			X														
Urine Cotinine			X														
Visual forearm check (including cosmetic assessment)	X		X	See Section 13.1.1.2 and Section 13.1.1.3 for visual forearm checks in relation to challenges													
AE / SAE review			SAEs collected from signing of informed consent form; AEs collected continuously from time of first dose														

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Procedure	Treatment Period 4																Notes
	Day -10 (±3	24-48h following Day -10 visit	Day -1	Day 1											Day 2	Day 3	If participants only take part in treatment Period 4 they will undergo screening assessments prior to this treatment Period as detailed in Section 13.1.1.
				Pre-dose	0 h	15 mins	30 mins	1 h	2 h	3 h	4 h	6h	8 h	12 h	24 h	48 h	
Concomitant Medication Review				Monitored from first dose until the end of the final treatment Period													
Treatment / agent administration and PK sampling																	
Study Drug / Placebo Administration					X												
In vivo LPS Challenge							<========= =>										LPS administration to be performed at GSK3358699 systemic C_{max}; anticipated to be between 0.5-2hrs post GSK3358699 dose.
OR in vivo GM-CSF Challenge							<========== =>										GM-CSF administration to be performed at GSK3358699 systemic C_{max}; GM-CSF will be administered as an infusion over 2 hours and the start of the infusion is anticipated to be between 0.5-2hrs post GSK3358699 dose.
Blood sampling for systemic PK **[S1]** and **[S2]**				X		X	X	X	X		X	X	X	X	X	X	
Blood sampling for intracellular PK **[S3]**											X				X		
Cantharidin application and PD sampling	See Section 13.1.1.2 and Section 13.1.1.3																

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13.1.1.2. Part A Period 4 Detailed SoA for LPS Challenge and Biomarker Sampling

Procedure	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Day -1	Day 1 - pre-dose and all post-dose times below are in relation to the administration time of LPS **not** GSK3358699 administration										Day 2	Day 3	Notes
				Pre-dose	0 h	20 mins	1 h	2 h	3h	4 h	6h	8 h	12 h	24 h	48 h	
LPS challenge administration					X											See Section 13.1.1.1 for timing of LPS administration in relation to GSK3358699 / placebo dose.
Visual forearm check (including blister healing and cosmetic assessment)	X		X	X										X	X	Pre-cantharidin check to be within three hours prior to cantharidin application.
Cantharidin application	X					X										Day – 10: to be applied in the morning. Day 1: to be applied 20 minutes post LPS challenge.
Intravenous hydration with normal Saline at a rate of 250 mL / hr				<==========									==>			From 4 hours prior to LPS challenge administration until 8 hours after LPS challenge administration.
Vital Signs			X	X	<==========								===>	X	X	BP, HR, temp, respiratory rate. Pre-dose vital signs to be taken pre-LPS challenge administration then post-LPS challenge as follows: every half hour for the first 4 hours, hourly until 12 hours, then 6- 8 hourly until discharge. Frequency can be increased if symptomatic.
Blood sample for circulating inflammatory biomarkers **[E2a]**				X			X	X		X	X			X	X	
Blood sample for cellular activation markers **[E2b]**				X			X				X			X		
Blood sample for gene panel **[E2d]**				X			X		X		X			X		

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Procedure	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Day -1	Day 1 - pre-dose and all post-dose times below are in relation to the administration time of LPS **not** GSK3358699 administration										Day 2	Day 3	Notes
				Pre-dose	0 h	20 mins	1 h	2 h	3h	4 h	6h	8 h	12 h	24 h	48 h	
Blister sample for biomarkers, blister volume and cell counts **[E3]**		X												X		Sample to be taken approx 24-48 hours post blister induction (time point being defined as part of ongoing enabling study).

13.1.1.3. **Part A Period 4 Detailed SoA for GM-CSF challenge and Biomarker Sampling**

Procedure	Day -10 (± 3 days)	24-48 hours following Day -10	Day -1	Day 1 - pre-dose and all post-dose times below are in relation to the **start time** of the GM-CSF infusion **not** GSK3358699 administration											Day	Day	Notes
				Pre-dose	0 h	1 h	2 h	2.3 h	3 h	4 h	5h	6 h	8 h	12 h	24 h	48 h	
GM-CSF challenge administration					<========== >												See Section 13.1.1.1 for timing of the start of the GM-CSF infusion in relation to GSK3358699 / placebo dose. GM-CSF will be administered as an infusion over 2 hours.
Visual forearm check (including blister healing and cosmetic assessment)	X		X			X									X	X	Pre-cantharidin check to be within three hours prior to cantharidin application.
Cantharidin application	X							X									Day – 10: to be applied in the morning. Day 1: 2 hours and 20 minutes after the start of the GM-CSF challenge.
Vital Signs			X	X	<========== =====>										X	X	BP, HR, temp, respiratory rate. Pre-dose vital signs to be taken pre-GM-CSF challenge administration then post-GM-CSF challenge as follows: every half hour for the first 4 hours,

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Procedure	Day -10 (± 3 days)	24-48 hours following Day -10	Day -1	Day 1 - pre-dose and all post-dose times below are in relation to the **start time** of the GM-CSF infusion **not** GSK3358699 administration											Day 24 h	Day 48 h	Notes
				Pre-dose	0 h	1 h	2 h	2.3 h	3 h	4 h	5h	6 h	8 h	12 h			
																	hourly until 8 hours, then 6- 8 hourly until discharge. Frequency can be increased if symptomatic.
Blood sample for circulating inflammatory biomarkers **[E2a]**				X			X		X	X	X	X	X		X	X	
Blood sample for cellular activation markers **[E2b]**				X			X		X		X		X		X		
Blood sample for gene panel **[E2d]**				X					X		X		X		X		
Blister sample for biomarkers, blister volume and cell counts **[E3]**		X													X		Sample to be taken approx 24-48 hours post blister induction (time point being defined as part of ongoing enabling study).

13.1.2. Part C General Schedule of Activities Cohorts 5-7 (no challenges)

Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period																	Follow-up 1 (7-14 days post-last dose)	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16		
General																				
Informed consent	X																			
Inclusion and exclusion criteria	X	X																		Day -1 assessment is to recheck eligibility against medical conditions, prior therapy etc, but not against Day -1 clinical chemistry and haematology results (see Section 9.4.7 of Protocol GlaxoSmithKline Document Number 2017N332348_05).
Demography	X																			
Medical/medication/ drug/alcohol history	X	X																		Includes substance usage and family history of premature CV disease and current medical conditions.
Admission to unit for in-patient stay		X																		
Discharge from Unit following in-patient stay																		X		
Outpatient visit	X																		X	
Safety Assessments including laboratory tests																				
Full Physical Exam	X																			
Brief Physical Exam		X																X	X	
Vital Signs	X	X	X	X		X				X				X	X	X	X	X	X	BP, HR, temperature, respiratory rate. See Section 13.1.2.1 for time points on Day 13, 14, 15 and 16. Measurements will be performed pre-dose on other dosing days.
12-Lead ECGs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	12 Lead ECGs will be performed in triplicate at screening, Day-1, pre-dose Day 1, Day 4, Day 8, Day 14 and Day 16. Single ECGs will be performed at other time points and if any cardiac symptoms are experienced. ECGs to

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period																	Follow-up 1 (7-14 days post-last dose)	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16		
																				be performed prior to any blood draws or dosing scheduled for the same nominal time point.
Telemetry			X			X				X						X				Continuous cardiac telemetry on each designated day from 1hr pre-dose until 24 h post-dose, and on other days if QTcF >450msec.
Holter monitoring (24 hours)	X																			If a participant is rescreened the Holter will not need to be repeated.
HIV, Hep B, Hep C	X																			
Haematology	X	X	X	X		X				X				X	X	X	X	X	X	Fasted screening samples. Sample to be taken pre-dose on Day 1, 2, 4, 8, 12 and 13. See Section 13.1.2.1 for haematology time points on Day 14, 15 and 16. Follow-up visit samples do not require fasting.
Coagulation	X	X				X				X						X			X	Fasted screening samples. Sample to be taken pre-dose on Day -1, 4 and 8. See Section 13.1.2.1 for further details of Day 14 sample timings. Follow-up visit samples do not require fasting
Fasting lipids and glucose	X	X				X				X						X				Fasted screening samples. Sample to be taken pre-dose on each day. Both fasting lipids and glucose will be tested from same sample. Follow-up visit samples do not require fasting
Clinical Chemistry	X	X	X	X		X				X				X	X		X	X	X	Fasted screening samples. Sample to be taken pre-dose on each day. Follow-up visit samples do not require fasting. GGT and CK to be included at screening, Day-1 and follow up only
Urinalysis	X	X	X	X		X				X				X				X	X	Fasted screening samples. Sample to be taken pre-dose on each day. Follow-up visit samples do not require fasting
Drug / Alcohol Test	X	X																		Ad-hoc testing to be performed in the event of any cardiac arrhythmias, as close as possible to the time of occurrence
Urine Cotinine	X	X																		
AE / SAE review	SAEs collected from signing of informed consent form until the final follow up visit; AEs collected continuously from time of first dose until the final follow up visit.																			

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period																	Follow-up 1 (7-14 days post-last dose)	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16		
Concomitant Medication Review			Monitored continuously from first dose until the end of the treatment period																	
Treatment / agent administration																				
Study Drug Administration			X	X	X	X	X	X	X	X	X	X	X	X	X	X				Once-daily in the morning on Days 1-14 inclusive.
Pharmacokinetics, Pharmacodynamics and Genetics Sample																				
Blood sampling for systemic PK **[S1]** and **[S2]**			X	X		X				X				X		X	X	X		On Day 1 samples will be taken at pre-dose, 15mins, 30mins, 1h, 2h, 4h, 6h, 8h, 12h and 24h post-dose, Pre-dose samples Days 4, 8 and 12. See Section 13.1.2.1 for Day 14, 15 and 16 sample timings. Ad-hoc sample to be taken in the event of any cardiac arrhythmias, as close as possible to the time of occurrence
Blood sampling for intracellular PK **[S3]**			X			X				X				X		X	X	X		On Day 1 samples will be taken at 1h, 4h and 8h post-dose. Pre-dose samples Days 4, 8 and 12. See Section 13.1.2.1 for Day 14, 15 and 16 sample timings.
Blood sample for ex vivo PD assay **[S4]**		X	X	X		X				X				X		X	X	X		Day -1 samples to be taken at approximately 13:00. Day 1 and Day 14 pre-dose samples to be taken at approximately 08:00. Day 1 post-dose samples to be taken at 1h, 4h and 8h post-dose. Samples to be taken pre-dose Days 2, 4, 8 and 12. See Section 2.3.1 of protocol for Cohorts 5-7 and Section 2.4.1 of protocol for Cohort 8, for Day 14, 15 and 16 sample timings . All sample timepoints pre- and post-dose require 1 LPS and 1 LPS + GSK3358699 sample.
Blood sample for circulating proteins **[E1a]**			X	X		X				X				X		X	X			On Day 1 samples will be taken at pre-dose, 2h, 4h and 8h post-dose. Samples to be taken pre-dose Day 2, 4, 8 and 12. See Section 13.1.2.1 for Day 14 and 15 sample timings.
Blood sample for gene panel **[E1b]**			X			X				X				X		X	X			On Day 1 samples will be taken at pre-dose, 2h and 4h post-dose. Samples to be taken pre-dose Days 4, 8 and 12. See Section 13.1.2.1 for Day 14 and 15 sample timings.

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Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Period																	Follow-up 1 (7-14 days post-last dose)	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16		
Blood sample for cellular activation markers **[E2b]**			X			X				X				X		X				Pre-dose samples Days 1, 4, 8 and 12. See Section 13.1.2.1 for Day 14 sample timings.
Blood sample for potential companion diagnostic development		X																		
Blood sample for *CES* genotyping and optional genetic research **[E5]**		X																		
Urine sample for metabolite analysis **[E4]**			X	X												X	X			A 0-24 urine collection will be made on Day 1 and Day 14. In each case, for the pre-dose sample, immediately prior to dosing participants will be instructed to void their bladder into a collection container. Following dosing participants will be instructed to collect all urine voided for a 0-24 hour collection.

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13.1.2.1. Part C Day 14 Detailed SoA for PK and PD / Biomarker Sampling Cohorts 5-7 (no challenges)

Procedure	Day 13	Day 14.										Day 15	Day 16	Notes
		Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6h	8 h	12 h	24 h	48 h	
Treatment / agent administration and PK sampling														
Study Drug / Placebo Administration			X											
Vital Signs	X	X								X		X	X	
Haematology	X									X		X	X	
Coagulation										X				
Blood sampling for systemic PK **[S1]** and **[S2]**		X		X	X	X	X	X	X	X	X	X	X	Ad-hoc sample to be taken in the event of any cardiac arrhythmias, as close as possible to the time of occurrence
Blood sampling for intracellular PK **[S3]**						X		X		X		X	X	
Blood sample for ex vivo PD assay **[S4]**		X				X		X		X		X	X	
Blood sample for circulating proteins **[E1a]**		X					X	X		X		X		
Blood sample for gene panel **[E1b]**		X					X	X				X		
Blood sample for cellular activation markers **[E2b]**		X						X						

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13.1.3. Part C General Schedule of Activities Cohorts 4 and 8 (with challenges)

Procedure	Screening (up to 45 Days prior to Day 1)	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Treatment Period																Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
				Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16			The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced
General																							
Informed consent	X																						
Inclusion and exclusion criteria	X			X																			Day -1 assessment is to recheck eligibility against medical conditions, prior therapy etc, but not against Day -1 clinical chemistry and haematology results (see Section 9.4.7 of Protocol GlaxoSmithKline Document Number 2017N332348_05).
Demography	X																						
Medical/medication/ drug/alcohol history	X			X																			Includes substance usage and family history of premature CV disease and current medical conditions.
Admission to unit for in-patient stay				X																			
Discharge from Unit following in-patient stay																				X			
Outpatient visit	X	X	X																		X	X	
Safety Assessments including laboratory tests																							
Full Physical Exam	X																						
Brief Physical Exam				X																X	X		
Body Weight	X																X						Body weight will be measured on Day 13 to calculate doses for challenges.
Vital Signs	X			X	X	X		X				X				X	X	X	X	X	X	X	BP, HR, temperature, respiratory rate. See Section 13.1.3.2 and Section 13.1.3.3 for time points on Day 13, 14, 15 and 16. Measurements will be performed pre-dose on other dosing days.

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Procedure	Screening (up to 45 Days prior to Day 1)	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Treatment Period																	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
				Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16			The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced
12-Lead ECGs	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		12 Lead ECGs will be performed in triplicate at screening, Day-1, pre-dose Day 1, Day 4, Day 8, Day 14 and Day 16. Single ECGs will be performed at other time points and if any cardiac symptoms are experienced. ECGs to be performed prior to any blood draws or dosing scheduled for the same nominal time point.
Telemetry					X			X				X						X					Continuous cardiac telemetry on each designated day from 1hr pre-dose until 24 h post-dose, and on other days if QTcF >450msec. For participants receiving the LPS-challenge, the Day 14 telemetry must be performed for a minimum of 12hrs post-LPS or until their telemetry shows no clinically significant findings for 4 hours (whichever is longer).
Holter monitoring (24 hours)	X																						If a participant is rescreened the Holter will not need to be repeated.
HIV, Hep B, Hep C	X																						
Haematology	X			X	X	X		X				X				X	X	X	X	X	X		Fasted screening samples. Sample to be taken pre-dose on Day 1, 2, 4, 8, 12 and 13. See Section 13.1.3.2 and Section 13.1.3.3 for haematology time points on Day 14, 15 and 16. Follow-up visit samples do not require fasting.
Coagulation	X			X				X				X					X	X			X		Fasted screening samples. Sample to be taken pre-dose on Day -1, 4, 8 and 13. See Section 13.1.3.2 for further details of Day 14 sample timings. Day 13 and Day 14 samples are only performed for subjects receiving LPS. Follow-up visit samples do not require fasting
Fasting lipids and glucose	X			X				X				X						X					Fasted screening samples. Sample to be taken pre-dose on each day. Both fasting lipids and glucose will be tested from same sample. Follow-up visit samples do not require fasting

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Procedure	Screening (up to 45 Days prior to Day 1)	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Treatment Period																Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
				Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16			The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced
Clinical Chemistry	X			X	X	X		X				X				X	X		X	X	X		Fasted screening samples. Sample to be taken pre-dose on each day. Follow-up visit samples do not require fasting GGT and CK to be included at screening, Day-1 and follow up only.
Urinalysis	X			X	X	X		X				X				X				X	X		Fasted screening samples. Sample to be taken pre-dose on each day. Follow-up visit samples do not require fasting
Drug / Alcohol Test	X			X																			Ad-hoc testing to be performed in the event of any cardiac arrhythmias, as close as possible to the time of occurrence
Urine Cotinine	X			X																			
Visual forearm check (including blister healing and cosmetic assessment)	X	X		X													X	X	X	X	X	X	Pre-cantharidin check to be within three hours prior to cantharidin application. See Section 13.1.3.2 and Section 13.1.3.3 for further details of timing of forearm checks on Day 13, 14, 15 and 16 in relation to challenges.
AE / SAE review	SAEs collected from signing of informed consent form until the final follow up visit; AEs collected continuously from time of first dose until the final follow up visit.																						
Concomitant Medication Review					Monitored continuously from first dose until the end of the treatment period																		
Treatment / agent administration																							
Study Drug Administration					X	X	X	X	X	X	X	X	X	X	X	X	X	X					Once-daily in the morning on Days 1-14 inclusive.
Cantharidin application		X																X					Day – 10: to be applied in the morning. See Section 13.1.3.2 and Section 13.1.3.3 for further details on Day 14 blister timings.
In vivo LPS or GM-CSF Challenge																		X					See Section 13.1.3.1 for further details.

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Procedure	Screening (up to 45 Days prior to Day 1)	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Treatment Period																Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
				Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16			The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced
Pharmacokinetics, Pharmacodynamics and Genetics Sample																						
Blood sampling for systemic PK **[S1]** and **[S2]**					X	X		X				X				X		X	X	X			On Day 1 samples will be taken at pre-dose, 15mins, 30mins, 1h, 2h, 4h, 6h, 8h, 12h and 24h post-dose, Pre-dose samples Days 4, 8 and 12. See Section 13.1.3.1 for Day 14, 15 and 16 sample timings. Ad-hoc sample to be taken in the event of any cardiac arrhythmias, as close as possible to the time of occurrence
Blood sampling for intracellular PK **[S3]**					X			X				X				X	X	X	X	X			On Day 1 and Day 13 samples will be taken at 1h, 4h and 8h post-dose. Pre-dose samples Days 4, 8 and 12. See Section 13.1.3.1 for Day 14, 15 and 16 sample timings.
Blood sample for ex vivo PD assay **[S4]**				X	X	X		X				X				X	X	X	X				Day -1 samples to be taken at approximately 13:00. Day 1 and Day 14 pre-dose samples to be taken at approximately 08:00. Day 1 post-dose samples to be taken at 1h, 4h and 8h post-dose. Samples to be taken pre-dose Days 2, 4, 8 and 12. See Section 2.3.1 of protocol for Cohorts 5-7 and Section 2.4.1 of protocol for Cohort 8, for Day 14, 15 and 16 sample timings . All sample timepoints pre- and post-dose require 1 LPS and 1 LPS + GSK3358699 sample.
Blood sample for circulating proteins **[E1a]**					X	X		X				X				X		X	X				On Day 1 samples will be taken at pre-dose, 2h, 4h and 8h post-dose. Samples to be taken pre-dose Day 2, 4, 8 and 12. See Section 13.1.3.1 for Day 14 and 15 sample timings.
Blood sample for gene panel **[E1b/E2d]**					X			X				X				X		X	X				On Day 1 samples will be taken at pre-dose, 2h and 4h post-dose. Samples to be taken pre-dose Days 4, 8 and 12. See Section 13.1.3.1, Section 13.1.3.2 and Section 13.1.3.3 for Day 14 and 15 sample timings for E2d.
Blood sample for circulating inflammatory biomarkers **[E2a]**																		X	X	X			See Section 13.1.3.2 and Section 13.1.3.3 for sample timings.

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Procedure	Screening (up to 45 Days prior to Day 1)	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Treatment Period																	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
				Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16			The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced
Blood sample for cellular activation markers **[E2b]**					X			X				X				X		X	X	X			Pre-dose samples Days 1, 4, 8 and 12. See Section 13.1.3.2 and Section 13.1.3.3 for Day 14, 15 and 16 sample timings.
Blister sample for biomarkers, blister volume and cell counts **[E3]**			X																	X			Blisters harvested approx 48 h post cantharidin application See Section 13.1.3.2 and Section 13.1.3.3 for further detail on Day 16 sample timings.
Blood sample for potential companion diagnostic development				X																			
Blood sample for *CES* genotyping and optional genetic research **[E5]**				X																			
Urine sample for metabolite analysis **[E4]**					X	X												X	X				A 0-24 urine collection will be made on Day 1 and Day 14. In each case, for the pre-dose sample, immediately prior to dosing participants will be instructed to void their bladder into a collection container. Following dosing participants will be instructed to collect all urine voided for a 0-24 hour collection.

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13.1.3.1. Part C Day 14 Detailed SoA for Challenge Administration and PK Sampling Cohorts 4 and 8 (with challenges)

Procedure	Day 13	Day 14 - pre-dose and all post-dose times below are in relation to the administration time of GSK3358699.										Day 15	Day 16	Notes
		Pre-dose	0 h	15 mins	30 mins	1 h	2 h	4 h	6h	8 h	12 h	24 h	48 h	
Treatment / agent administration and PK sampling														
Study Drug / Placebo Administration			X											
In vivo LPS Challenge					< ========== >									LPS administration may be performed at low systemic GSK3358699 concs when intracellular levels of GSK3206944 are high; the decision on the timepoint will be based on emerging data and will be no more than 24hrs after dosing on Day 14.
OR in vivo GM-CSF Challenge					< ========== >									GM-CSF administration may be performed at low systemic GSK3358699 concs when intracellular levels of GSK3206944 are high; the decision on the timepoint will be based on emerging data. GM-CSF will be administered as an infusion over 2 hours and the start of the infusion will be no more than 24hrs after dosing on Day 14.
Blood sampling for systemic PK **[S1]** and **[S2]**		X		X	X	X	X	X	X	X	X	X	X	Ad-hoc sample to be taken in the event of any cardiac arrhythmias, as close as possible to the time of occurrence
Blood sampling for intracellular PK **[S3]**	X					X		X		X		X	X	Pre-challenge samples. To be collected only until the start of challenge administration
Blood sample for ex vivo PD assay **[S4]**	X	X				X		X		X		X		Pre-challenge samples. To be collected only until the start of challenge administration.
Blood sample for circulating proteins **[E1a]**		X					X	X		X		X		Pre-challenge samples. To be collected only until the start of challenge administration.
Blood sample for gene panel **[E1b]**		X					X	X		X		X		Pre-challenge samples. To be collected only until the start of challenge administration.
Cantharidin application and PD sampling	See Section 13.1.3.2 and Section 13.1.3.3													

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13.1.3.2. Part C Day 14 Detailed SoA for LPS Challenge and Biomarker Sampling Cohorts 4 and 8 (with challenges)

Procedure	Day 13	Day 14 - pre-dose and all post-dose times below are in relation to the administration time of LPS **not** GSK3358699 administration										Day 15	Day 16	Notes
		Pre-dose	0 h	20 mins	1 h	2 h	3 h	4 h	6h	8 h	12 h	24 h	48 h	
LPS challenge administration			X											See Section 13.1.3.1 for timing of LPS administration in relation to GSK3358699 / placebo dose.
Visual forearm check (including blister healing and cosmetic assessment)	X	X										X	X	Pre-cantharidin check to be within three hours prior to cantharidin application.
Cantharidin application				X										To be applied 20 minutes post LPS challenge.
Intravenous hydration with normal Saline at a rate of 250 mL / hr		<==========												From 4 hours prior to LPS challenge administration until 8 hours after LPS challenge administration.
Vital Signs	X	X	<==========									X	X	BP, HR, temperature, respiratory rate. Pre-dose vital signs to be taken pre-LPS challenge administration then post-LPS challenge as follows: every half hour for the first 4 hours, hourly until 12 hours, then 6- 8 hourly until discharge. Frequency can be increased if symptomatic.
Haematology	X								X		X	X	X	
Coagulation	X							X						
Blood sample for circulating inflammatory biomarkers **[E2a]**		X			X	X	X		X			X	X	
Blood sample for cellular activation markers **[E2b]**		X			X				X			X	X	
Blood sample for gene panel **[E2d]**		X			X		X		X			X		
Blister sample for biomarkers, blister volume and cell counts **[E3]**													X	Blisters harvested approx 48 h post cantharidin application.

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13.1.3.3. Part C Day 14 Detailed SoA for GM-CSF Challenge and Biomarker Sampling Cohorts 4 and 8 (with challenges)

Procedure	Day 13	Day 14 - pre-dose and all post-dose times below are in relation to the **start time** of the GM-CSF infusion **not** GSK3358699 administration											Day 15	Day 16	Notes
		Pre-dose	0 h	1 h	2 h	2h 20mins	3 h	4 h	5h	6 h	8 h	12 h	24 h	48 h	
GM-CSF challenge administration			<==========												See Section 13.1.3.1 for timing of the start of the GM-CSF infusion in relation to GSK3358699 / placebo dose. GM-CSF will be administered as an infusion over 2 hours.
Visual forearm check (including blister healing and cosmetic assessment)	X			X									X	X	Pre-cantharidin check to be within three hours prior to cantharidin application.
Cantharidin application						X									2 hours and 20 minutes after the start of the GM-CSF challenge.
Vital Signs	X	X	<==========										X	X	BP, HR, temperature, respiratory rate. Pre-dose vital signs to be taken pre-GM-CSF challenge administration then post-GM-CSF challenge as follows: every half hour for the first 4 hours, hourly until 8 hours, then 6- 8 hourly until discharge. Frequency can be increased if symptomatic.
Haematology	X							X			X		X	X	
Blood sample for circulating inflammatory biomarkers **[E2a]**		X		X	X		X	X			X		X	X	
Blood sample for cellular activation markers **[E2b]**		X			X			X			X		X	X	
Blood sample for gene panel **[E2d]**		X					X		X		X		X		
Blister sample for biomarkers, blister volume and cell counts **[E3]**														X	Blisters harvested approx 48 h post cantharidin application.

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board / Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent (ICF).
- Acceptable time windows around the nominal time points for specific assessments will be included in the Study Reference Manual (SRM) and assessments performed within these time windows will not constitute a protocol deviation.

13.2. Appendix 2: Assessment Windows

13.2.1. Definitions of Assessment Windows for Analyses

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

13.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

13.3.1. Study Phases for Parts A and C

Assessments and events will be assigned to the relevant treatment Period dependent on whether they are spontaneous events (i.e. data collected in a log such as Adverse Events and Concomitant Medications, and Disposition) or planned events (i.e. data with timeslicing assigned such as ECG, Laboratory, and Vital Signs).

Spontaneous events are assigned to period according to the time of occurrence relative to the start date/time of the study treatment within the period up to, but not including, the start date/time of the study treatment in the next period. Planned assessments, including unscheduled visits are assigned to period according to the date of first visit of that period (including Day -1 and Day -10 assessments as applicable) up to the day prior to the first visit of the next period or day prior to Follow-Up visit (including Day -1 and Day -10 assessments as applicable).

For planned events, assessments prior to the date of first visit in Period 1 for Part A (or Period 7 for Part C) are assigned as Screening. For spontaneous events, events prior to the datetime of first dose in Period 1 for Part A are assigned as Pre-Treatment (or Period 7 for Part C).

For planned events, assessments on or later than date of first Follow-Up visit are assigned as Follow-Up. For spontaneous events, events later than date of last dose + 7 days are assigned as Follow-Up.

13.3.1.1. 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

1. NOTE:

- Refer to Appendix 6: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in the table above if concomitant medication date is completely missing.
- Pre-trial medications are assumed concomitant if the stop date is within 28 days of the screening visit.

13.3.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date +1. • For crossover parts (Part A), if AE onset is during one period and worsens during a later period it would be counted in both periods. For the initial period the logic would be as above. For the later period the logic would use the treatment dates associated with the later period: Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date + 1 days.

NOTES:

- If the AE start/worsening date is on or after treatment start date, and treatment stop date is missing, then the AE will be considered to be Treatment Emergent.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: \arprod\gsk3358699\mid207546\data_look_01 : \arprod\gsk3358699\mid207546\final_01
Analysis Datasets	
• Analysis datasets will be created according to Integrated Data Standards Library (IDSL) Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for all tables within the final_01 reporting effort for SAC.	

13.4.2. Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (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
- Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings
- All data displays (Tables, Figures and Listings) will use the term “Subject” which reflects CDISC and GSK data display standards terminology.

Formats

- GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) 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.

<table>
<tr><td colspan="2">

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 participant's listings.

</td></tr>
<tr><td colspan="2">Unscheduled Visits</td></tr>
<tr><td colspan="2">• Unscheduled visits will not be included in summary tables and figures.
• All unscheduled visits will be included in listings.</td></tr>
<tr><td colspan="2">Descriptive Summary Statistics</td></tr>
<tr><td>Continuous Data</td><td>Refer to IDSL Statistical Principle 6.06.1 – do not report 95% CI unless otherwise specified.</td></tr>
<tr><td>Categorical Data</td><td>N, n, frequency, %</td></tr>
<tr><td colspan="2">Graphical Displays</td></tr>
<tr><td colspan="2">• Refer to IDSL Statistical Principals 7.01 to 7.13.</td></tr>
</table>

13.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to PKOne standards. Note: Concentration values will be imputed as per GUI_51487
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 summarised graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between subject geometric coefficient of variation (CVb (%)) will be reported. CVb (%) = $\sqrt{(\exp(SD^2) - 1)} * 100$ (SD = SD of log transformed data)
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to *Standards for the Transfer and Reporting of PK Data using HARP*.

13.5. Appendix 5: Derived and Transformed Data

13.5.1. General (Parts A and C)

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, except for blood pressure measurements as only the average of the 3 blood pressure readings will be recorded on the CRF. • Subjects who have both high and low values for Normal Ranges at any post-baseline visit 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 date ≥ first dose date → study day = (ref date – first dose date) + 1

Age

• Birth date will be presented in listings as 'YYYY'. 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 = 30th June YYYY
• Age calculated based on the data of screening date:
  Age = integer part (date of screening – 30th June YYYY) / 365.25.

Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)²]

13.5.2. Study Population

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** • Participants who were randomised 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 = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly. • Average dose is the cumulative dose divided by the duration of exposure.

13.5.3. Pharmacokinetics

Monocyte concentration

- In addition to the intracellular GSK3206944 raw concentration, x, which is measured as ng per mL in reagent, it will be also derived the molar concentration within the monocytes, y, which is:
  y(nM) = x(ng/mL)/MMV/MW/20*10^9
  where the mean monocyte volume (MMV) is equal to 261 fL which is derived from the average of 150[a], 250[a], 480[a], 167[b] fL reported in literature,
  the molecular weight (MW) is equal to 468.6 (see Technical Evidence Document)
  and assuming that 20 is the number of millions of cells per mL of reagent. In practical terms this is equivalent to y(nM) = x(ng/mL)*408.8154.

[a] https://www.ncbi.nlm.nih.gov/pubmed/7354131
[b] https://www.sciencedirect.com/science/article/pii/S0009898118301311#f0005

13.5.4. Pharmacodynamic

Percent inhibition

- The percentage inhibition (Truculture assay), to be calculated for select biomarkers, is defined as the reduction from baseline in %, e.g. a 15% reduction from baseline would be a 15% inhibition.
- The predicted percentage inhibition (y) in undiluted samples, to be calculated for selected biomarkers, from the above percentage inhibition (z(%)) in the 3-fold diluted samples of Truculture assay as:

$$y(\%) = \frac{100}{1 + \left(\frac{1}{DF}\right)^{hill} * \frac{100 - z(\%)}{z(\%)}}$$

  where the dilution factor (DF) is equal to 3
  Hill coefficient (hill) is equal to 1.4
  The above formula assumes that the in vivo-inhibition versus PK concentration follows the in vitro Emax model relationship with the same concentration generating 50% effect, ec50, and the same hill coefficient and same Emax=1.
  In fact from

$$z(\%) = \frac{x^{hill}}{x^{hill} + ec50^{hill}} \cdot 100$$

  it is possible to derive

$$ec50^{hill} = \frac{x^{hill} \cdot 100 - z(\%) \cdot x^{hill}}{z(\%)}$$

  and substituting $ec50^{hill}$ in the equation of undiluted samples, where the ec50 is DF fold lower we obtain:

$$y(\%) = \frac{x^{hill}}{x^{hill} + \left(\frac{ec50}{DF}\right)^{hill}} \cdot 100 = \frac{x^{hill}}{x^{hill} + \frac{x^{hill} \cdot 100 - z(\%) \cdot x^{hill}}{DF^{hill} \cdot z(\%)}} \cdot 100$$

  which, after simplification by x^{hill} , results in the above equation

Biomarkers

Biomarker Code (BICATCD), Biomarker Test Code (BITESTCD), Biomarker Testing Method Code (BIMETHCD) and Units of Measurement (BIORRESU) are summarised below.

Name (Analyte)	Biomarker Description	BICATCD	BITESTCD/ BIMETHCD/ BIORRESU	SAC ENDPOINTS
Soluble Inflammatory Mediators (Blood) TruCulture	Interleukin 6	IL6	CONC/ ECLIA/ PG/ML	S4
	Monocyte chemotactic protein-1	MCP1	CONC/ ECLIA/ PG/ML	S4
	Tumour necrosis factor alpha (TNF-α)	TNFA	CONC/ ECLIA/ PG/ML	S4

13.6. Appendix 6: Reporting Standards for Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail
General	• A participant is considered to have completed: o Part A (Cohorts 1 and 2) of the study if he has completed all the periods of Part A, including both follow-up visits. o Part C of the study if he has completed all visits including both follow-up visits. • Withdrawn participants may be replaced in the study. Additional replacement participants may be randomised to guarantee that sufficient participants are treated with GSK3358699 at any given dose before escalating to the following dose. Replacement participants will be assigned to the same treatment sequence (Parts A) or treatment (Part C) but have different subject numbers and randomisation numbers assigned. • All available data from participants 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. • Data from withdrawal visits will be listed. • In Part C, Cohorts 4 and 5 were terminated prematurely while some subjects were part way through the treatment phase. Safety and PK data collected after the date of termination in each cohort should not be included in summary tables/figures, but should be listed under a visit label of 'Early Termination'. The dates of termination were: o Cohort 4: 14NOV2018 o Cohort 5: 18MAR2019

13.6.2. 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: o These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the listing. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

13.6.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant 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: o 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 Section 13.3. o 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	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' (last day of the relevant month) will be used for the day and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

13.7. Appendix 7: Values of Potential Clinical Importance and Normal Ranges

13.7.1. 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
Respiratory Rate	breaths/min	< 11	> 20
Temperature	°C	< 35.5	> 38.0

13.7.2. Laboratory Values

Hematology – PCI Criteria			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1		0.54
Hemoglobin	g/L		180
Lymphocyte Count	$x10^9$/ L	0.8	
Neutrophil Count	$x10^9$/ L	1.5	
Platelet Count	$x10^9$/ L	100	550
White Blood Cell Count (WBC)	$x10^9$/ L	3	20

Hematology – Normal Ranges			
Laboratory Parameter	**Units**	**Normal Range**	
		Low Flag (< x)	**High Flag (>x)**
Activated Partial Thromboplastin Time (APTT)	secs	25	37
Basophil Count	$x10^9$/ L	0.0	0.1
Eosinophil Count	$x10^9$/ L	0.0	0.4
Fibrinogen	g/L	1.5	4.0
Mean Corpuscle Hemoglobin (MCH)	pg	26.0	33.5
Mean Corpuscle Volume (MCV)	fL	80	99
Monocyte Count	$x10^9$/ L	0.2	1.0

Hematology – Normal Ranges			
Laboratory Parameter	**Units**	**Normal Range**	
		Low Flag (< x)	**High Flag (>x)**
Prothrombin Time (PT)	secs	10	12
Red Blood Cell Count (RBC)	$x10^{12}$/ L	4.4	5.8
Reticulocyte Count	%	0.38	2.64

Clinical Chemistry – PCI Criteria			
Laboratory Parameter	**Units**	**Clinical Concern Range**	
		Low Flag (< x)	**High Flag (>x)**
Albumin	G/L	30	
Calcium	mmol/L	2	2.75
Creatinine	mmol/L		1.3 X ULN
Glucose	mmol/L	3	9
Potassium	mmol/L	3	5.5
Sodium	mmol/L	130	150

Clinical Chemistry – Normal Ranges			
Laboratory Parameter	**Units**	**Normal Range**	
		Low Flag (< x)	**High Flag (>x)**
Alanine Aminotransferase (ALT)	IU/L	10	50
Alkaline Phosphatase (ALP)	IU/L	40	129
Aspartate Aminotransferase (AST)	IU/L	0	37
Blood Urea Nitrogen (BUN)	mg/dL	4.76	23.24
C-reactive Protein	mg/L	0.0	5.0
Cholesterol	mmol/L	2.3	4.9
Direct Bilirubin	umol/L	0	5
High Density Lipoprotein	mmol/L	0.9	1.5
Low Density Lipoprotein	mmol/L	0	3.0
Total Bilirubin	umol/L	0	20
Total Protein	g/L	63	83
Triglycerides	mmol/L	0	2.3

13.7.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec		>450
Absolute PR Interval	msec	<110	>220
Absolute QRS Interval	msec	<75	>110
Change from Baseline			
Increase from Baseline QTcF	msec		>60

13.8. Appendix 8: Abbreviations & Trade Marks

13.8.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
BMI	Body Mass Index
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DEC	Dose Escalation Committee
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RD	Repeat Dose
SAC	Statistical Analysis Complete
SD	Single Dose
SDSP	Study Data Standardization Plan
SOP	Standard Operation Procedure
TA	Therapeutic Area

Abbreviation	Description
TLF	Tables, Listings and Figures

13.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

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

13.9. Appendix 9: List of Data Displays

13.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.21	-
Safety	2.1 to 2.44	2.1 to 2.2
Pharmacokinetic	3.1 to 3.9	3.1 to 3.18
Pharmacodynamic	5.1 to 5.4	5.1 to 5.4
Section	**Listings**	
ICH Listings	1 to 64	
Other Listings	65 to 76	

13.9.2. Mock Example Shell Referencing

Table, listing and figure shells will be produced in documents separate to the RAP. These shells will follow the IDSL standards as appropraite and include study specific programming notes to facilitate programming.

13.9.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

13.9.4. Study Population Tables

Part A

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disposition					
1.1.	Safety	ES1a	Part A: Summary of Subject Disposition for the Subject Conclusion Record	Add footnote: Note: "Subjects" is used to refer to "Participants" in all data displays to reflect GSK display standards. Note: Three Subjects were enrolled in more than one cohort of Study 207546. They are considered distinct subjects for the purposes of reporting. Subject PPD (Part A Cohort 1) is the same subject as subject PPD (Part C Cohort 4). Subject PPD (Part A Cohort 2) is the same subject as subject PPD (Part C Cohort 5). Subject PPD (Part C Cohort 4) is the same subject	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				as subject PPD (Part C Cohort 5).	
1.2.	Safety		Part A: Summary of Subject Disposition for the Subject Conclusion Record at Each Study Period/Phase by Arm		SAC
1.3.	Screened	ES6	Part A: Summary of Screening Status and Reasons for Screen Failure		SAC
1.4.	Safety	ES4	Part A: Summary of Subject Disposition at Each Study Epoch	Crossover part: the "treatment group" column will indicate the treatment that the subject was exposed to most recently at the time of withdrawal.	SAC
1.5.	Enrolled	NS1	Part A: Summary of Number of Subjects Enrolled by Country and Centre ID		SAC
Protocol Deviations					
1.6.	Safety	DV1	Part A: Summary of Important Protocol Deviations	Crossover part: only totals are presented	SAC
Demography					
1.7.	Safety	DM3	Part A: Summary of Demographic Characteristics	Crossover part: only totals are presented	SAC
1.8.	Safety		Part A: Summary of Demographic Characteristics by Arm		SAC
1.9.	Enrolled	DM11	Part A: Summary of Age Ranges	Crossover part: only totals are presented.	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				Add footnote: For calculating Age, birth date is imputed as 30th June in the year of birth.	
1.10.	Safety	DM5	Part A: Summary of Race and Racial Combinations	Report only categories if n>0 count; crossover part: only totals are presented	SAC
Concomitant Medications					
1.11.	Safety	CM1	Part A: Summary of Concomitant Medications		SAC

Part C

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disposition					
1.12.	Safety	ES1	Part C: Summary of Subject Disposition for the Subject Conclusion Record	Note: Three Subjects were enrolled in more than one cohort of Study 207546. They are considered distinct subjects for the purposes of reporting. Subject PPD (Part A Cohort 1) is the same subject as subject PPD (Part C Cohort 4). Subject PPD (Part A Cohort 2) is the same subject as subject PPD (Part C Cohort	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				5). Subject PPD (Part C Cohort 4) is the same subject as subject PPD (Part C Cohort 5).	
1.13.	Screened	ES6	Part C: Summary of Screening Status and Reasons for Screen Failure		SAC
1.14.	Safety	ES4	Part C: Summary of Subject Disposition at Each Study Epoch		SAC
1.15.	Enrolled	NS1	Part C: Summary of Number of Subjects Enrolled by Country and Centre ID		SAC
Protocol Deviations					
1.16.	Safety	DV1	Part C: Summary of Important Protocol Deviations		SAC
Demography					
1.17.	Safety	DM1	Part C: Summary of Demographic Characteristics		SAC
1.18.	Enrolled	DM11	Part C: Summary of Age Ranges	Add footnote: For calculating Age, birth date is imputed as 30th June in the year of birth.	SAC
1.19.	Safety	DM5	Part C: Summary of Race and Racial Combinations	Report only categories if n>0 count	SAC
Concomitant Medications					
1.20.	Safety	CM1	Part C: Summary of Concomitant Medications		SAC
Exposure					
1.21.	Safety	EX1	Part C: Summary of Exposure to Study Treatment		SAC

13.9.5. Safety Tables

Part A

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	Safety	AE5a	Part A: Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Add footnote listing the subjects who re-enrolled in other Parts (only add this footnote if they had AEs both here and in another Part) Include total column.	SAC
2.2.	Safety	AE5a	Part A: Summary of All Drug Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Include total column.	SAC
2.3.	Safety	AE16	Part A: Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	For studies with few events/participants listing is sufficient: discuss this option with your disclosure representative.	SAC
2.4.	Safety	AE15	Part A: Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.5.	Safety	AE3	Part A: Summary of Common (>=5%) Adverse Events by Overall Frequency		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	Safety	AE3	Part A: Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC
2.7.	Safety	AE3	Part A: Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency		SAC
2.8.	Safety	AE3	Part A: Summary of Serious Drug-Related Adverse Events by Overall Frequency		SAC
Laboratory					
2.9.	Safety	LB1	Part A: Summary of Chemistry Changes from Baseline	Order parameters alphabetically.	SAC
2.10.	Safety	LB17	Part A: Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with PCI criteria listed in Appendix 7.	SAC
2.11.	Safety	LB15	Part A: Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with Normal Ranges listed in Appendix 7.	SAC
2.12.	Safety	LB1	Part A: Summary of Hematology Changes from Baseline	Order parameters alphabetically.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	Safety	LB17	Part A: Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with PCI criteria listed in Appendix 7.	SAC
2.14.	Safety	LB15	Part A: Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with Normal Ranges listed in Appendix 7.	SAC
ECG					
2.15.	Safety	EG1	Part A: Summary of ECG Findings	Crossover part: counts and percentages are based on the number of subjects in each treatment, so participants will appear in multiple treatments.	SAC
2.16.	Safety	EG10	Part A: Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category	Crossover part: counts and percentages are based on the number of subjects in each treatment, so participants will appear in multiple treatments.	SAC
2.17.	Safety	EG11	Part A: Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline by Category	Crossover part: counts and percentages are based on the number of subjects in each treatment, so participants will appear in multiple treatments.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18.	Safety	EG2	Part A: Summary of Change from Baseline in ECG Values by Visit	Crossover part: counts and percentages are based on the number of subjects in each treatment, so participants will appear in multiple treatments.	SAC
Holter					
2.19.	Safety	HM1	Part A: Summary of Holter Interpretations		SAC
2.20.	Safety	HM2	Part A: Summary of Holter Abnormalities		SAC
Vital Signs					
2.21.	Safety	VS1	Part A: Summary of Change from Baseline in Vital Signs	Crossover part: counts and percentages are based on the number of subjects in each treatment, so participants will appear in multiple treatments.	SAC
2.22.	Safety	VS7	Part A: Summary of Worst Case Vital Sign Results by PCI Criteria Post-Baseline Relative to Baseline	Crossover part: counts and percentages are based on the number of subjects in each treatment, so participants will appear in multiple treatments.	SAC

Part C

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.23.	Safety	AE5a	Part C: Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Include total column.	SAC
2.24.	Safety	AE5a	Part C: Summary of All Drug Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	Include total column.	SAC
2.25.	Safety	AE16	Part C: Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurances)		SAC
2.26.	Safety	AE3	Part C: Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency		SAC
2.27.	Safety	AE15	Part C: Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.28.	Safety	AE3	Part C: Summary of Common (>=5%) Adverse Events by Overall Frequency		SAC
2.29.	Safety	AE3	Part C: Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency		SAC
2.30.	Safety	AE3	Part C: Summary of Serious Drug-Related Adverse Events by Overall Frequency		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
2.31.	Safety	LB1	Part C: Summary of Chemistry Changes from Baseline	Order parameters alphabetically.	SAC
2.32.	Safety	LB17	Part C: Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with PCI criteria listed in Appendix 7.	SAC
2.33.	Safety	LB15	Part C: Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with Normal Ranges listed in Appendix 7.	SAC
2.34.	Safety	LB1	Part C: Summary of Hematology Changes from Baseline	Order parameters alphabetically.	SAC
2.35.	Safety	LB17	Part C: Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with PCI criteria listed in Appendix 7.	SAC
2.36.	Safety	LB15	Part C: Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	Order parameters alphabetically, include parameters with Normal Ranges listed in Appendix 7.	SAC
ECG					
2.37.	Safety	EG1	Part C: Summary of ECG Findings		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.38.	Safety	EG10	Part C: Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category		SAC
2.39.	Safety	EG11	Part C: Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline by Category		SAC
2.40.	Safety	EG2	Part C: Summary of Change from Baseline in ECG Values by Visit		SAC
Holter					
2.41.	Safety	HM1	Part C: Summary of Holter Interpretations		SAC
2.42.	Safety	HM2	Part C: Summary of Holter Abnormalities		SAC
Vital Signs					
2.43.	Safety	VS1	Part C: Summary of Change from Baseline in Vital Signs		SAC
2.44.	Safety	VS7	Part C: Summary of Worst Case Vital Sign Results by PCI Criteria Post-Baseline Relative to Baseline		SAC

13.9.6. Safety Figures

Part A

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1.	Safety	AE10	Part A: Plot of Common (>=5%) Adverse Events and Relative Risk		SAC

Part C

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.2.	Safety	AE10	Part C: Plot of Common (>=5%) Adverse Events and Relative Risk		SAC

13.9.7. Pharmacokinetic Tables

Part A

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1.	PK	PK01	Part A: Summary of Plasma Pharmacokinetic Concentration-time Data by Compound (GSK3358699 or GSK3206944)	By treatment group and compound (GSK3358699 or GSK3206944).	SAC
3.2.	PK	PK01	Part A: Summary of Intracellular Pharmacokinetic Concentration-time Data	By treatment group.	SAC
3.3.	PK	PK01	Part A: Summary of Intracellular Molar Concentration Pharmacokinetic Concentration-time Data	By treatment group.	SAC
PK Derived Parameters					
3.4.	PK	PK06	Part A: Summary of Derived Plasma Pharmacokinetic Parameters (Non-transformed and Log-transformed) by Compound (GSK3358699 or GSK3206944)	By treatment group and compound (GSK3358699 or GSK3206944).	SAC
Dose Proportionality					
3.5.	PK	[Non standard] PK_T1	Part A: Summary of Estimated Slope and 90% CI of Dose Proportionality Model	By endpoint (AUC(0-t), AUC(0-∞), Cmax).	SAC

Part C

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.6.	PK	PK01	Part C: Summary of Plasma Pharmacokinetic Concentration-time Data by Compound (GSK3358699 or GSK3206944)	By treatment group and compound (GSK3358699 or GSK3206944).	SAC
3.7.	PK	PK01	Part C: Summary of Intracellular Pharmacokinetic Concentration-time Data	By treatment group.	SAC
3.8.	PK	PK01	Part C: Summary of Intracellular Molar Concentration Pharmacokinetic Concentration-time Data	By treatment group.	SAC
PK Derived Parameters					
3.9.	PK	PK06	Part C: Summary of Derived Plasma Pharmacokinetic Parameters (Non-transformed and Log-transformed) by Compound (GSK3358699 or GSK3206944)	By treatment group and compound (GSK3358699 or GSK3206944).	SAC

13.9.8. Pharmacokinetic Figures

Part A

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1.	PK	PK16b	Part A: Individual Subject Plot: Plasma Concentration by Subject (Linear and Semi-log) by Compound (GSK3358699 or GSK3206944)	Page by compound (GSK3358699 or GSK3206944).	SAC
3.2.	PK	PK16b	Part A: Individual Subject Plot: Intracellular Concentration by Subject (Linear and Semi-log)		SAC
3.3.	PK	PK16b	Part A: Individual Subject Plot: Intracellular Molar Concentration by Subject (Linear and Semi-log)		SAC
Mean/Median Concentration Plots					
3.4.	PK	PK17	Part A: Mean Plot: Plasma Concentrations (Linear and Semi-log) by Compound (GSK3358699 or GSK3206944)	Page by compound (GSK3358699 or GSK3206944).	SAC
3.5.	PK	PK17	Part A: Mean Plot: Intracellular Concentrations (Linear and Semi-log)		SAC
3.6.	PK	PK17	Part A: Mean Plot: Intracellular Molar Concentrations (Linear and Semi-log)		SAC
3.7.	PK	PK18	Part A: Median Plot: Plasma Concentrations (Linear and Semi-log) by Compound (GSK3358699 or GSK3206944)	Page by compound (GSK3358699 or GSK3206944).	SAC
3.8.	PK	PK18	Part A: Median Plot: Intracellular Concentrations (Linear and Semi-log)		SAC
3.9.	PK	PK18	Part A: Median Plot: Intracellular Molar Concentrations (Linear and Semi-log)		SAC

Part C

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.10.	PK	PK16a	Part C: Individual Subject Plot: Plasma Concentration by Subject (Linear and Semi-log) by Compound (GSK3358699 or GSK3206944)	Page by compound (GSK3358699 or GSK3206944)	SAC
3.11.	PK	PK16a	Part C: Individual Subject Plot: Intracellular Concentration by Subject (Linear and Semi-log)		SAC
3.12.	PK	PK16a	Part C: Individual Subject Plot: Intracellular Molar Concentration by Subject (Linear and Semi-log)		SAC
Mean/Median Concentration Plots					
3.13.	PK	PK17	Part C: Mean Plot: Plasma Concentrations (Linear and Semi-log) by Compound (GSK3358699 or GSK3206944)	Page by compound (GSK3358699 or GSK3206944)	SAC
3.14.	PK	PK17	Part C: Mean Plot: Intracellular Concentrations (Linear and Semi-log)		SAC
3.15.	PK	PK17	Part C: Mean Plot: Intracellular Molar Concentrations (Linear and Semi-log)		SAC
3.16.	PK	PK18	Part C: Median Plot: Plasma Concentrations (Linear and Semi-log) by Compound (GSK3358699 or GSK3206944)	Page by compound (GSK3358699 or GSK3206944)	SAC
3.17.	PK	PK18	Part C: Median Plot: Intracellular Concentrations (Linear and Semi-log)		SAC
3.18.	PK	PK18	Part C: Median Plot: Intracellular Molar Concentrations (Linear and Semi-log)		SAC

13.9.9. Pharmacodynamic Tables

Part A

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Soluble Inflammatory Mediators					
5.1.	Safety		Part A: Summary of Absolute Values and Percentage Inhibition of Soluble Inflammatory Mediators in Blood After Ex-Vivo LPS Activation	Page by Biomarker [S4] (note: this "[S4]" refers to the endpoint corresponding to this display; use the table in Section 13.5.4 for a list of biomarkers for each endpoint; applies to all PD displays).	SAC
5.2.	Safety		Part A: Summary of Predicted Percentage Inhibition of Soluble Inflammatory Mediators in Blood After Ex-Vivo LPS Activation	Page by Biomarker [S4].	SAC

Part C

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Soluble Inflammatory Mediators					
5.3.	Safety		Part C: Summary of Absolute Values and Percentage Inhibition of Soluble Inflammatory Mediators in Blood After Ex-Vivo LPS Activation	Page by Biomarker [S4].	SAC
5.4.	Safety		Part C: Summary of Predicted Percentage Inhibition of Soluble Inflammatory Mediators in Blood After Ex-Vivo LPS Activation	Page by Biomarker [S4].	SAC

13.9.10. Pharmacodynamic Figures

Part A

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Soluble Inflammatory Mediators					
5.1.	Safety		Part A: Individual Plot of Soluble Inflammatory Mediators in Blood Over Time After Ex-Vivo LPS Activation	[S4] Page by dose, then individual.	SAC
5.2.	Safety		Part A: Mean (+/- SE) Plot of Soluble Inflammatory Mediators in Blood Over Time After Ex-Vivo LPS Activation	[S4].	SAC

Part C

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Soluble Inflammatory Mediators					
5.3.	Safety		Part C: Individual Plot of Soluble Inflammatory Mediators in Blood Over Time After Ex-Vivo LPS Activation	[S4].	SAC
5.4.	Safety		Part C: Mean (+/- SE) Plot of Soluble Inflammatory Mediators in Blood Over Time After Ex-Vivo LPS Activation	[S4].	SAC

13.9.11. ICH Listings

Part A

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Part A: Listing of Reasons for Screen Failure		SAC
2.	Safety	ES3	Part A: Listing of Reasons for Study Withdrawal		SAC
3.	Safety	BL2	Part A: Listing of Subjects for Whom the Treatment Blind was Broken		SAC
4.	Safety	TA1	Part A: Listing of Planned and Actual Treatment		SAC
Protocol Deviations					
5.	Safety	DV2a	Part A: Listing of Important Protocol Deviations		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.	Safety	IE4	Part A: Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Demography					
7.	Safety	DM4	Part A: Listing of Demographic Characteristics		SAC
8.	Safety	DM10	Part A: Listing of Race		SAC
Populations Analysed					
9.	Screened	SP3a	Part A: Listing of Subjects Excluded from Any Population		SAC
Concomitant Medications					
10.	Safety	CM5	Part A: Listing of Concomitant Medications		SAC
Exposure					
11.	Safety	EX4	Part A: Listing of Exposure Data		SAC
Adverse Events					
12.	Safety	AE9CP	Part A: Listing of All Adverse Events		SAC
13.	Safety	AE7	Part A: Listing of Subject Numbers for Individual Adverse Events		SAC
14.	Safety	AE2	Part A: Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
15.	Safety	AE14	Part A: Listing of Reasons for Considering as a Serious Adverse Event		SAC
16.	Safety	AE9CPa	Part A: Listing of Serious Adverse Events		SAC
17.	Safety	AE9CP	Part A: Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
18.	Safety	LB6	Part A: Listing of All Laboratory Data for Subjects with Any Value Outside of Normal Range or of Potential Clinical Importance		SAC
19.	Safety	LB6	Part A: Listing of All Laboratory Values Outside of Normal Range or of Potential Clinical Importance		SAC
20.	Safety	LB14	Part A: Listing of Laboratory Data with Character Results		SAC
21.	Safety	UR2B	Part A: Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
22.	Safety	MH2	Part A: Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
23.	Safety	SU2	Part A: Listing of Subtance Use for Subjects with Liver Stopping Events		SAC
24.	Safety	LIVER6	Part A: Listing of Liver Stopping Event Information for RUCAM Score		SAC
25.	Safety	LIVER5	Part A: Listing of Liver Monitoring/Stopping Event Reporting		SAC
ECG					
26.	Saftey	EG4	Part A: Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
27.	Safety	EG4	Part A: Listing of ECG Values of Potential Clinical Importance		SAC
28.	Safety	EG6	Part A: Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		SAC
29.	Safety	EG6	Part A: Listing of Abnormal ECG Findings		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
30.	Safety	VS5	Part A: Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance		SAC
31.	Safety	VS5	Part A: Listing of Vital Signs of Potential Clinical Importance		SAC

Part B

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
32.	Screened	ES7	Part B: Listing of Reasons for Screen Failure		SAC
Demography					
33.	Safety	DM4	Part B: Listing of Demographic Characteristics		SAC

Part C

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
34.	Screened	ES7	Part C: Listing of Reasons for Screen Failure		SAC
35.	Safety	ES2	Part C: Listing of Reasons for Study Withdrawal		SAC
36.	Safety	BL1	Part C: Listing of Subjects for Whom the Treatment Blind was Broken		SAC
37.	Safety	TA1	Part C: Listing of Planned and Actual Treatment		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Protocol Deviations					
38.	Safety	DV2	Part C: Listing of Important Protocol Deviations		SAC
39.	Safety	IE3	Part C: Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Demography					
40.	Safety	DM2	Part C: Listing of Demographic Characteristics		SAC
41.	Safety	DM9	Part C: Listing of Race		SAC
Populations Analysed					
42.	Screened	SP3	Part C: Listing of Subjects Excluded from Any Population		SAC
Concomitant Medications					
43.	Safety	CM3	Part C: Listing of Concomitant Medications		SAC
Exposure					
44.	Safety	EX3	Part C: Listing of Exposure Data		SAC
Adverse Events					
45.	Safety	AE8CP	Part C: Listing of All Adverse Events		SAC
46.	Safety	AE7	Part C: Listing of Subjects Numbers for Individual Adverse Events		SAC
47.	Safety	AE2	Part C: Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
48.	Safety	AE14	Part C: Listing of Reasons for Considering as a Serious Adverse Event		SAC
49.	Safety	AE8CPa	Part C: Listing of Serious Adverse Events		SAC
50.	Safety	AE8CP	Part C: Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
51.	Safety	LB5	Part C: Listing of All Laboratory Data for Subjects with Any Value Outside of Normal Range or of Potential Clinical Importance		SAC
52.	Safety	LB5	Part C: Listing of All Laboratory Values Outside of Normal Range or of Potential Clinical Importance		SAC
53.	Safety	LB14	Part C: Listing of Laboratory Data with Character Results		SAC
54.	Safety	UR2A	Part C: Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance	PCI is defined as per IDSL - an increase in Protein or Occult Blood post-baseline relative to baseline, or if microscopy is performed.	SAC
55.	Safety	MH2	Part C: Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
56.	Safety	SU2	Part C: Listing of Subtance Use for Subjects with Liver Stopping Events		SAC
57.	Safety	LIVER6	Part C: Listing of Liver Stopping Event Information for RUCAM Score		SAC
58.	Safety	LIVER5	Part C: Listing of Liver Monitoring/Stopping Event Reporting		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
59.	Saftey	EG3	Part C: Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
60.	Safety	EG3	Part C: Listing of ECG Values of Potential Clinical Importance		SAC
61.	Safety	EG5	Part C: Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		SAC
62.	Safety	EG5	Part C: Listing of Abnormal ECG Findings		SAC
Vital Signs					
63.	Safety	VS4	Part C: Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance		SAC
64.	Safety	VS4	Part C: Listing of Vital Signs of Potential Clinical Importance		SAC

13.9.12. Non-ICH Listings

Part A

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
65.	PK	PK08	Part A: Listing of GSK3358699 Plasma Pharmacokinetic Concentration-time Data		SAC
66.	PK	PK08	Part A: Listing of GSK3206944 Plasma Pharmacokinetic Concentration-time Data		SAC
67.	PK	PK08	Part A: Listing of GSK3206944 Intracellular Pharmacokinetic Concentration-time Data		SAC
68.	PK	PK14	Part A: Listing of Derived GSK3358699 Plasma Pharmacokinetic Parameters		SAC
69.	PK	PK14	Part A: Listing of Derived GSK3206944 Plasma Pharmacokinetic Parameters		SAC
Biomarkers: Soluble Inflammatory Mediators					
70.	Safety	[Non standard] BIO_L1	Part A: Listing of Absolute Values Percentage Inhibition and Predicted Percentage Inhibition of Soluble Inflammatory Mediators in Blood After Ex-Vivo LPS Activation	S4	SAC

Part C

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
71.	PK	PK07	Part C: Listing of GSK3358699 Plasma Pharmacokinetic Concentration-time Data		SAC
72.	PK	PK07	Part C: Listing of GSK3206944 Plasma Pharmacokinetic Concentration-time Data		SAC
73.	PK	PK07	Part C: Listing of GSK3206944 Intracellular Pharmacokinetic Concentration-time Data		SAC
74.	PK	PK13	Part C: Listing of Derived GSK3358699 Plasma Pharmacokinetic Parameters		SAC
75.	PK	PK13	Part C: Listing of Derived GSK3206944 Plasma Pharmacokinetic Parameters		SAC
Biomarkers: Soluble Inflammatory Mediators					
76.	Safety	[Non standard] BIO_L1	Part C: Listing of Absolute Values, Percentage Inhibition and Predicted Percentage Inhibition of Soluble Inflammatory Mediators in Blood After Ex-Vivo LPS Activation	S4	SAC

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