TITLE PAGE

Protocol Title: 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.

Protocol Number: 207546/ Amendment 4

Short Title: First-time-in-Human Study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of single (in both fed and fasted states) or repeat doses of GSK3358699.

Compound Number: GSK3358699

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information: Can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): EudraCT number: 2017-003997-15

Approval Date: 11-DEC-2018

SPONSOR SIGNATORY:

PPD

PPD

11 DECEMBER 2018

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Interim Head of Discovery Medicine
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Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	11-DEC-2018
Amendment 3	29-MAY-2018
Amendment 2	21-MAR-2018
Amendment 1	25-JAN-2018
Original Protocol	30-NOV-2017

Amendment 4: 11-DEC-2018

Overall Rationale for the Amendment:

Four asymptomatic, non-serious, non-severe and self-limiting cardiac arrhythmias were observed in the study. A temporary dosing hold was implemented during Cohort 4 (Part C) to allow sufficient time for safety panel review of these events. As described in this protocol amendment, Part C of the study will commence from Cohort 5 with an additional cohort added to provide four full planned cohorts (Cohorts 5-8).

Additionally, the randomization ratio has been changed to 1:1 (Active:Placebo) in Part C, to provide a balanced comparison between subjects on active and placebo. Furthermore, the Part C study design has been modified to remove the *in vivo* challenges from Cohorts 5, 6 and 7 to limit unnecessary exposure of participants receiving placebo to immunological challenge, and to attenuate study duration and complexity.

Exclusion criteria have been revised to exclude individuals who may be at higher natural risk of cardiac arrhythmias.

An interim analysis following Cohort 7 has also been included to allow formal readout of data obtained up to that point whilst Cohort 8 (which are primarily experimental endpoints) is still ongoing.

In addition, further administrative clarifications have been made.

The specific revisions are summarised below:

Section # and Name	Description of Change	Brief Rationale
Sponsor Signatory page	Change of Sponsor Signatory to Nicolas Wisniacki.	Sponsor Signatory has changed.
Synopsis and Section 5.1; Overall Design	Added 'is planned to' to final sentence regarding Part C and amended number of cohorts.	Increased flexible wording; change in study design.
Synopsis; Number of participants	Table updated to reflect new cohorts and number of participants required for each. Text added to state that Part C participants may take part in a later Part C cohort if they fulfil all eligibility criteria. Last paragraph updated to include revisions to participant numbers for additional cohorts and added text on alternative dosing regimens including for challenges.	Change in study design / randomisation requirements. Increased flexibility. Increased flexibility.
Synopsis; Treatment Groups and Duration Part A	Text revised to confirm blister harvest timepoint of 48h post-induction and confirm LPS dose of 0.75 ng/kg.	Blister harvest timepoint and LPS dose was confirmed during Part A after completion of enabling study 207654.
Synopsis; Treatment Groups and Duration Part B, and Section 5.1.2 Part B Food Effect	Added text 'dose level chosen for Part B will be within the range already evaluated….'	Clarification in line with Part A and C wording.
Synopsis; Treatment Groups and Duration Part C	Schematic updated with revised cohort information. Text updated to describe Cohorts 5-7, where there are now no *in vivo* challenges, separately from Cohorts 4 and 8.	Change in study design. Change in study design / randomisation requirements.
Part B SoA	12h sample timepoint for S4 removed and notes updated to reflect changes to sampling requirements	Updated based on emerging data
Part B and C SoAs	Additional notes added for haematology, coagulation, clinical chemistry and urinalysis. Gamma-glutamyl transferase and creatine kinase added at selected timepoints. Note added to Drug / Alcohol test and Blood sampling for systemic PK rows to allow ad-hoc testing in the event of a cardiac arrhythmia.	Clarification. Additional monitoring Additional monitoring
Part C SoAs	Section 2.3 and Section 2.3.1 now contain new SoA tables covering	Change in study design.

Section # and Name	Description of Change	Brief Rationale
	assessments required for Cohorts 5-7 with no *in vivo* challenges. Section 2.4, Section 2.4.1, Section 2.4.2 and Section 2.4.3 SoA tables are the previous challenge tables but now only apply to Cohorts 4 and 8. Some study assessments have also been updated.	 Some study assessments were altered during the course of Part A based on newly available data and documented *via* File Note and in the SRM. They are now being incorporated into Protocol Amendment 4.
Section 3.3. Benefit / Risk Assessment	Text inserted to capture potential risk, given NSVTs observed during study to date.	Included to transparently capture clincal observations to date.
Section 3.3.1 Risk Assessment	LPS text in mitigation strategy amended to confirm LPS dose. Text inserted to capture potential risk, given NSVTs observed during study to date.	LPS dose was confirmed during Part A after completion of enabling study 207654. Included to transparently capture clincal observations to date.
Section 4 Objectives and Endpoints	Deleted exploratory endpoint for inflammatory markers following LPS challenge / ex-vivo incubation	Relates to E2c sampling in SoA table which has now been removed based on emerging data.
Section 5.1.1.2 Part A LPS or GM-CSF challenge	LPS text amended to confirm LPS dose.	Blister harvest timepoint and LPS dose was confirmed during Part A after completion of enabling study 207654.
Section 5.1.3 Part C Study Design	Schematic updated with revised cohort information. Separate sub-sections created and updated to describe Cohorts 5-7, where there are now no *in vivo* challenges, separately from Cohorts 4 and 8 as follows: Section 5.1.3.1 Part C Multiple Ascending Doses Cohort 4 added (refers to Section 5.1.3.3 for further details on study design as for Cohort 8). Section 5.1.3.2 Part C Multiple Ascending Doses Cohorts 5, 6 and 7 added. Section 5.1.3.3 Part C Repeat Dosing Followed by LPS or GM-CSF Challenge with Cantharidin-Induced Blisters Cohort 4 and 8 updated to revise detail of Cohorts and number of participants.	Change in study design. Change in study design / randomisation requirements. This section was previously Section 5.1.3 and the study design is fundamentally the same as was described in that section for the challenge cohorts.
Section 5.2 Number of Participants	Table updated to reflect new cohorts and number of participants required	Change in study design / randomisation requirements.

Section # and Name	Description of Change	Brief Rationale
	for each. Text added to first paragraph under the table to state that Part C participants may take part in a later Part C cohort if they fulfil all eligibility criteria. Second paragraph below table updated to include revisions to participant numbers for additional cohorts and added text on alternative dosing regimens including for challenges.	Increased flexibility. Increased flexible wording.
Section 5.4 Scientific Rationale for Study Design	Updated 3rd bullet to state that 'In Part C it is planned that five cohorts…' Added reference to Cohorts 4 and 8 for Part C challenge cohorts. Changed Part C challenge administration time from 'will be administered at a timepoint of low systemic….' to 'may be administered at a timepoint of low systemic….' Bullet on rationale for exclusion of females from the study revised.	Increased flexible wording and change in study design. Clarification in relation to revised study design. Increased flexible wording around timing of Part C challenge admin in the event that emerging data suggests different admin timepoints may be optimal. The embryo-foetal toxicology studies referred to in the previous version of the protocol have now been completed.
Section 5.5.1 Part A Dose Justification	LPS text amended to confirm LPS dose.	LPS dose was confirmed during Part A after completion of enabling study 207654.
Section 5.5.3 Part C Dose Justification	Updated to revise number of cohorts to five and add flexibility in number of days dosing for Cohort 8. LPS text amended to confirm LPS dose. Text deleted on additional cohorts, alternative dosing schedules etc and Section 7.2 referenced instead.	Change in study design. LPS dose was confirmed during Part A after completion of enabling study 207654. Reduction of repetition; dose / treatment related modifications that could be required are detailed in Section 7.2.
Section 6.1 Inclusion Criteria	Inclusion #1 age range split out for each study Part.	Increased clarity.
Section 6.2 Exclusion Criteria	Exclusion criteria modified (cardiac disease deleted from Exclusion #1, Exclusions #4 and #5 (new numbering) added / updated,	In line with overall rationale for amendment.

Section # and Name	Description of Change	Brief Rationale
	Exclusions #7, #8 and #9 (new numbering) added. Exclusion #3 updated to remove reference to fair / dark skin. Exclusion #24 (new numbering) amended to fasted glucose ≥7.0	 Implications discussed with participant rather than being an exclusion. In line with requirement for screening samples to be fasted.
Section 6.3.1 Meals and Dietary Restrictions	Part C Day 1 post-dose fast amended to 4 hours	To make consistent with Day 14.
Section 7.1 Treatment Administration Table 5	LPS text amended to confirm LPS dose.	LPS dose was confirmed during Part A after completion of enabling study 207654.
Section 7.2 Dose Modification	Section updated to describe in greater detail the possible dose / challenge related modifications that could potentially be required based on emerging data.	Increase clarity / flexible wording.
Section 7.3 Method of Treatment Assignment Part C	Text for 5:2 randomisation ratio clarified as being for Cohort 4. Text for Cohort 8 1:1 randomisation ratio added.	Change in study design.
Section 7.4 Blinding	Added that certain analytical lab staff at site can be unblinded	To reduce analytical burden at site for the monocyte isolation process with increased number of placebo intracellular PK samples which would not subsequently be analysed by GSK.
Section 8.1.6 Individual Safety Stopping Criteria	New criteria added.	Additional safety measure in line with overall rationale for amendment.
Section 9.4.2 Body Weight	Text revised to add specific Cohort numbers 4 and 8 and that body weight will be measured on day prior to challenge (as opposed to Day 13).	Clarification on Cohorts as this body weight assessment is for dose calculation of challenges and therefore does not apply to non-challenge cohorts 5-7. Removed reference to Day 13 for added flexibility in the event that fewer than 14 days dosing is required in Cohort 8.
Section 9.4.4 Vital Signs	Detail on blood pressure and pulse split out for Cohorts 5-7 separately from Cohorts 4 and 8.	Day 14 measurements in Cohorts 4 and 8 are more intensive due to monitoring requirements post-challenges. Less intensity required for Cohorts 5-7.
Section 9.4.5 Electrocardiograms	'or other exclusionary criteria' added to the end of third bullet on Holter monitoring.	To broaden this text to encompass other criteria that may apply.
Section 9.4.7	Additional bullet included to state that a PK sample and drugs of abuse test	Additional monitoring in line with overall rationale for the amendment.

Section # and Name	Description of Change	Brief Rationale
	should be taken if a cardiac arrhythmia occurs	
Section 9.6.1 Ex-vivo PD sample [S4]	Text revised to remove reference to 'TruCulture null' tubes and add reference to 'GSK3358699 LPS' tubes.	Emerging data indicates that a positive control sample is anticipated to be of more value than null samples.
Section 9.8.1.1 Cellular activation markers blood sample [E2b]	Heading text updated to add 'all cohorts in Part C'	Clarification
Section 9.8.1.2 Circulating inflammatory biomarkers blood sample [E2a]	Heading text updated to add "challenge cohorts only".	Clarification as this sample no longer applies to non-challenge cohorts 5-7.
Section 9.8.1.3 Ex-vivo LPS stimulation blood sample [E2c]	Section deleted.	Emerging data demonstrated that this sample would be of little value.
Section 9.8.1.3 Gene array panels	New section number now that LPS sample E2c is deleted. Heading text updated to add "challenge cohorts only".	Clarification as this sample no longer applies to non-challenge cohorts 5-7.
Section 10.2.1 Sample size assumptions Part C	Updated to detail and split out participant numbers and randomisation ratios for Cohort 4, Cohorts 5-7 and Cohort 8. Text deleted on additional cohorts, alternative dosing / randomisation schedules etc and Section 7.2 referenced instead.	Change to study design. Reduction of repetition; dose / treatment related modifications that could be required are detailed in Section 7.2.
Section 10.4.4 Interim Analyses	Text revised to include a formal interim analysis after Cohort 7, in the event that Cohort 8 is required.	To allow reporting on Part A, Part B and Cohorts 5-7 in Part C for primary and secondary study objectives whilst exploratory evaluation is ongoing.
Section 12.2 Appendix 2: Clinical Laboratory Tests	Gamma-glutamyl transferase and Creatine kinase added to laboratory assessments table	Additional monitoring
Section 12.3 Appendix 3; Dose Escalation Committee	Reference to Cohort 8 added.	Change to study design.

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: 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.

Short Title: First-time-in-Human Study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of single (in both fed and fasted states) or repeat doses of GSK3358699.

Rationale:

This first time in human (FTIH) study intends to identify doses of GSK3358699 that are well tolerated whilst delivering a robust pharmacodynamic response. As such, the study will involve the first administration of GSK3358699 to humans and will evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic profile of single (in both fed and fasted states) and multiple ascending doses of GSK3358699 in healthy male participants within a pre-defined and controlled pharmacodynamic and pharmacokinetic range. Further, this study will seek to understand the effect of GSK3358699 on systemic markers of inflammation following low dose *in vivo* Lipopolysaccharide (LPS) or Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) challenge and local inflammation in cantharidin-induced blisters as exploratory objectives. This experimental approach has been carefully designed to explore and inform the potential for GSK3358699 to become a transformative medicine for patients in multiple immuno-inflammatory disease indications.

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.	• Adverse event (AE) reporting. • Laboratory safety data (clinical chemistry, haematology, urinalysis). • Vital signs (blood pressure, heart rate, body temperature). • 12 lead electrocardiograms (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.

Objectives	Endpoints
• **[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.
• **[S5]** To assess the effect of food on the PK and pharmacodynamics (PD) of GSK3358699 and GSK3206944 following single doses in healthy male participants.	• Plasma concentrations of GSK3358699 and GSK3206944 plus derived PK parameters. • Monocyte intracellular quantification of GSK3206944. • Plasma concentrations of MCP-1, IL-6 and 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
S5: Secondary Objective 5 – Effect of food on PK and PD

Overall 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).

Number of Participants:

The number of participants and the required number of evaluable participants are outlined below:

Part	**Participants per cohort**	**Evaluable participant number per cohort**	**Evaluable participant definition**
A (Cohorts 1-2)	9 (6:3 GSK3358699 : Placebo)	6	Complete both screening and all their planned treatment Periods.
B (Cohort 3)	6 (all receive GSK3358699)	5	Complete both screening and both treatment Periods.
C (Cohort 4)	14 (10:4 GSK3358699 : Placebo)	9	Complete both screening and the 14 day treatment Period and subsequent 48 h assessment Period.
C (Cohorts 5-7)	18 (9:9 GSK3358699 : Placebo)	12	Complete both screening and the 14 day treatment Period and subsequent 48 h assessment Period.
C (Cohort 8)	20 (10:10 GSK3358699 : Placebo)	14	Complete both screening and the 14 day treatment Period and subsequent 48 h assessment Period.

Participants who are randomized into a particular part of the study can be enrolled in another part of the study, as well as be enrolled in a later cohort of the same part of the study in Part C, 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).

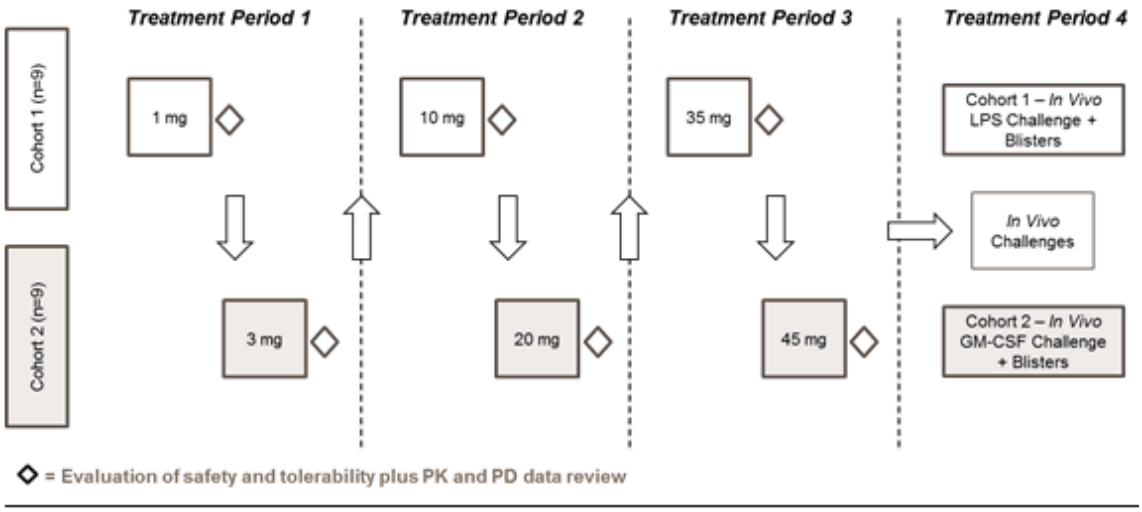
Additional participants/cohorts may be enrolled in Part A or Part C to allow for evaluation of additional dose levels or alternative regimens, including for challenges. No more than 9 additional participants will be included as part of a new cohort in Part A and no more than 20 additional participants will be allowed as part of a new cohort in Part C (ie in addition to Cohort 4-8 participants).

Treatment Groups and Duration:

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.

Part A: Single Ascending Doses and LPS / GM-CSF/ cantharidin blister challenges (Cohorts 1 and 2)

Part A Schematic: Planned Doses



In the Part A single dose escalation phase (treatment Periods 1-3), there will be two interlocking cohorts (Cohorts 1 and 2) each with 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 with planned doses of between 1 mg and 45 mg GSK3358699.

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 will be recruited for treatment Period 4 only and will be regarded as a replacement subject.

During each treatment Period, participants in an individual cohort will be admitted to the clinical unit on Day -1 and will remain there until completion of all assessments on Day 3 (at approximately 48 hours post-dose).

Upon conclusion of the dose escalation phase of Part A, an additional dosing Period (treatment Period 4) will be included. Eligible 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 approximately 48hrs post blister induction. Participants in Cohort 1 will be administered intravenous (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). Similarly, participants in Cohort 2 will be administered 60 μg/m^2 IV *in vivo* GM-CSF challenge

following treatment with GSK3358699 or placebo and will then have blisters induced on the forearm (0.2% cantharidin).

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. The doses of LPS and GM-CSF to be administered to participants have been defined as part of an ongoing clinical enabling study (Study ID 207654) and will be administered around the time of the GSK3358699 systemic maximum concentration (C_{max}) defined from data gathered in treatment Periods 1-3. The dose levels of GSK3358699 administered to either cohort in Period 4 will be identical and will be decided by the dose escalation committee (DEC). This will be a single dose of GSK3358699 that is within the range investigated in treatment Periods 1-3 of Part A.

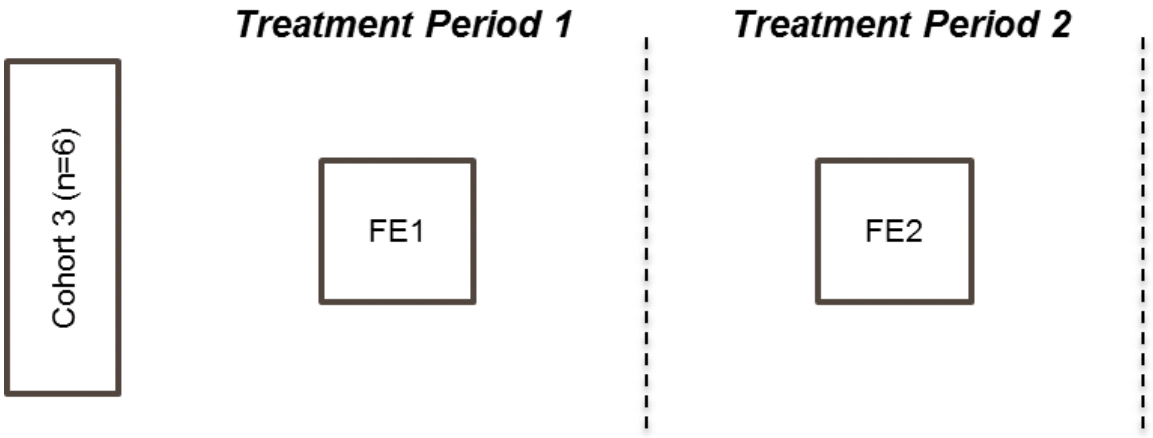
The duration of treatment Period 4 from Day -1 onwards and the implementation of sentinel dosing will be the same as for each of the treatment Periods 1-3.

There will be a minimum 14 days between each dosing in Cohort 1 and Cohort 2, and therefore a minimum 28 day washout period between the start of dosing, (ie dosing of sentinel participants) in each treatment Period for a particular cohort (including between Periods 3 and 4).

The total duration of this part of the study for each participant, including screening and follow-up, is approximately 19 weeks for participants taking part in all three dose escalation treatment Periods and 23 weeks if a participant takes part in all four treatment Periods. For replacement participants only taking part in the challenge treatment Period (Period 4), approximate study duration is 10 weeks.

Part B Food Effect (Cohort 3)

Part B Schematic



In Part B there will be one cohort of 6 participants (Cohort 3), taking part in a two-way crossover study. Each participant will receive a single oral dose of GSK3358699 under fed conditions in one of the two treatment Periods and under fasted conditions in the other treatment Period. The dose level chosen for Part B will be a dose level within the

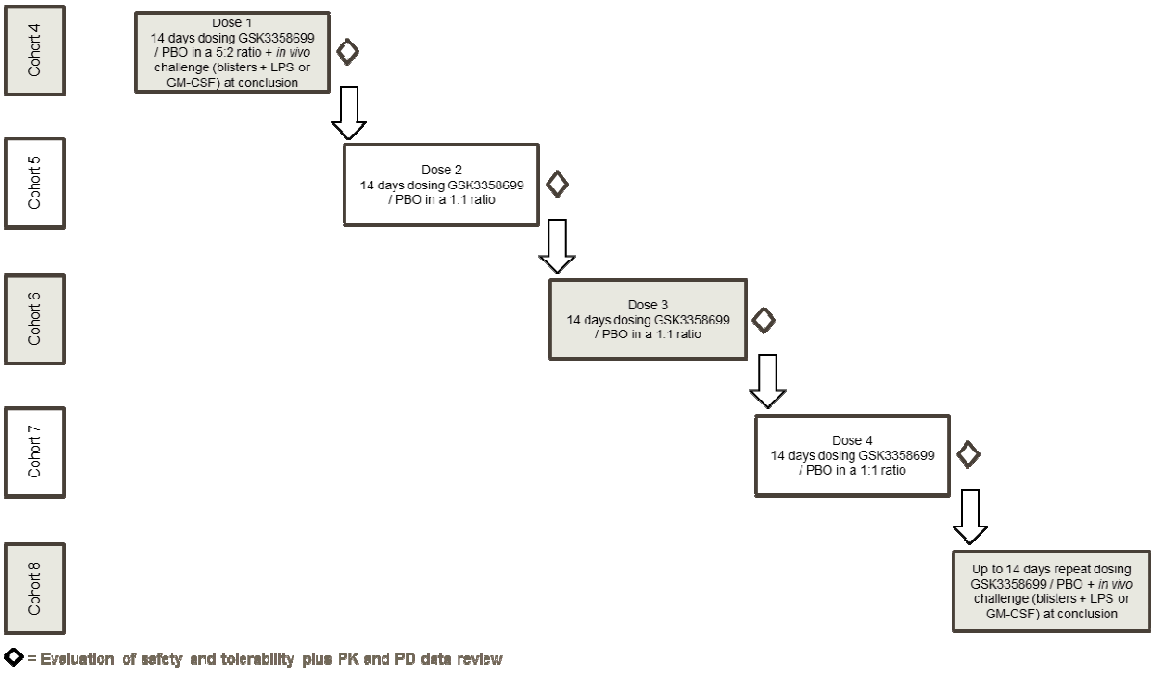
range already evaluated in the dose escalation part of the study (Part A) and one in which, based on *in silico* modelling, the maximum exposure will not be exceeded following either fed or fasted administration. The decision on the dose level of GSK3358699 to be administered in Part B will be made by the DEC.

During each treatment Period participants will be admitted to the clinical unit on Day -1 and will remain there until completion of all assessments on Day 3 (at approximately 48 hours post-dose).

There will be a minimum of 14 days between each dose. The total duration of this part of the study for each participant, including screening and follow-up, is approximately 9 weeks.

Part B will only be conducted after completion of the dose escalation phase of Part A and may be conducted in parallel with Part C.

Part C: Multiple Ascending Doses (Cohorts 4-8)
Part C Schematic



In Part C of the study there are 5 planned cohorts (Cohorts 4-8). Each cohort will take part in one repeat dose treatment Period with up to 14 days of once-daily dosing.

Cohort 4

Cohort 4 of the study is comprised of 14 participants, taking part in one repeat dose treatment Period, and 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. Participants 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 blister samples taken at approximately 48 hours post-blister induction.

On the final day of dosing either an IV *in vivo* LPS challenge, at a dose of 0.75 ng/kg or a 60 μg/m^2 GM-CSF IV infusion challenge will be administered followed by blister induction as described for Part A Period 4.

Half the participants will be randomised to receive cantharidin induced blisters with the LPS challenge and half will receive the cantharidin induced blisters with the GM-CSF challenge. In Cohort 4, 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.

The total duration of the study for each participant in Cohort 4, including screening and follow-up, is approximately 12 weeks.

Cohorts 5-7

Cohorts 5-7 will each comprise of 18 healthy male participants. Each cohort will take part in one repeat dose treatment Period. The 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.

All participants will be admitted to the clinical unit on the day prior to dosing (Day -1) and will remain in the Unit until after the 48 hour assessments following the Day 14 GSK3358699 / placebo dose administration have been completed (Day 16). Participants will then be discharged from the unit.

The total duration of the multiple ascending dose phase of Part C for each participant in Cohorts 5-7 , including screening and follow-up, is approximately 10 weeks.

Cohort 8

Upon conclusion of the multiple ascending dose phase of Part C (Cohorts 5 – 7), an additional Cohort (Cohort 8) is planned to be included. This cohort will be comprised of 20 participants, taking part in one repeat dose treatment period. Participants will be randomised in a 1:1 ratio to receive GSK3358699 or placebo once daily for up to 14 days. The actual duration of dosing will be decided by the DEC and will not exceed 14 consecutive days.

Participants 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 blister samples taken at approximately 48 hours post-blister induction.

On the final day of dosing either an IV *in vivo* LPS challenge, at a dose of 0.75 ng/kg or a 60 μg/m^2 GM-CSF IV infusion challenge will be administered followed by blister induction as described for Part A Period 4.

Half the participants will be randomised to receive cantharidin induced blisters with the LPS challenge and half will receive the cantharidin induced blisters with the GM-CSF

challenge. In Cohort 8, of the 10 participants receiving each challenge, it is planned that 5 will be randomised to receive GSK3358699 and 5 to receive placebo.

The randomisation ratio of active to placebo for Cohort 8 and any subsequent additional cohorts may be altered by the DEC based on all available safety, PK and PD data following the conclusion of Cohort 7.

Data from Part A of this study and from Cohorts 4 - 7 in Part C will be used to confirm the decision to include challenges in Part C Cohort 8. The decision will be made by the DEC.

The total duration of the study for each participant in Cohort 8, including screening and follow-up, is approximately 14 weeks.

In all cohorts, participants will be admitted to the clinical unit on the day prior to dosing (Day -1) and will remain in the Unit until after the 48 hour assessments following the final day of GSK3358699 / placebo dosing and challenge administrations have been completed.

The actual doses of GSK3358699 to be administered in Part A or Part C may be adjusted based on review of the safety, tolerability, PK and PD data from prior dose levels by the DEC. These dose adjustments may involve either an increase or a decrease in the planned dose. Safety, PK and PD stopping criteria will be strictly applied. Doses investigated in Part B or Part C will not exceed the magnitude of those investigated in Part A.

The dosing schedule may also be adjusted to expand a cohort to further evaluate safety, PK or PD findings at a given GSK3358699 dose level, or to add cohorts to evaluate additional dose levels or a change in the dosing regimen to less than or more than once daily. Dosing may also be halted before all planned dose levels have been completed if stopping criteria have been met or if a review of the data determines that evaluation of further dose levels is not necessary to meet study objectives.

In addition, decisions relating to the challenge agent administrations may be altered during the course of the study based on newly available data. This may include decisions to alter the timing of the LPS or GM-CSF challenge agent administration, or to evaluate more than one challenge agent administration timing. The evaluation of alternative LPS or GM-CSF challenge timings may involve inclusion in earlier cohorts, or expansion or addition of cohorts. Additionally it may be decided to include the blister induction and blister fluid harvest in cohorts prior to Cohort 8. It may also be decided that fewer than 14 days dosing is required in the challenge cohort.

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2. SCHEDULE OF ACTIVITIES (SOA)

2.1. 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				The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced i.e. treatment period 4
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).
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																
Discharge from Unit following in-patient stay														X				
Outpatient visit	X															X	X	

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
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 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.
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

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				
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: • 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 2.1.1. • Follow-up visits 1 and 2 (blister healing)

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
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															
Treatment Administration																		
Study Drug / Placebo Administration				X											See Period 4 SoA			

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
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.
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.

2.1.1. Part A Period 4 Schedule of Activities

Procedure	Treatment Period 4																Notes
	Day -10 (±3 days)	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 2.1.
				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 2.1.1.1 and Section 2.1.1.2. 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 2.1.1.1 and Section 2.1.1.2 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 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.

Procedure	Treatment Period 4															Notes
	Day -10 (±3 days)	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 2.1.
				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	
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 2.1.1.1 and Section 2.1.1.2 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														
Concomitant Medication Review				Monitored from first dose until the end of the final treatment Period													

Procedure	Treatment Period 4																Notes
	Day -10 (±3 days)	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 2.1.
				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	
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 2.1.1.1 and Section 2.1.1.2																

2.1.1.1. 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 2.1.1 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 in TruCulture tube for inflammatory markers **[E2c]**				X							X					Pre-dose and 6 hours post LPS challenge: Null and LPS tubes at both time points.
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).

2.1.1.2. Part A Period 4 Detailed SoA for GM-CSF 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 **start time** of the GM-CSF infusion **not** GSK3358699 administration											Day 2	Day 3	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 2.1.1 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, 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).

2.2. Part B Food Effect Schedule of Activities

Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Periods 1 and 2													Follow-up 1 (7-14 days post-last dose)	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															
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).
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	BP, HR, temperature, respiratory rate.

Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Periods 1 and 2												Follow-up 1 (7-14 days post-last dose)	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	
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, pre-dose Day 1, 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 any blood draws or dosing scheduled for the same nominal time point.
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. Follow-up visit samples do not require fasting.
Coagulation	X										X		X	X	X	Fasted screening samples. Follow-up visit samples do not require fasting.
Clinical Chemistry	X	X									X		X	X	X	Fasted screening samples. Follow-up visit samples do not require fasting. Gamma-Glutamyl Transferase (GGT) and creatine kinase (CK) to be included at screening, Day-1 and follow up only.
Urinalysis	X	X									X		X	X	X	Fasted screening samples. 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.															
Concomitant Medication Review			Monitored from first dose until the end of the final treatment Period													

Procedure	Screening (up to 35 Days prior to Day 1)	Treatment Periods 1 and 2												Follow-up 1 (7-14 days post-last dose)	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	
Treatment administration															
High Fat Breakfast			X												Participants will receive a high fat breakfast prior to dosing in one of the two treatment Periods only. See Section 6.3.1 for further details.
Study Drug Administration				X											
Pharmacokinetics, Pharmacodynamics and Genetics Sample															
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	X	In total six samples (3 LPS and 3 LPS + GSK3358699) 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 LPS + GSK3358699) to be taken at approximately 08:00. All sample timepoints pre- and post-dose require 1 LPS and 1 LPS + GSK3358699 sample.
Blood sample for potential companion diagnostic development		X													Sample to be taken on Day -1 in treatment Period 1 only.
Blood sample for *CES* genotyping and optional genetic research **[E5]**		X													Sample to be taken on Day -1 in treatment Period 1 only.

2.3. 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).
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 2.3.1 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 be performed prior to any blood draws or dosing scheduled for the same nominal time point.

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		
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 2.3.1 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 2.3.1 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.																			
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																				

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 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 2.3.1 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		On Day 1 samples will be taken at 1h, 4h and 8h post-dose. Pre-dose samples Days 4, 8 and 12. See Section 2.3.1 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, 17:00 and 20:00. 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 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 2.3.1 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 2.3.1 for Day 14 and 15 sample timings.
Blood sample for cellular activation markers **[E2b]**			X			X				X				X		X				Pre-dose samples Days 1, 4, 8 and 12. See Section 2.3.1 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.

2.3.1. 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						

2.4. 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).
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 2.4.2 and Section 2.4.3 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 be performed prior to any blood draws or dosing scheduled for the same nominal time

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
																								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 2.4.2 and Section 2.4.3 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 2.4.2 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
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																				

Procedure	Screening (up to 45 Days prior to Day 1)	Day -10 (± 3 days)	24-48 hours following Day -10 visit	Treatment Period: 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	Follow-up 1 (7-14 days post-last dose)	Follow-up 2 (5 weeks after last dose ± 3 days)	Notes
																							The 2nd follow up visit is only required for those participants where challenges are being administered and blisters induced
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 2.4.2 and Section 2.4.3 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 2.4.2 and Section 2.4.3 for further details on Day 14 blister timings.
In vivo LPS or GM-CSF Challenge																		X					See Section 2.4.1 for further details.
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 2.4.1 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 2.4.1 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, 17:00 and 20:00. Day 1 and Day 14 pre-dose samples to be taken at approximately 08:00. Day 1 and Day 13 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 2.4.1 for Day 14 and 15 sample timings. All sample timepoints pre- and post-dose require 1 LPS and 1 LPS + GSK3358699 sample.
Blood sample for					X	X		X				X				X		X	X				On Day 1 samples will be taken at pre-dose, 2h, 4h and 8h

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
circulating proteins **[E1a]**																								post-dose. Samples to be taken pre-dose Day 2, 4, 8 and 12. See Section 2.4.1 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 2.4.1, Section 2.4.2 and Section 2.4.3 for Day 14 and 15 sample timings for E2d.
Blood sample for circulating inflammatory biomarkers **[E2a]**																		X	X	X				See Section 2.4.2 and Section 2.4.3 for sample timings.
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 2.4.2 and Section 2.4.3 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 2.4.2 and Section 2.4.3 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.

2.4.1. 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 2.4.2 and Section 2.4.3													

2.4.2. 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 2.4.1 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.

2.4.3. 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 2.4.1 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.

3. INTRODUCTION

GSK3358699 is a targeted inhibitor of the bromodomain and extra-terminal domain (BET) family of epigenetic reader proteins [Ferri et al 2016, Chung et al 2012, Filippakopoulos et al 2014]. Recent literature reports have demonstrated that inhibitors of this protein family profoundly affect many of the pro-inflammatory molecular and cellular mechanisms which underpin a multitude of immuno-inflammatory diseases [Nicodeme et al 2010, Mele et al 2013, Klein et al 2016]. To date, however, the clinical evaluation of panBET inhibitors such as GSK525762 [Mirguet et al 2013] has centred on oncology, with no reports citing the use of this pharmacology outside malignant neoplastic diseases [Jung et al 2015, Belkina et al 2012, Yu et al 2015, Dawson et al 2012]. With a view to further exploring the potential of BET family inhibition in human disease, GlaxoSmithKline (GSK) is developing GSK3358699, a mononuclear myeloid targeted BET inhibitor. Based on pre-clinical work to date GSK3358699 has the potential to effect positive outcomes in myeloid-centric diseases with unmet need; including but not limited to rheumatoid arthritis (RA), psoriasis, fibrotic liver disease and inflammatory bowel disease (IBD), with the potential to provide an improved safety profile compared to other panBET inhibitors [GlaxoSmithKline Document Number 2017N333959_00].

In contrast to conventional inhibitors of the BET proteins and unique within this target class, GSK3358699 encompasses within its chemical structure an Esterase Sensitive Motif (ESM) [Needham et al 2011]. This cell targeting technology enables preferential delivery of the BET pharmacology to cells expressing human carboxyesterase-1 (*CES*-1), thereby limiting less desirable systemic effects. These target cells are primarily those of the mononuclear-myeloid lineage, including monocytes, macrophages and dendritic cells, but also include hepatocytes.

More specifically, GSK3358699 is selectively hydrolysed by the esterase *CES*-1 in target cells to form a pharmacologically active carboxylic acid, GSK3206944. Like GSK3358699, this acid metabolite is a potent BET inhibitor, which, because of its charged nature, is selectively retained in high local concentrations within mononuclear myeloid cells.

Targeting inflammatory cells that are sensitive to BET inhibition and play a key role in many inflammatory diseases [Chan et al 2015] should reduce non-target side effects leading to a wider therapeutic window relative to conventional non-targeted BET inhibitors. As a result, GSK3358699 has the potential to become a novel and important therapeutic modality for the treatment of inflammatory and fibrotic disorders.

3.1. Study Rationale

This first time in human (FTIH) study intends to identify doses of GSK3358699 that are well tolerated whilst delivering a robust pharmacodynamic response. As such, the study will evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile of single (in both fed and fasted states) and multiple ascending doses of GSK3358699 in healthy male participants within a pre-defined and controlled pharmacodynamic and pharmacokinetic range for each cohort. Compound exposures

investigated as part of this study will not intentionally exceed pre-defined PK and PD stopping criteria as highlighted in Section 8.

Further, this study will seek to understand the effect of GSK3358699 on systemic markers of inflammation following low dose *in vivo* lipopolysaccharide (LPS) or Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) challenge and local inflammation in cantharidin-induced blisters. This experimental approach has been carefully designed to explore the *in vivo* biology of the target and to inform potential immuno-inflammatory indications where GSK3358699 could provide substantial efficacy to address unmet clinical need.

3.2. Background

Pre-clinically, BET inhibitors have demonstrated profound anti-inflammatory and anti-fibrotic effects, driven by their ability to regulate gene expression at an epigenetic level. Indeed, non-targeted BET inhibitors have been shown to interact *in vitro* with multiple cellular effectors of disease and are efficacious in a range of animal models of disease [Nadeem et al 2015, Meng et al 2014, Cheung et al 2017]. As the first targeted BET inhibitor, GSK3358699 has exhibited potent immuno-modulatory effects *in vitro*, for example in human whole blood assays stimulated with LPS or GM-CSF, as well as in samples from rheumatoid arthritis patients. Further to this, GSK3358699, when investigated in a mouse model of arthritis, effectively inhibited joint inflammation and bone erosion, and abrogated cytokine production in an acute LPS challenge in cynomolgus monkeys. A detailed description of the chemistry, pharmacology and safety of GSK3358699 is provided in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2017N333959_00].

3.3. Benefit/Risk Assessment

There is no direct benefit to the participants taking part in this study.

The risk assessment of GSK3358699 is based on the pre-clinical studies conducted to date. Summaries of findings from these pre-clinical studies can be found in the IB. Details of these risks, as well as the risks associated with the challenge agents, and the proposed strategy to mitigate/monitor these risks are detailed in Section 3.3.1. For transparency, emerging clinical data from this study on NSVTs is also included as a potential risk, although causality with GSK3358699 has not been established and similar findings were not observed preclinically.

In this study, safety will be monitored closely both by subjective reporting and by objective means, i.e. serial assessments of vital signs, clinical laboratory information and cardiac monitoring. The study will be run in a clinical unit with immediate access to hospital facilities for the treatment of medical emergencies. Participants will remain monitored in the clinic for the duration of each treatment Period and will only be discharged from the unit at the end of each treatment Period if the investigator deems it safe to do so.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events may be found in the Participant Information Leaflet for GM-CSF and cantharidin and in previous literature for LPS [Fullerton et al 2016].

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Investigational Medicinal Product (IMP) GSK3358699		
Lipid elevations	• Non-adverse increased triglyceride was evident in female monkeys given ≥ 1 mg/kg/day. Higher triglyceride and/or cholesterol concentrations were also seen in rats given ≥10 mg/kg/day. The effects on triglycerides in monkeys and rats and the no observed effect level (NOEL) for rats are below the maximum predicted human exposure (AUC) at 45 mg.	**Participant Selection / Monitoring / Stopping criteria:** • Specific eligibility and withdrawal criteria (see Section 6.2 and Section 8). • The protocol includes laboratory assessments for triglycerides. Fasting lipids will additionally be monitored during part C (repeat dosing) of the study. • Relevant lipid data from the current and any previous cohort will be considered as part of dose escalation decisions.
Coagulation	• Non-adverse increases in anticoagulant (prothrombin time (PT) and activated partial thromboplastin time (APTT)) and procoagulant (fibrinogen) factors were evident in rats at ≥ 10 mg/kg/day and in individual monkeys given ≥ 10 mg/kg/day in a dose ranging study for 15 days. No changes in PT or APTT were seen in monkeys given GSK3358699 for 6 weeks. The effects on fibrinogen and the NOEL for clotting times in rat are below the maximum predicted human exposure (AUC) at 45 mg.	**Participant Selection / Monitoring / Stopping criteria:** • Specific eligibility criteria based on history of prior thrombotic or bleeding disease (see Section 6.2). • The protocol includes evaluation of clotting parameters to assess potential changes in fibrinogen, PT and APTT. • Relevant coagulation and thrombotic safety data from the current and any previous cohort will be considered as part of dose escalation decisions.
Kidney function	• Non-adverse increased urinary glucose concentration was seen in female monkeys and rats given ≥10 mg/kg/day. Other clinical pathology that may be related to perturbations in kidney function were seen in monkeys or rats. Monkeys given ≥3 mg/kg/day for 6 weeks had decreased plasma albumin; rats given ≥10 mg/kg/day for 6 weeks had decreased urinary volume, lower urinary total protein and protein concentrations, variable changes in plasma creatinine concentration and urea, higher glucose and phosphorus concentrations and slightly lower sodium,	**Participant Selection / Monitoring/ Stopping Criteria:** • Specific eligibility - criteria (see Section 6.2). • The protocol includes laboratory assessments for renal function, electrolytes, fasting glucose, as well as urinary glucose assessment. • Relevant renal and glycaemic safety data from the current and any previous cohort will be considered as part of dose escalation decisions.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
	potassium and chloride concentrations. • No histological changes were seen in the kidneys of monkeys given GSK3358699. Tubular dilatation and higher kidney weight was evident at the non-tolerated 100 mg/kg/day dose in male rats. • Some of the urinary effects in rats are evident below the maximum predicted human exposure (AUC) at 45 mg and the NOEL in monkeys at or below parity to the maximum predicted human exposure (AUC) at 45 mg.	
Gastrointestinal (GI)	• Gastrointestinal toxicity was observed following repeat oral dosing in rats and cynomolgus monkeys at ≥100 and ≥10 mg/kg/day, respectively. In rats and monkeys there is an approximately 6-fold margin from the maximum predicted human exposure (AUC) at 45 mg to the no observed adverse effect limit (NOAEL) for gastrointestinal effects in the 6 week studies. No gastrointestinal effects were observed in the predicted clinical range up to a maximum of 45 mg. • Clinical presentation included body weight reductions and/or loose feces, emesis and reduced food consumption and were dose limiting at ≥100 mg/kg in rats and 30 mg/kg in monkeys. • Effects in monkeys dosed for 6 weeks were limited to non-adverse slight erosion, oedema, haemorrhage and inflammatory cell infiltrate in the stomach of a single animal given 10 mg/kg/day. Similar findings, extending to the intestines, were seen in a different study where monkeys were dosed at ≥10 mg/kg for up to 15 days. Effects seen at 30 mg/kg/day for up to 15 days were of greater severity, extended to the intestines and contributed to the morbidity of a single animal. Effects in rats dosed up to 6 weeks included atrophy and ulceration and were considered adverse.	**Dose Selection:** • Doses administered as part of this study will not intentionally exceed the GSK3358699 area under the concentration – time curve (AUC) of 255 ng/ml.h, systemic maximum concentration (C_{max})42 ng/ml which are the predicted AUC and C_{max} at 45 mg once daily (QD). **Participant Selection / Monitoring / Stopping Criteria:** • Specific eligibility and withdrawal criteria (see Section 6.2 and Section 8) are included. • Participant monitoring will be based on prior clinical experience with inhibitors from this target class, Medical history, physical examination and AE reporting will be used to monitor for toxicity in the GI tract. Supportive therapy will be provided as per standard medical practice. In the event of clinically significant toxicity, the participant will be withdrawn and supportive therapy provided according to standard medical practice. • Relevant GI safety data from the current and any previous cohort will be considered as part of dose escalation decisions.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
QTc prolongation	• QTc prolongation was observed in cynomolgus monkeys following single and repeat doses of ≥ 10 mg/kg, up to a maximum of 38 msec increase (16% change from pretreatment), but importantly, no arrhythmias were observed. There is a 3 fold margin and approximate parity to the maximum predicted human exposure (free C_{max} and AUC respectively) at 45 mg to the NOEL for QTc prolongation in monkeys. • The QTc prolongation was not induced by direct inhibition of hERG binding with a > 164 fold from the hERG binding inhibitory concentration (IC)50 (89.97 μM) to the GSK3358699 free maximum plasma concentration (C_{max}) at 10 mg/kg in monkeys.	**Dose Selection:** • Doses administered as part of this study will not intentionally exceed the GSK3358699 AUC of 255 ng/ml.h, C_{max} 42 ng/ml which are the predicted AUC and C_{max} at 45 mg QD. **Participant Selection/ Monitoring / Stopping Criteria:** • Specific eligibility and withdrawal criteria (see Section 6.2 and Section 8). • The protocol includes cardiac monitoring (12 lead ECGs and telemetry) of participants at each dose level investigated. • Relevant cardiovascular safety data from the current and any previous cohort will be considered as part of dose escalation decisions.
Phototoxicity	• The ultraviolet (UV)/visible (VIS) spectrum for GSK3358699 showed absorbance in the region of concern which indicate a potential for a human phototoxicity risk.	**Participant Selection / Monitoring:** • Participants will be advised not to sunbathe or use sunbeds and to wear suitable clothing that minimises exposed areas of skin and to use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) on exposed areas when outdoors. • In addition, participants should wear sunglasses that filter UVA and UVB rays. These protections are recommended from day-1 for a minimum of 5 half-lives after GSK3358699 discontinuation. • Specific eligibility criteria (see Section 6.2) • Physical examination and AE reporting will be used to identify and assess phototoxicity. • Relevant safety data from the current and any previous cohort will be considered as part of dose escalation decisions.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Testicular	• No testicular findings were observed in monkeys dosed up to 6 weeks at the maximum tolerated dose of 10 mg/kg/day. • In the rat, testicular findings (sperm retention and/or minimal to slight germ cell degeneration, tubular vacuolation and multinucleate germ cells) were evident at non-tolerated doses of ≥100 mg/kg/day with an 8-fold margin from the maximum predicted human exposure (AUC) at 45 mg to the NOAEL for testicular effects.	**Dose Selection:** • Doses administered as part of this study will not intentionally exceed the GSK3358699 AUC of 255 ng/ml.h, C_{max} 42 ng/ml which are the predicted AUC and C_{max} at 45 mg QD. **Participant Selection / Monitoring:** • AE reporting will be used to identify and assess any signs and symptoms related to testicular safety. • Appropriate contraceptive measures for participants is included in Section 6.1 and Section 12.5. • Relevant safety data from the current and any previous cohort will be considered as part of dose escalation decisions.
Aneugenicity	• GSK3358699 has been determined to be an aneugen with a 7.-fold margin to the maximum predicted human exposure (C_{max}) at 45 mg to the NOEL for aneugenicity in rats. • GSK3359699 is derived from a series of benzimidazoles. Benzimidazoles as a class are known aneugens and the rodent carcinogenicity data and clinical exposure data for benzimidazoles indicates that there is no evidence for translation of the observed aneuploidy in to a carcinogenic risk for humans.	**Dose Selection:** • Doses administered as part of this study will not intentionally exceed the GSK3358699 AUC of 255 ng/ml.h, C_{max} 42 ng/ml which are the predicted AUC and C_{max} at 45 mg QD.
Haematologic	• Variable changes in red blood cell parameters were noted at non-tolerated doses in both rats and monkeys. At tolerated doses, no hematological changes were seen in monkey and increased red cell distribution width (RDW), reticulocytes and/or MCV were seen in rats. • No microscopic changes were observed in the hematopoietic and lymphoid organs of monkeys and those evident in rats given ≥ 100 mg/kg/day were considered	**Dose Selection:** • Doses administered as part of this study will not intentionally exceed the GSK3358699 AUC of 255 ng/ml.h, C_{max} 42 ng/ml which are the predicted AUC and C_{max} at 45 mg QD. **Participant Selection / Monitoring / Stopping Criteria:** • Specific eligibility and withdrawal criteria (see Section 6.2

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
	non-adverse. Further details are in the IB Section 2. • Decreases in platelet count were not observed preclinically with GSK3358699 but have been observed with panBET inhibitors in the clinic.	and Section 8). • The protocol includes laboratory haematological assessments. • Relevant haematological safety data from the current and any previous cohort will be considered as part of dose escalation decisions.
Hepatic	• Findings in the liver of monkeys dosed for 6 weeks consisted of non-adverse centrilobular vacuolation in a single animal given 10 mg/kg/day. Cytoplasmic rarefaction, hepatocellular hypertrophy and microvesicular vacuolation were seen in dose ranging monkey study. Non-adverse effects were also seen in rats given 100 mg/kg/day for 6 weeks and included cytoplasmic vacuolation, cytoplasmic basophilia and decreased inflammatory infiltration. • Clinical pathology changes potentially related to the liver findings include higher alkaline phosphatase (ALP) and aspartate aminotransferase (AST) activities in rats given 100 mg/kg/day. Increases in total bilirubin was also evident in rats given 100 mg/kg/day. There was no evidence of hepatobiliary damage in any toxicology studies conducted with GSK3358699. • There is approximate parity and a 7- fold margin from the maximum predicted human exposure (AUC) at 45 mg to the NOEL for liver effects in monkeys and rats respectively.	**Dose Selection:** • Doses administered as part of this study will not intentionally exceed the GSK3358699 AUC of 255 ng/ml.h, C_{max} 42 ng/ml which are the predicted AUC and C_{max} at 45 mg QD. **Participant Selection / Monitoring / Stopping Criteria:** • Specific eligibility and withdrawal criteria (see Section 6.2 and Section 8). • The protocol includes laboratory liver chemistry assessments. • Relevant liver safety data from the current and any previous cohort will be considered as part of dose escalation decisions.
Non-sustained ventricular tachycardia (NSVT)	• Four cases of asymptomatic, non-serious, non-severe and self-limiting NSVT were observed in this study (207546); 2 in Part A and 2 in Part C. There was a lack of correlation between measured GSK3358699 systemic concentrations and the NSVTs. Similar findings were not observed preclinically.	**Participant Selection / Monitoring / Stopping criteria:** • Specific eligibility criteria (see Section 6.2). • Additional withdrawal criterion based on investigator and medical monitor judgement (see Section 8.1.6.). • The protocol includes cardiac screening and monitoring (12 lead ECGs and telemetry) of participants at each dose level

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		investigated. • Randomisation ratio in Part C has been changed to 1:1 (GSK3358699:placebo) Relevant cardiovascular safety data from the current and any previous cohort will be considered as part of dose escalation decisions.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Haemodynamic	• An increase in heart rate (increased by up to 46 beats per minute (bpm)) was observed after 13 doses of a non-tolerated 30 mg/kg/day dose in a single cynomolgus monkey with a 16 fold margin to the NOEL (free C_{max}). • No abnormalities were observed histologically in the hearts of rats or monkeys given GSK3358699 for up to 6 weeks.	**Dose Selection:** • Doses administered as part of this study will not intentionally exceed the GSK3358699 AUC of 255 ng/ml.h, C_{max} 42 ng/ml which are the predicted AUC and C_{max} at 45 mg QD. **Participant Monitoring:** • The protocol includes cardiac monitoring (vital signs, 12 lead ECGs and telemetry) of participants at each dose level investigated. • Relevant cardiovascular safety data from the current and any previous cohort will be considered as part of dose escalation decisions.
Drug-Drug Interactions (DDIs)	• GSK3358699 is a weak metabolism dependent inhibitor of Cytochrome P450 3A4 (CYP3A4) hence there is a risk of inhibiting CYP3A4 substrate con-meds resulting in clinically relevant DDIs.	**Study Design:** • GSK3358699 will not be administered with any other drug or known CYP3A4 substrate as part of this FTIH protocol. • Human PK data generated as part of this study will be used with in vitro data to inform the DDI risk associated with GSK3358699 and future clinical mitigation strategies.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Low-dose LPS, GM-CSF and cantharidin are established models in healthy volunteer studies and are expected to be well tolerated. The information on the challenge agents in this section is provided in the interest of full disclosure of all potential risks		
Intravenous LPS Challenge Agent		
Immune response leading to influenza – like symptoms.	• Previous studies have shown that single intravenous doses of 0.5 ng/kg (6 EU/ng) has been well tolerated in healthy male participants, however literature reports of 2 ng/kg (10 EU/ng) and above are very poorly tolerated and elicit considerable symptoms. • Observed adverse events were of mild severity and self-limiting without therapeutic intervention.	• LPS will be used at a concentration of 0.75 ng/kg. A low, single dose of LPS is planned which means that systemic exposure will be limited. • The participants will be dosed with LPS in a Medicines and Healthcare Products Regulatory Agency (MHRA) accredited clinical research unit and will have regular monitoring of vital signs post dose. • Participants will receive telemetry for a minimum of 12 hours post-LPS dose or until their telemetry shows no clinically significant findings for 4 hours (whichever is longer). • Participants will be prehydrated with intravenous fluids prior to LPS challenge, and intravenous fluid hydration will continue following the challenge. Normal saline will be infused at a rate of 250ml/hr for 4 hours prior to LPS dosing and 8 hours subsequently. • Participants with previous history of frequent vasovagal syncope will be excluded from the study • Participants with previous experimental exposure to IV LPS will be excluded.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Intravenous GM-CSF Challenge Agent		
Risk of respiratory, hepatic, renal and cardiovascular symptoms in addition to fluid retention.	• If used at high doses, GM-CSF administration might result in increased risk of respiratory, hepatic, renal and cardiovascular symptoms in addition to fluid retention; fluid retention findings were observed in patients with cancer in receipt of chemotherapy. • Observed adverse events were of mild severity and self-limiting without therapeutic intervention.	• GM-CSF will be used at a dose of 60 µg/m^2 that has previously been safely explored in a GSK sponsored study conducted in healthy male participants (207654). A low, single dose of GM-CSF is planned which means that systemic exposure will be limited. • Individuals with prior incidence of respiratory or cardiovascular diseases or pre-existing renal or hepatic dysfunction will be excluded from the study. In addition, we will use telemetry for a minimum of 6 hours following dosing, or until normal for 4 hours (whichever is longer). • Use of healthy volunteers is a mitigation for the fluid retention finding. In addition, a lower, single dose of GM-CSF is planned which means that the AUC and C_{max} will be lower than in the patients in which this was observed.
Topical Cantharidin Challenge Agent		
Irritation, burning or toxicity.	• Cantharidin is a corrosive chemical substance which when used inappropriately may cause skin irritation, burning or toxicity.	• Cantharidin has been used clinically to treat warts and extensively in a clinical setting in experimental medicine studies to chemically induce blisters. • Cantharidin will be used at a known concentration lower than has been safely explored in GSK sponsored studies conducted in patients and healthy participants, (ie reduced in this study from 0.7% to 0.2 %). • Participants with a history of lymphangitis and/or lymphoedema or any participant who has undergone surgery resulting in loss of tissue associated with lymphoid drainage (e.g. certain breast surgery procedures) are excluded. • Participants will be advised to wear loose clothing at the site of blistering to minimise hyperaesthesia and discomfort that may occur.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		• For immediate relief of any discomfort, paracetamol, at doses of ≤2 grams/day will be given to the participant, unless, in the opinion of the investigator and sponsor, the medication will interfere with the study. • Participants with history of keloids, skin allergy, hypersensitivity, or contact dermatitis, including previous reactions to dressings to be used in this study or any chronic skin disorder (e.g. psoriasis, atopic dermatitis, vitiligo) excepting isolated lesions remote from intended site of application of cantharidin are excluded. Appropriate skin care to avoid dyspigmentation and hypertrophic scar will be implemented. • To minimize the risk of infection, appropriate clean procedures will be followed. Participants will be instructed to visually inspect blister sites on a daily basis and are informed what signs of inflammation/infection to watch for and contact the investigator with any concerns. • Cantharidin will not be dispensed to participants and all applications will be done at the research centre by suitably trained personnel.

3.3.2. Benefit Assessment

There will be no direct benefit to the healthy participants in this trial. However, the information obtained from this study will critically inform the conduct of future clinical studies to develop new therapies in immuno-inflammation indications in areas of unmet medical need.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK3358699, LPS, GM-CSF and cantharidin at the doses to be administered are considered minimal and are justified.

4. 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.
• **[S5]** To assess the effect of food on the PK and PD of GSK3358699 and GSK3206944 following single doses in healthy male participants.	• Plasma concentrations of GSK3358699 and GSK3206944 plus derived PK parameters. • Monocyte intracellular quantification of GSK3206944.

Objectives	Endpoints
	• Plasma concentrations of MCP-1, IL-6 and TNF in blood stimulated *ex vivo* with LPS over time.
Exploratory	
• **[E1]** To investigate effects on basal production of biomarkers of target engagement following single and repeat oral doses of GSK3358699 in healthy male participants.	• Time course of circulating leukocyte numbers and circulating proteins; may include but is not limited to MCP-1, IL-12p40 and matrix metallopeptidase (MMP)-9. • Gene panel using participant whole blood.
• **[E2]** To investigate effects on inflammatory biomarkers after low dose *in vivo* LPS or GM-CSF challenge following single and repeat oral doses of GSK3358699 in healthy male participants.	• Time course of circulating soluble inflammatory biomarkers; may include but is not limited to IL-1β, IL-6, IL-8, TNF, MCP-1, GM-CSF, C-reactive protein (CRP). • Time course of leukocyte numbers and cellular activation markers may include, but not limited to expression of cluster of differentiation (CD) molecules CD16, CD86, CD80, CD163, CD206, CD83, CD40, CD209, Human Leukocyte Antigen – antigen D Related (HLA-DR) in circulating leukocytes. • Gene panel using participant whole blood.
• **[E3]** To investigate effects on chemotaxis and inflammatory mediators in cantharidin-induced blisters following single and repeat oral doses of GSK3358699 in healthy male participants.	• Soluble inflammatory biomarkers in skin blisters; may include but is not limited to IL-1β, IL-6, IL-8, TNF, MCP-1, GM-CSF. Blister volumes and differential cell counts; cellular activation markers that may include, but not limited to expression of CD16, CD86, CD80, CD163, CD206, CD83, CD40, CD209, HLA-DR in blister leukocytes.
• **[E4]** To collect residual plasma following GSK3358699 & GSK3206944 analysis, and urine samples, for analysis of metabolites of GSK3358699	• Metabolites of GSK3358699 in plasma and urine. These analyses will be run and reported under a separate protocol.
• **[E5]** To explore the impact of CES genetic variation on PK and PD parameters of GSK3358699 and GSK3206944.	• Genotype results using participant whole blood.

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
S5: Secondary Objective 5 – Effect of food on PK and PD
E1: Exploratory Objective 1 – Effect on basal production of biomarkers of TE
E2: Exploratory Objective 2 – Effects on inflammatory biomarkers after low dose in vivo LPS or GM-CSF challenge
E3: Exploratory Objective 3 – Biomarkers in blisters
E4: Exploratory Objective 4 – PK metabolite analysis
E5: Exploratory Objective 5 – CES genetic variation

5. STUDY DESIGN

5.1. Overall 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).

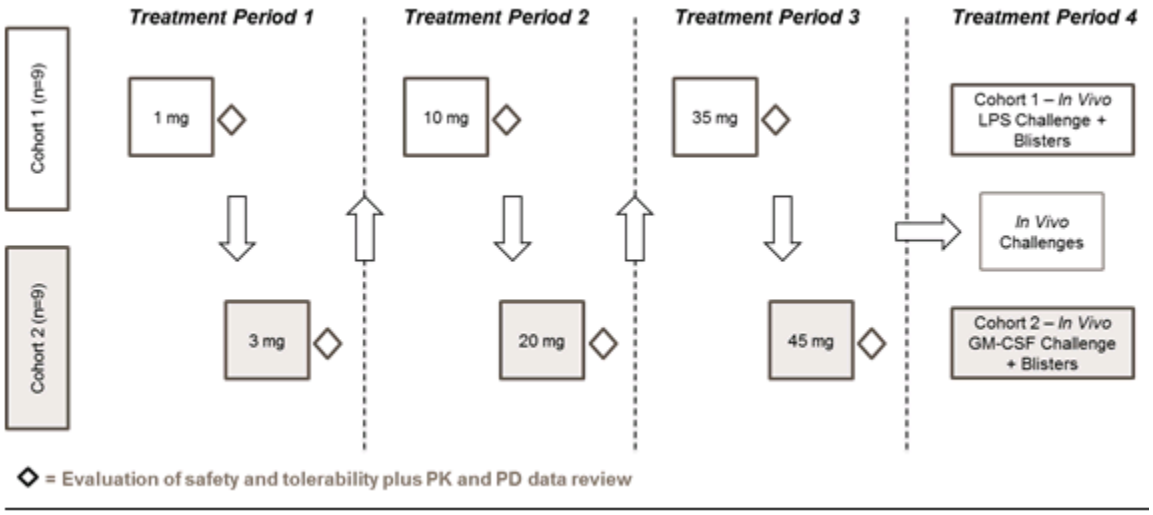
All participants in Part A, Part B and Part C of the study will attend a screening visit within 35 days prior to their first dose (with the exception of Cohort 8 where the screening visit will be within 45 days prior to their first dose) and a follow up visit within 7-14 days of their last dose. A second 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.

5.1.1. Part A

5.1.1.1. Part A Single Ascending Doses – Cohort 1 and Cohort 2:

In the Part A dose escalation phase (treatment Periods 1-3), there will be two interlocking cohorts (Cohorts 1 and 2) each with 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 as illustrated in Figure 1 below.

Figure 1 Part A Schematic Planned Single Ascending Doses and LPS / GM-CSF challenges



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) as detailed in Section 5.1.1.2. 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 will be recruited for treatment Period 4 only and will be regarded as a replacement subject.

During each treatment Period, participants in an individual cohort will be admitted to the clinical unit on Day -1 and will remain there until completion of all assessments on Day 3 (at approximately 48 hours post-dose). Participants will then be discharged from the unit.

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 approximately 48 hrs post-dose, the remaining participants in the cohort can then be dosed from the morning of Day 2.

Data will be reviewed between each treatment Period, and hence dose level, and there will be a minimum 14 days between the start of dosing, (ie 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 based on:

- assessment of safety, measurable plasma GSK3358699 PK concentrations and derived PK parameters and TE data obtained in a minimum of 6 participants (a minimum of 48 hours post-dose) in the most recently dosed group of subjects. Individual safety data (AEs, laboratory safety tests, ECGs and vital signs) will be reviewed.

- evaluation of all available safety, tolerability, PK, and PD data accumulated from preceding dose levels.

Safety stopping criteria will be strictly applied, precise details of these criteria can be found in Section 8. In addition, specific PK and PD stopping criteria will apply to this FTIH study:

- Dose escalation will be halted if the mean cohort exposure exceeds or is predicted to exceed a ***GSK3358699 C_{max} of 42 ng/ml or a total daily GSK3358699 AUC of 255 ng/ml.h***, which are the predicted exposures of the planned maximum dose of 45 mg.

- Individuals in each cohort will be monitored throughout the study. If 2 or more participants in a given cohort at the same dose level exceed C_{max} of 42 ng/ml or total daily AUC of 255 ng/ml.h, dose escalation will be halted.

- Based on the PD of GSK3358699, dose escalation will be halted if mean target engagement within a cohort, as measured by MCP-1 and TNF inhibition in participant blood stimulated *ex vivo* with LPS, exceeds or is predicted to exceed the desired profile: ***maintenance of ≥ 90% MCP-1 and TNF inhibition for a minimum of 12 hours post dose relative to baseline***.

- Additionally, if the PD effect of GSK3358699 appears to have become saturated over the course of 2 consecutive dose levels, dose escalation will be halted.

Furthermore, throughout all parts of the study, either a population PK model or the results of a non-compartmental analysis will be used to help inform the choice of the next dose level as part of dose escalation discussions. For either approach, it is planned that the 95th percentile for the predicted total daily AUC values will not exceed 1/3 of the mean AUC observed at the cynomolgus monkey NOAEL and the 95th percentile of the predicted C_{max} will not exceed 1/3 of the mean C_{max} observed at the cynomolgus monkey NOAEL.

Further details of the DEC remit are provided in Section 12.3 and in the Dose Escalation Plan (DEP). This plan outlines how the study team will ensure data integrity used in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions, as well as outlining the responsibilities of the investigators and site staff for reporting safety data, participation during dose escalation meetings, and confirmation that the data used for dose escalation are accurate and complete.

Further information on dose decisions / modifications is provided in Section 7.2.

5.1.1.2. Part A LPS or GM-CSF challenge with cantharidin-induced blisters – Cohort 1 and Cohort 2:

Upon conclusion of the dose escalation phase of Part A, an additional dosing Period (treatment Period 4) will be included. Eligible 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 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. Similarly, participants in Cohort 2 will be administered 60 $\mu g/m^2$ *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.

The duration of treatment Period 4 from Day -1 onwards and the implementation of sentinel dosing will be the same as for each of treatment Periods 1-3. The dose levels of GSK3358699 administered to either cohort in treatment Period 4 will be identical and will be decided by the DEC.

The doses of LPS and GM-CSF to be administered to participants have been defined as part of a clinical enabling study [GlaxoSmithKline Document Number 2016N309726_01 Study ID 207654] and will be administered at the GSK3358699 systemic C_{max} defined from data gathered in treatment Periods 1-3. The dose levels of GSK3358699 administered to either cohort in treatment Period 4 will be identical. This will be a single dose of GSK3358699 that is within the range investigated in treatment Periods 1-3 of Part A and the decision on the dose level will be made by the DEC based on all available safety, tolerability, PK and PD data from treatment Periods 1-3.

The *in vivo* challenges included in treatment Period 4 will act as a pre-determinant to their inclusion in Part C. That is, if GSK3358699 treatment does not robustly inhibit production of inflammatory mediators and leukocyte activation following either low dose *in vivo* LPS or GM-CSF challenges and blisters in Part A, the same challenge will not be investigated in Part C. Inclusion of challenges in Part C will be decided once all the data has been generated from treatment Period 4 in Part A, and the criteria will be specific for each challenge. Inclusion of the challenges in Part C will be based on inhibition of multiple inflammatory biomarkers which may include, but are not limited to, TNF, IL-6, MCP-1 and CRP for the LPS challenge, leukocyte activation markers, thymus and activation regulated chemokine (TARC) and Macrophage-Derived Chemokine (MDC) for the GM-CSF challenge, and leukocyte counts, interferon gamma-induced protein-10 (IP-10), MMP-9, transforming growth factor (TGF)-β and leukocyte activation markers for the cantharidin-induced blisters.

5.1.1.3. Part A Dose Escalation / Challenge Total Duration:

There will be a minimum of 14 days between each dosing in Cohort 1 and Cohort 2 to ensure that appropriate dose decisions can be made during the dose escalation phase. This results in a minimum 28 day washout Period between dosing in each treatment Period for a particular cohort (including between treatment Periods 3 and 4).

The total duration of this part of the study for each participant, including screening and follow-up, is approximately 19 weeks for participants taking part in all three dose escalation treatment Periods and 23 weeks if a participant takes part in all four treatment

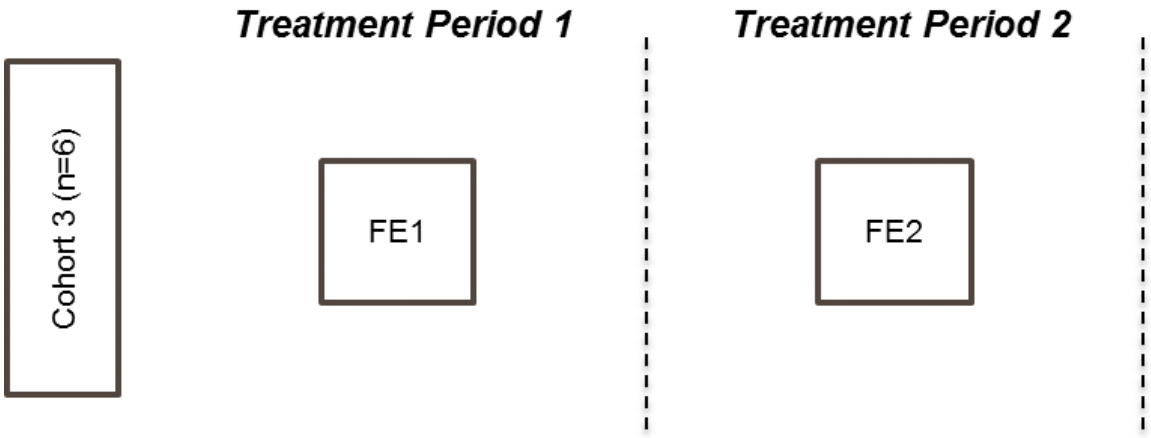
Periods. For replacement participants only taking part in the challenge treatment Period (treatment Period 4), approximate study duration is 10 weeks.

5.1.2. Part B Food Effect - Cohort 3

In Part B there will be one cohort of 6 participants (Cohort 3), taking part in a two-way crossover study as per the schematic in Figure 2. Each participant will receive a single oral dose of GSK3358699 under fed conditions in one of the two treatment Periods and under fasted conditions in the other treatment Period, according to the randomisation schedule.

Part B will only be conducted after completion of the dose escalation phase of Part A and may be conducted in parallel with Part C.

Figure 2 Part B Food Effect - Cohort 3



The dose level chosen for Part B will be a dose level within the range already evaluated in the dose escalation part of the study (Part A) and one in which, based on *in silico* modelling, the maximum exposure is estimated to not exceed the maximum threshold allowed in this protocol (see Section 7.2). following either fed or fasted administration. The decision on the dose level of GSK3358699 to be administered in Part B will be made by the DEC.

During each treatment Period participants will be admitted to the clinical unit on Day -1 and will remain there until completion of all assessments on Day 3 (at approximately 48 hours post-dose). Participants will then be discharged from the unit.

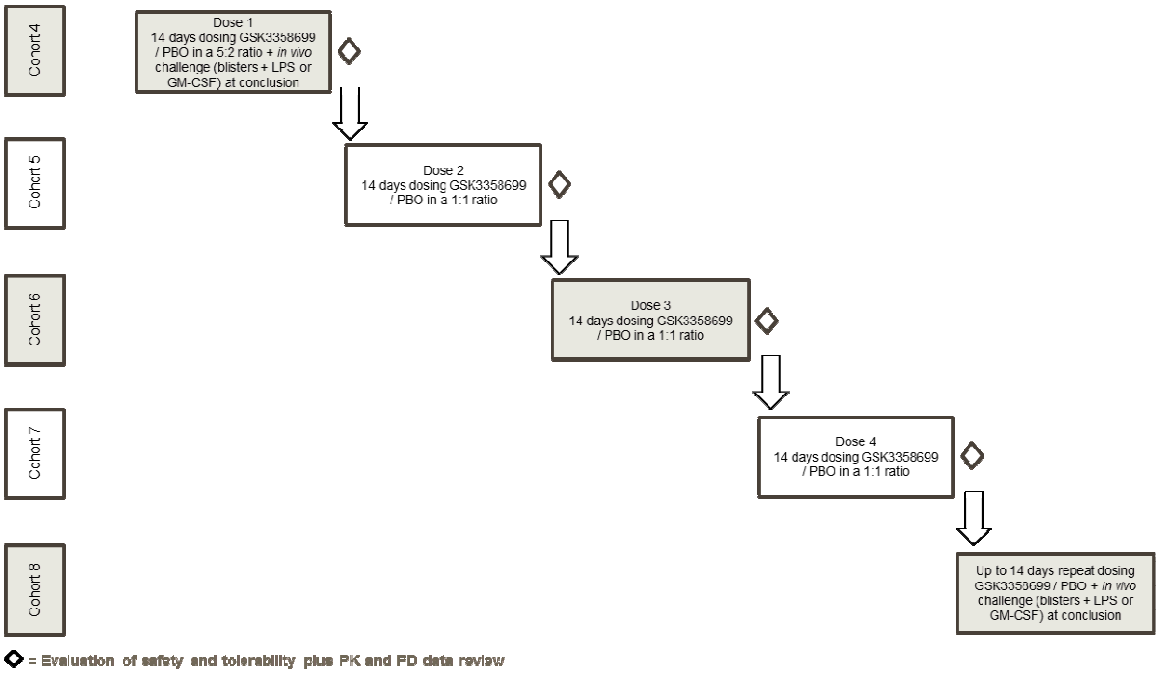
There will be a minimum of 14 days between each dose.

The total duration of this part of the study for each participant, including screening and follow-up, is approximately 9 weeks.

5.1.3. Part C

Part C of this study intends to investigate doses of GSK3358699 which deliver a robust pharmacodynamic response with adequate safety/tolerability and does not intend to dose escalate beyond the PK and PD stopping criteria detailed in Section 8.

Figure 3 Part C Schematic



5.1.3.1. Part C Multiple Ascending Doses Cohort 4

Cohort 4 of the study is comprised of 14 participants, taking part in one repeat dose treatment Period as illustrated in Figure 3, and 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 (note that Cohort 4 was started but not completed due to the temporary halt).

See Section 5.1.3.3. for study design.

5.1.3.2. Part C Multiple Ascending Doses Cohorts 5, 6 and 7

In the multiple ascending dose phase of Part C there are 3 cohorts planned (Cohorts 5-7), each with 18 healthy male participants. Each cohort will take part in one repeat dose treatment Period as illustrated in Figure 3. The 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.

All participants will be admitted to the clinical unit on the day prior to dosing (Day -1) and will remain in the Unit until after the 48 hour assessments following the Day 14 GSK3358699 / placebo dose administration have been completed (Day 16). Participants will then be discharged from the unit.

Staggering of the first two participants (sentinel dosing) will be implemented for each cohort where a new GSK3358699 dose regimen is being tested. 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 after the first 48 hours of dosing, the

remaining participants in the cohort can then be dosed. If a sentinel subject withdraws after the first 48 hours, the remainder of the cohort can still be dosed.

The decision on the dose level of GSK3358699 to be administered in Cohort 5 will be made at a DEC meeting based on all available safety, tolerability, PK, PD and TE data accumulated from Part A of the study, Part C Cohort 4, and the dose modification / stopping criteria detailed in Section 7.2 and Section 8.

The decision on the dose level of GSK3358699 for the next repeat dose cohort (Cohort 6 onwards) will be made at a DEC meeting following completion of a minimum 14 days dosing in no fewer than 12 participants in the current repeat dose cohort and will be based on:

- assessment of all available safety, tolerability, PK, PD and TE data accumulated from Part A of the study.
- assessment of safety, plasma GSK3358699 PK concentrations and TE data obtained in a minimum of 12 participants in the most recently dosed group of subjects. Individual safety data (AEs, laboratory safety tests, ECGs and vital signs) will be reviewed.
- evaluation of all available safety, tolerability, PK, PD and TE data accumulated from the previous repeat dose cohorts.

As part of this decision making process, the DEC may decide to escalate or de-escalate the dose. Safety, PK and PD stopping criteria will be strictly applied as in Part A of the study. Details of these criteria can be found in Section 8.

Further information on dose decisions / modifications is provided in Section 7.2.

The total duration of the multiple ascending dose phase of Part C, including screening and follow-up, is approximately 10 weeks for each participant in Cohorts 5 - 7.

5.1.3.3. Part C Repeat Dosing Followed by LPS or GM-CSF Challenge with Cantharidin-Induced Blisters Cohort 4 and 8

Upon conclusion of the multiple ascending dose phase of Part C (Cohorts 5 – 7), an additional Cohort (Cohort 8) is planned to be included (Figure 3). This cohort will be comprised of 20 participants, taking part in one repeat dose treatment period.

Participants will be randomised in a 1:1 ratio to receive GSK3358699 or placebo once daily for up to 14 days. The actual duration of dosing will be decided by the DEC and will not exceed 14 consecutive days.

Participants 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 at approximately 48 hours post-blister induction.

On the final day of dosing, 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 as per the timepoints detailed in the SoA (Section 2.4.1), followed by blister induction (as described in Section 5.1.1.2 Part A, treatment Period 4).

Half the participants will be randomised to receive the LPS challenge and half will receive the GM-CSF challenge. In Cohort 4, 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 10 participants receiving each challenge, it is planned that 5 will be randomised to receive GSK3358699 and 5 to receive placebo.

The randomisation ratio of active to placebo for Cohort 8 and any subsequent additional cohorts may be altered by the DEC based on all available safety, PK and PD data following the conclusion of Cohort 7.

Data from Part A of this study and from Cohorts 4 - 7 in Part C will be used to confirm the decision for inclusion of the challenges in Part C Cohort 8. The decision will be made by the DEC.

All participants will be admitted to the clinical unit on the day prior to dosing (Day -1) and will remain in the Unit until after the 48 hour assessments following the final day of GSK3358699 / placebo dosing and challenge administration have been completed. Participants will then be discharged from the unit.

Staggering of the first two participants (sentinel dosing) will be implemented. 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 after the first 48 hours of dosing, the remaining participants in the cohort can then be dosed. If a sentinel subject withdraws after the first 48 hours, the remainder of the cohort can still be dosed and the challenges administered. The staggering of the participants will be such that the post-challenge safety data from previous participants can be reviewed prior to further participants receiving challenges. The decision to administer a challenge to a participant will be based on that individual's safety profile as well as continuous review of safety/tolerability of the challenges.

The decision on the dose level of GSK3358699 to be administered in Cohort 4 will be made at a DEC meeting based on all available safety, tolerability, PK, PD and TE data accumulated from Part A of the study and the dose modification / stopping criteria detailed in Section 7.2 and Section 8.

The decision on the dose level of GSK3358699 to be administered in Cohort 8 will be made at a DEC meeting based on all available safety, tolerability, PK, PD and TE data accumulated from Part A of the study, the previous Part C cohorts, and the dose modification / stopping criteria detailed in Section 7.2 and Section 8.

As part of this decision making process, the DEC may decide to escalate or de-escalate the dose. Safety, PK and PD stopping criteria will be strictly applied as in Part A of the study. Details of these criteria can be found in Section 8.

Further information on dose decisions / modifications is provided in Section 7.2. This includes any potential changes to the randomisation and administration and timing of challenge agents, as well as any changes related to the dose levels or dosing regimen of GSK3358699.

The total duration of Part C of the study, including screening and follow-up, is approximately 12 weeks for participants in Cohort 4 and approximately 14 weeks for participants in Cohort 8.

5.2. Number of Participants

The number of healthy male participants and the required number of evaluable participants are outlined in Table 1.

Table 1 Number of Participants

Part	Participants per cohort	Evaluable participant number per cohort	Evaluable participant definition
A (Cohorts 1-2)	9 (6:3 GSK3358699 : Placebo)	6	Complete both screening and all their planned treatment Periods.
B (Cohort 3)	6 (all receive GSK3358699)	5	Complete both screening and both treatment Periods.
C (Cohort 4)	14 (10:4 GSK3358699 : Placebo)	9	Complete both screening and the 14 day treatment Period and subsequent 48 h assessment Period.
C (Cohorts 5-7)	18 (9:9 GSK3358699 : Placebo)	12	Complete both screening and the 14 day treatment Period and subsequent 48 h assessment Period
C (Cohort 8)	20 (10:10 GSK3358699 : Placebo)	14	Complete both screening and the 14 day treatment Period and subsequent 48 h assessment Period.

Participants who are randomized into a particular part of the study can be enrolled in another part of the study, as well as be enrolled in a later cohort of the same part of the study in Part C, 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).

Additional participants/cohorts may be enrolled in Part A or Part C to allow for evaluation of additional dose levels or alternative regimens, including for challenges, as detailed in Section 7.2. No more than 9 additional participants will be included as part of a new cohort in Part A and no more than 20 additional participants will be allowed as part of a new cohort in Part C (ie in addition to Cohort 4-8 participants).

If participants prematurely discontinue the study during Part A, additional replacement participants may be recruited and assigned to the same treatment sequence, starting from the next planned dosing Period following the premature discontinuation, at the discretion of the Sponsor in consultation with the investigator.

If a participant chooses to participate in, or is eligible for, the dose escalation treatment Periods only in Part A as described in Section 5.1.1.1, a new participant will be recruited for the challenge treatment period (treatment Period 4) only and will be regarded as a replacement subject, assigned to the same treatment sequence. This will occur at the discretion of the Sponsor in consultation with the investigator.

If participants prematurely discontinue the study during Part B, additional replacement participants may be recruited and assigned to the same treatment sequence, starting from the beginning of the first treatment Period, at the discretion of the Sponsor in consultation with the investigator.

If participants prematurely discontinue the study during Part C, additional replacement participants may be recruited and assigned to the same treatment sequence, starting at the beginning of the treatment Period, at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he has completed all study visits, including the follow up visits, for which he was eligible or to which he consented.

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

5.4. Scientific Rationale for Study Design

This study will be the first administration of GSK3358699 in human participants. The primary purpose of the current study is to characterise the safety and tolerability of GSK3358699 in healthy male participants within a pre-defined and controlled PK and PD range. The study will additionally seek to understand the secondary and exploratory endpoints highlighted in Section 4. Specific scientific considerations which contribute to the study design include:

- In Part A, this study employs an interlocking crossover design to allow more accurate extrapolation of PK and PD data within participants at different dose levels. In addition, this design minimises participant numbers across the single ascending dose (SAD) part of the study and allows for a minimum 28 day washout Period between doses for a particular cohort. To maximise the safety, PK and PD 'within-participant' information gathered during the dose escalation period, which will adequately inform dosing in treatment Period 4 and in Parts B and C of the study, the flexibility of participation in Part A has been enhanced to facilitate subject recruitment and retention.
- In Part B, the effect of food will be investigated. An early understanding of any effect of food on exposure or PD will improve dose selection in future clinical studies with GSK3358699. Data from Part B is not intended to inform the conduct of Part C of the present study.
- In Part C, it is planned that five repeat dose cohorts will be administered multiple doses of GSK3358699 or placebo. As part of this, investigations into the dose response will be made.
- According to a Physiologically Based Pharmacokinetic (PBPK) model established pre-clinically, GSK3358699 is predicted to have a short systemic half-life of approximately 3 hours. However, the intracellular pharmacokinetics of GSK3206944 are less readily predicted. The study will therefore include intracellular quantification of GSK3206944 in all three parts.

To further investigate the potential use of GSK3358699 in immuno-inflammatory diseases, *in vivo* inflammatory challenges (blisters, LPS and GM-CSF) will be administered in both Part A (treatment Period 4 only) and Part C (Cohorts 4 and 8) of the study, should data support this. GSK3358699 modulates multiple pro-inflammatory pathways *in vitro* [GlaxoSmithKline Document Number 2017N333959_00], and therefore has potential utility across a broad range of diseases. With this in mind, cantharidin-induced blisters, LPS and GM-CSF challenges have been specifically selected as inflammatory challenges that are representative of the immune response encountered across a range of inflammatory conditions including fibrosis and RA. Inclusion of these challenges will illuminate which of these disease-relevant mechanisms GSK3358699 modulates most efficiently in an *in vivo* setting.

In Part A, these challenges will be administered at GSK3358699 C_{max}. In Part C the challenges may be administered at a time-point of low systemic GSK3358699 concentration, but high intracellular GSK3206944 concentrations. Taken together, this data may inform on systemic versus intracellular compound exposure as a key driver of PD response following pro-inflammatory *in vivo* challenges. A summary and rationale for the challenges to be used as part of this study is below:

- *Ex vivo* LPS challenge – GSK3358699 has shown concentration dependent inhibition of cytokine production in LPS stimulated blood *in vitro*. *Ex vivo* LPS challenge of blood from participants dosed with GSK3358699 is a minimally invasive high throughput method through which to investigate target engagement.

- *In vivo* LPS challenge - Human *in vivo* LPS challenges have been used as a methodology to induce systemic inflammation and produce many of the immunological (changes in leukocyte numbers and induction of inflammatory mediators and cellular activation markers) and physical signs of acute and chronic disease. The human LPS model of systemic inflammation has been applied to clinical pharmacology studies to assess therapeutic interventions for analgesics, asthma, effective adjuvants, sepsis, trauma, Type-2 diabetes, Alzheimer's disease and others [Fullerton et al 2016]. This study will investigate the effect of GSK3358699 on LPS-induced inflammation as measured by the phenotype of peripheral leukocytes and the production of inflammatory mediators and acute phase proteins over time.
- *In vivo* GM-CSF challenge - GM-CSF has a broad range of activities across innate and adaptive immune cells and is recognised as a key mediator in a number of inflammatory diseases, such as arthritis, multiple sclerosis, colitis, pain and interstitial lung disease [Wicks et al 2016]. Leukine (Sargramostim) given intravenously results in a systemic GM-CSF challenge that mobilises neutrophils, eosinophils and monocytes from the bone marrow. A GM-CSF dose of 5 µg/kg (equivalent to intravenous infusion of 60 $\mu g/m^2$), administered subcutaneously, is associated with a measurable leukocyte response but is well tolerated based on the literature [Gianni et al 1990, Lieschke et al 1989]. 1.5µg/kg dose infused intravenously over 2 hours provides the same exposure (AUC) due to the increased bioavailability and higher C_{max} concentrations (Cebon et al 1990). This study will investigate the effect of GSK3358699 on GM-CSF induced inflammation as measured by leukocyte numbers, soluble inflammatory mediators, as well as cellular activation markers on leukocytes, particularly monocytes, over a defined time course.
- Chemically induced skin blisters - Cantharidin is a vesicant (an agent that causes blisters) and a strong inhibitor of protein phosphatases type 1 and 2A [Honkanen et al 1993], used clinically for the treatment of warts and molluscum contagiosum. Following contact with the skin, it is absorbed into the epidermis and activates proteases leading to intra-epidermal blistering [Bertaux et al 1988]. Blistering is limited to the suprabasal epidermis and lesions heal without scarring. Skin blister induction by cantharidin has been utilised in clinical pharmacology for more than 50 years as a model of acute inflammation, and provides methodology to investigate leukocyte trafficking, cellular activation states and detection of plethora of inflammatory mediators, including pro-fibrotic mediators, in the blister fluid. The combination of blisters with systemic inflammation (induced by LPS or GM-CSF) provides a unique methodology to detect the effects of systemic inflammation on local inflammation. This study will investigate the effect of GSK3358699 on cantharidin induced blisters in the presence of systemic inflammation, as measured by leukocyte numbers, cellular activation markers and soluble inflammatory mediators associated with autoimmune and fibrotic diseases.

This study will be conducted in healthy male participants for the following reasons:

- Patients with immuno-inflammatory diseases may have existing co-morbidities or be taking medications that may confound the interpretation of data for GSK3358699.
- It is yet to be determined whether patients would derive benefit from a short duration of dosing of GSK3358699; however, taking part in this study may stop them receiving other required treatments.
- Females are excluded from this study as the potential benefits do not outweigh the risks, particularly to women of child bearing potential and additionally, the use of challenge agents is not as well characterised in females.
- The pre-clinical testicular toxicology findings show that there is a sufficient safety margin to allow the inclusion of males, including males of reproductive potential, in this study.

This study includes a placebo component to allow for a valid evaluation of AEs attributable to treatment versus those independent of treatment and to serve as valid controls for the PD assessments.

5.5. Dose Justification

This study will assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single (in the fed (Part B) and fasted state, Part A and B) and multiple (Part C) doses of GSK3358699 in healthy volunteers. Target engagement will be determined by the extent of MCP-1 inhibition following *ex vivo* LPS stimulation of participant blood. This PD end point will form a central parameter to be considered along with PK, safety and tolerability during dose escalation decisions. Additional endpoints such as TNF and IL-6 inhibition will also be considered.

5.5.1. Part A

The planned doses of GSK3358699 for Part A are shown in Table 2 and have been selected on the basis of the TE expected at the correspondent model predicted human PK exposures.

A dose of 1 mg resulting in a maximum MCP-1 target engagement below 10% has been selected as the starting dose. This dose is below the minimum anticipated biological effect level (MABEL) for GSK3358699, which is considered to be 3 mg QD, based on anticipated levels of target engagement at that dose. Human PK/PD predictions together with a description of PD assays are described further below. The 1 mg dose is below the maximal recommended starting dose based on Food and Drug Administration (FDA) Guidance for Industry Estimating Maximum Safe Starting Dose in Initial Clinical Trial for Therapeutics in Adult Healthy Volunteers [U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2005]. Using the multiplication method, this includes a safety factor of greater than 200-fold based on the cynomolgus monkey NOAEL (10 mg/kg) which equates to a Human Equivalent Dose (HED) of 227 mg for a 70 kg human.

Table 2 Planned GSK3358699 doses

Planned dose (mg)	Max TE (%)	C_{max} (ng/ml)	AUC (ng/ml h)	Monkey Gender-averaged NOAEL fold cover		Rat Gender-averaged NOAEL fold cover	
				C_{max}	**AUC**	**C_{max}**	**AUC**
1	9	1	6	612	275	1473	316
3	32	3	17	205	92	493	105
10	72	9	57	61	28	148	32
20	87	19	113	31	14	74	16
35	94	32	199	18	8	42	9
45	95	42	255	14	6	33	7

The current knowledge of pan-BET inhibitors suggests that a short duration, high level of target engagement is associated with a clinical reduction in inflammatory biomarkers.

Based on this, PK/PD modelling, where the PK was described by a compartment model and the PK/PD relationship by a maximum effect possible (E_{max}) model, suggests efficacy could be achieved at 35 to 45 mg QD, a dose giving 90% target engagement for 4 h.

The dose of GM-CSF to be administered to participants in treatment Period 4 of Part A will be 60 $\mu g/m^2$. The dose of LPS to be administered to participants in treatment Period 4 of Part A will be 0.75 ng/kg. The dose of cantharidin will be a standard dose as detailed in Section 7.1, and used in the enabling study 207654 [GlaxoSmithKline Document Number 2016N309726_01]. This dose represents a substantial reduction in exposure compared to that recommended for therapeutic use; it is the dose that will be used for all blister induction in this study.

A solution formulation will be used for doses of < 10 mg GSK3358699, and a capsule formulation for higher doses. Currently, there is no indication as to the taste or palatability of GSK3358699 administered as a solution. For this reason, participants receiving GSK3358699 or placebo as a solution in water (in any part of this study) may also need to consume a flavoured sweet (for example a hard boiled sweet) prior to or immediately following dosing, provided this does not interfere with ongoing monitoring or study procedures. The need for ongoing taste masking will be determined by the DEC.

5.5.2. Part B

The dose level of GSK3358699 selected to be administered with or without a high fat meal in Part B will have been previously investigated in Part A of the study and will have demonstrated adequate exposure, safety and tolerability to support its inclusion in the food effect investigation. The dose of GSK3358699 administered will be decided by the dose escalation committee.

5.5.3. Part C

Five dosing cohorts are planned for Part C. Once-daily dosing (QD) of GSK3358699 is planned for 14 consecutive days in Cohorts 4 – 7 and for up to 14 consecutive days in Cohort 8. The selection of appropriate doses will be performed upon consideration of

available safety and tolerability, PK and PD data from Part A and/or any preceding repeat dose cohorts in Part C.

The dose of GM-CSF to be administered to participants in Part C will be 60 μg/m^2. The dose of LPS to be administered to participants in Part C will be 0.75 ng/kg.

Administration of the challenge agents will be on Day 14 in Cohort 4 and is planned to be on the final day of dosing in Cohort 8; the time point will be based on an estimate of the intracellular acid kinetics determined in the preceeding cohorts of the study and will be no more than 24 h after dosing with GSK3358699 or placebo on that day.

Based on emerging data, the DEC may decide to modify the dosing frequency to less than once daily or more than once daily, as well as make other modifications as detailed in Section 7.2.

5.5.4. Human PK and PK/PD predictions

The PK of GSK3358699 in humans has been predicted by PBPK modelling using software Gastroplus. The human PBPK model was based on scaling of the monkey parameters, hepatic and renal clearance, except for the human acid metabolite (GSK3206944) liver clearance which was based on scaling of the dog *in vivo* liver clearance. Based on this model a compartment model was built for selecting doses and predicting exposures (see Section 5.5.1).

LPS-induced MCP-1 inhibition is considered a robust measurement of BET protein target engagement. Human predicted MCP-1 inhibition levels (Figure 5) were based on results from *in vitro* human whole blood assay (LPS stimulated) data which provided an estimated pIC$_{50}$ of 8.13, which translates to a plasma IC$_{50}$ of 4.8 ng/ml and a plasma IC$_{90}$ of 22.9 ng/ml (Hill slope=1.4).

As shown in Figure 4, Figure 5 and Table 2, the doses of GSK3358699 to be explored as part of the FTIH study have been carefully modelled to ensure a controlled dose escalation, such that the Brd4 BD1 IC$_{50}$ (25 ng/ml) is only exceeded at small multiples and only at the highest doses proposed. Brd4 BD1 is one of the two bromodomains present in the Brd4 protein and is used here as a comparative indicator of systemic bromodomain inhibition. Non-targeted bromodomain inhibitors have classically relied on sustained systemic concentrations over and above the Brd4 BD1 IC$_{90}$ to drive anti-inflammatory and anti-proliferative effects. Given the targeted nature of GSK3358699 and in contrast to prior clinical investigations with panBET inhibitors, GSK3358699 Brd4 BD1 IC$_{90}$ (128 ng/ml) will not be exceeded systemically at any dose planned.

Importantly, the potency advantage derived from the ESM ensures that even at these comparatively low levels of systemic BET inhibition, MCP-1 inhibition is expected to be essentially complete at doses greater than 20 mg GSK3358699 QD (Figure 5 and Table 2). Based on this modelling, the current anticipated GSK3358699 dose levels are considered appropriate to the objectives of this FTIH investigation.

Figure 4 GSK3358699 Predicted Human PK Profile

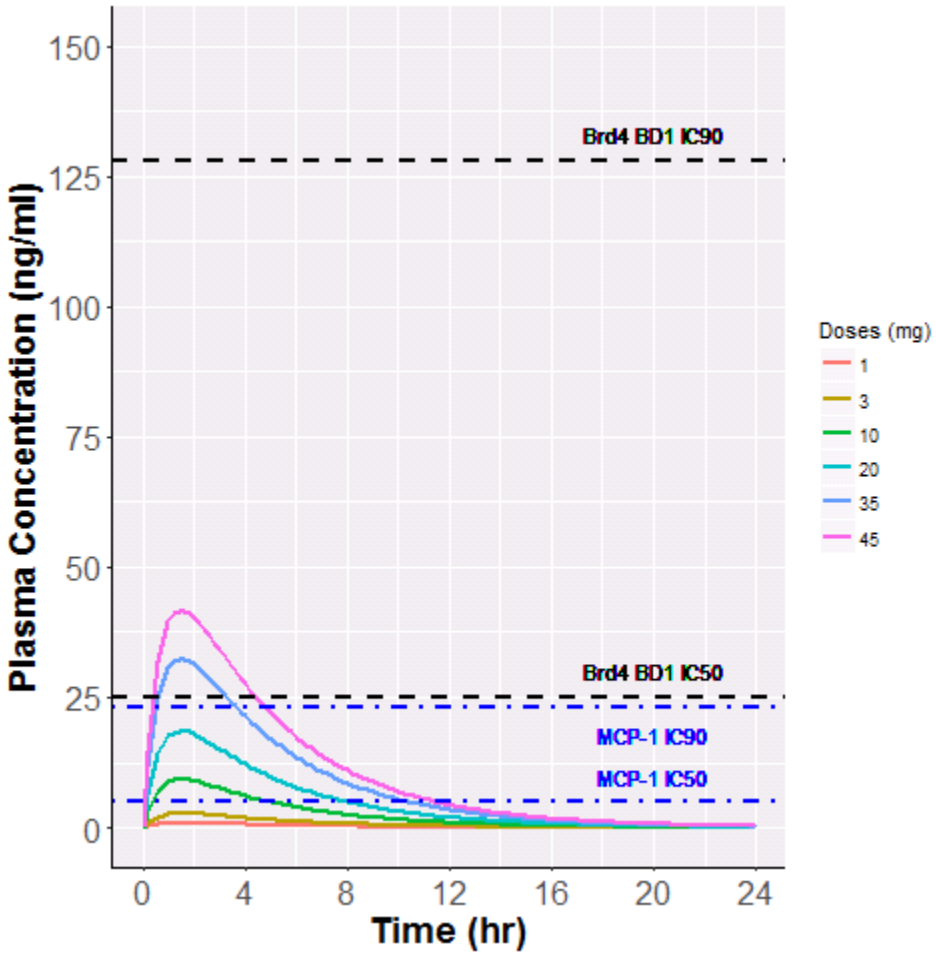
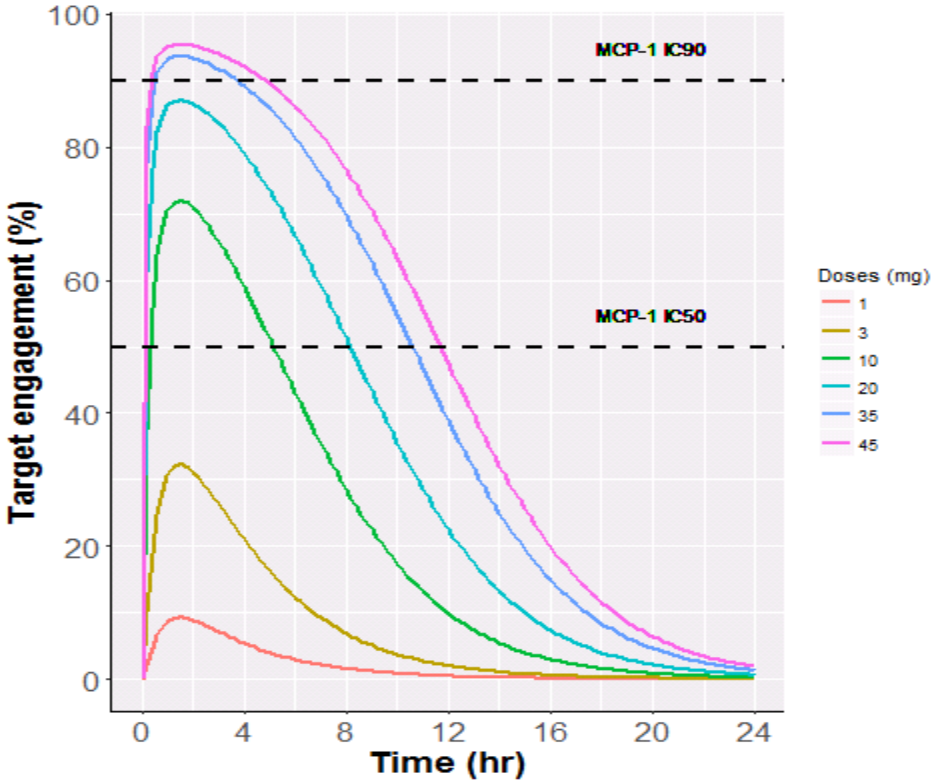


Figure 5 Human predicted MCP-1 inhibition levels (*ex vivo* LPS stimulation)



6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. Participant age range:
    a. Part A (Cohort 1 and 2, no LPS or GM-CSF administration, ie if choosing not to take part in Treatment Period 4); participants enrolled into the study must be 18 to 65 years of age inclusive at the time of signing the informed consent form.
    b. Part A (Cohort 1 and 2, LPS or GM-CSF administration); participants enrolled into the study, must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

c. Part B (Cohort 3, no LPS or GM-CSF administration); participants enrolled into the study must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

d. Part C (Cohorts 5 to 7, no LPS or GM-CSF administration); participants enrolled into the study must be 18 to 65 years of age inclusive at the time of signing the informed consent form.

e. Part C (Cohort 8, LPS or GM-CSF administration) - Participants enrolled into the study must be 18 to 55 years of age inclusive at the time of signing the informed consent form.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

Weight

3. Body weight ≥ 50 kg and body mass index (BMI) within the range 18.5-35.0 kg/m^2 (inclusive).

Sex

4. Male

a. Male participants:

Where relevant (see Section 12.5) male participants must agree to use contraception as detailed in Section 12.5 during the treatment Period and for at least 91 days, after the last dose of study treatment and refrain from donating sperm during this Period.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF).

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Current or chronic history of:
   - pancreatitis.
   - diabetes mellitus or impaired glucose tolerance.
   - gastrointestinal disease.
   - liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

- anaphylaxis, and /or anaphylactoid (resembling anaphylaxis) reactions [Sampson et al 2006].
- renal disease where clinically significant (minor abnormalities may be permitted base on discussion between investigator and medical monitor).
- respiratory disease or conditions including but not limited to asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis and any current respiratory infection (childhood asthma is not an exclusion criterion).
- sensitivity or severe allergic responses to any of the challenge agents or cantharidin, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor, contraindicates their participation.
- frequent vasovagal syncope.
- surgery requiring general anaesthetic or significant trauma in 3 months leading to study enrolment.
- relevant skin conditions (e.g. recent history of eczema or recurrent eczema, keloid, skin allergies, psoriasis, atopic dermatitis, and vitiligo) which in the opinion of the investigator could pose safety issues or cause interference with study procedures.
- sepsis.
- coagulation disorders.
- peripheral oedema, lymphangitis, lymphoedema, pleural or pericardial effusion.
- haemorrhage (eg sub-arachnoid) or hemophilia or a related bleeding disorder.

2. History of malignancies e.g. recurrent basal cell carcinoma, haematological malignancy.
3. For participants receiving cantharadin: Presence on either forearm of tattoos, naevi, hypertrophic scars, keloids, hyper– or hypo- pigmentation that may, in the opinion of the Investigator, interfere with study assessments. Participants with excessive hair or any skin abnormalities that may, in the opinion of the Investigator, interfere with study assessments.
4. History of cardiac disease e.g. congenital heart disease, valvular heart disease, ischemic heart disease, clinically significant atrial or ventricular arrhythmias, QTc prolongation, or cardiac arrest.
5. Family history of premature cardiovascular disease, long QT syndrome or sudden death.
6. QTcF > 450 msec, based on averaged QTcF values of triplicate ECGs obtained over a brief recording Period.

   NOTES:

   - The QTcF is the QT interval corrected for heart rate according to Fridericia's formula (QTcF) machine-read or manually over-read.

- For purposes of data analysis QTcF will be used as specified in the Reporting and Analysis Plan (RAP).

7. Any clinically relevant abnormality on the screening ECG.
8. Non-sustained ventricular tachycardia (NSVT) – defined as ventricular triplet or longer), or more than 30 Ventricular Premature Depolarisation (VPD)/hour on screening Holter.
9. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.

Prior/Concomitant Therapy

10. Unable or unwilling to refrain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit. Paracetamol, at doses of ≤ 2 grams/day, is permitted for use any time during the study except as detailed in Section 7.7. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

Prior/Concurrent Clinical Study Experience

11. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) or currently in a study of an investigational device.
12. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
13. Previous exposure to intravenous LPS in a clinical research setting.

Diagnostic assessments at screening

14. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
15. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
17. A positive pre-study drug/alcohol screen.
18. A positive test for human immunodeficiency virus (HIV) antibody.
19. Persistent clinically significant abnormal CRP levels at screening.
20. Persistent clinically significant abnormal white cell count (WCC) levels at screening (if clinically significant abnormality is detected, WCC can be retested as clinically indicated).

21. Platelets < 150 x 10^9/L.
22. Fasted Triglycerides >3.4 mmol/L.
23. Fasted Total cholesterol >7.7 mmol/L.
24. Fasted glucose ≥7.0 mmol/L
25. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months prior to screening.

Other Exclusions

26. History of regular alcohol consumption within 6 months of the study defined as:
    - an average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
27. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period.
28. Unable to comply with precautions to minimise phototoxicity risk.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- In Part A dose escalation and challenge treatment Periods, participants will fast from approximately midnight on the day prior to GSK3358699 / placebo dosing and will remain fasted until 4 hours post-dose (with the exception of the flavoured sweet used to mask the taste of the GSK3358699 solution formulation). Water will be allowed as desired except for one hour before and one hour after study treatment administration (with the exception of the water administered with the study treatment). At all other times whilst participants are in the unit they will receive standardised meals scheduled at the same time in each treatment Period of the study. After breakfast on Day 2 the timing of the meals is at the unit's discretion.
- In Part B when participants are administered GSK3358699 under fasted conditions, they will follow the same fasting requirements as those described for Part A of the study. When the participants are administered GSK3358699 with food, they will fast from approximately midnight on the day prior to dosing and will receive the standard FDA high fat, high calorie meal 30 minutes prior to GSK3358699 dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur approximately 30 minutes after the start of meal consumption. Participants will not receive any further food until 4 hours post-dose. Water will be allowed as desired except for one hour before and after study treatment administration (with the exception of the water administered with the study treatment). At all other times whilst participants are in the unit they will receive standardised meals scheduled at the same time in each treatment Period of the study. After breakfast on Day 2 the timing of the meals is at the unit's discretion.
- In Part C, on Days 2-13, participants will fast from midnight prior to each GSK3358699 / placebo dosing and will remain fasted until 2 hours post-dose (with

the exception of the flavoured sweet used to mask the taste of the GSK3358699 solution formulation). On Day 1 and Day 14 (ie the days on which full PK profiling is conducted) participants will fast from approximately midnight on the day prior to GSK3358699 / placebo dosing and will remain fasted until 4 hours post-dose. Water will be allowed as desired except for one hour before and after study treatment administration on each dosing day (with the exception of the water administered with the study treatment). At all other times whilst participants are in the unit they will receive standardised meals. The timing of the meals is at the unit's discretion.

- Participants will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, from 7 days before the start of study treatment until after the final dose.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final sample in each treatment Period.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final sample in each treatment Period.
- Only non-smokers are allowed to participate in this study, therefore use of tobacco products will not be allowed during the study.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, walking, watching television, reading).
- Those participants who have blisters induced in Part A or Part C should avoid:
  - Strenuous exercise to the upper limbs whilst blister is present.
  - Getting the blister dressing wet during bathing.
  - Topical application of any creams to the forearms during the treatment Period where blisters are induced, from 24 hours prior to the start of the treatment Period until the blisters have healed.
- From 24 hours prior to each dose of study treatment and until discharge at the end of each treatment Period, participants will wear suitable clothing to minimise exposed areas of skin and will use a broad spectrum UVA/UVB sunscreen and lip balm (SPF $\geq$ 30) on exposed areas when outdoors (note exception for blister treatment Period). In addition, participants should wear sunglasses that filter UVA and UVB rays.
- Participants must not sunbathe or use sun-beds from 24 hours prior to each dose of study treatment and until discharge at the end of each treatment Period.

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants can be re-screened only on approval of the GSK Medical Monitor and only once. Re-screening is allowed when a participant failed inclusion/exclusion criteria or some other screening condition initially, but the Investigator believes there is a reasonable probability that the participant would be eligible if re-screened. In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window without this being considered a rescreen. If a retest result is again outside the reference range and considered clinically significant by the investigator and GSK medical monitor, the participant will be considered a screen failure.

Individuals who meet the eligibility criteria and are reserve participants who are subsequently not required for that cohort may also be rescreened for later cohorts.

If a subject is re-screened within the same cohort then they will retain the same subject number. If a subject is re-screened for a new cohort then they will be assigned a subject number within the numbering range for that cohort. All previously collected data will be automatically updated with the new number.

7. TREATMENTS

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

7.1. Treatments Administered

Table 3 Investigational Product and Placebo to match

Study Treatment name	GSK3358699		Placebo	
Formulation description	Solution of API in water for injection (0.2 mg/mL)	API filled capsule	Water for injection	Microcrystalline Cellulose filled capsule
Dosage form	Oral solution	Capsules	Oral solution	Capsules
Unit dose strength (Part A)	From 1 mg up to 10 mg*	From 10 mg to 70 mg**	N/A	N/A
Unit dose strength (Part B)	To be confirmed (TBC) following Part A	TBC following Part A; minimum unit dose strength will be 3 mg*, maximum unit dose strength will be 70 mg**	N/A	N/A
Unit dose strength (Part C)	TBC following Part A	TBC following Part A; minimum unit dose strength will be 3 mg*, maximum unit dose strength will be 70 mg**	N/A	N/A
Route of administration	Oral	Oral	Oral	Oral
Dosing Instructions	Required volume of 0.2 mg/mL aqueous solution to be swallowed. Following the solution administration a further 100mL of water will be added to the same vessel from which the treatment solution was administered and swallowed.	One capsule to be swallowed with 240mL of water.	Required volume of water to be swallowed Following the initial water administration a further 100mL of water will be added to the same vessel from which the treatment solution was administered and swallowed.	One capsule to be swallowed with 240mL of water.
Physical description	Clear colourless solution	Orange size 0 capsules	Clear colourless solution	Orange size 0 capsules
Packaging and Labelling	The study treatment and excipients will be provided in bulk in labelled bags within a labelled keg. The label will detail product description, lot number, expiry date, storage conditions and quantity.			
Manufacturer	GSK to provide bulk GSK3358699 active pharmaceutical ingredient (API), placebo excipient, capsule shells to clinical site. Clinical site to manufacture the products extemporaneously according to a manufacturing batch record.			

* It is planned that doses of 3 mg and above will be administered as a capsule formulation in Part B and Part C of the study, however the solution formulation dose strength range of 1 mg up to 10 mg will be retained for flexibility.
** Dose strengths up to 45 mg are planned for this study but higher doses may be required if predicted PK is not achieved with planned doses.

The formulation, method of preparation and dosing instructions will be same as for each part of the study.

The planned doses of GSK3358699 for Periods 1-3 of Part A are as detailed in Section 5.5 and in Table 4. The planned doses may be adjusted as detailed in Section 7.2.

Table 4 Example Illustration of Planned Treatments for Dose Escalation in Part A.

		Treatment Period 1		Treatment Period 2		Treatment Period 3	
Cohort 1	N=3	P		10 mg		35 mg	
	N=3	1 mg		P		35 mg	
	N=3	1 mg		10mg		P	
Cohort 2	N=3		P		20 mg		45 mg
	N=3		3 mg		P		45 mg
	N=3		3 mg		20 mg		P

P= Placebo
1-45 mg = 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 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 as further detailed in Section 5.5 and Section 7.2.

Table 5 Challenge Agents

Study Treatment Name:	**Cantharone (Cantharidin)**	**LPS**	**GM-CSF**	**Intravenous Hydration with saline solution (for LPS only)**
Dosage formulation:	Liquid (mixture) Ether (42.8 % W/V), Acetone (36.0 % V/V), Alcohol (14.2 % W/V), Camphor (1.2 % W/V), Cantharidin (0.7 % W/V) Balance (5.1%W/V) mixture of pyroxylin and castor oil	LPS is lyophilized in a 1 microgram vial, formulated in 1% lactose and 0.1% PEG6000.	The vial of lyophilized LEUKINE contains 250 mcg (1.4×10^6 IU/vial) sargramostim. The reconstituted lyophilized LEUKINE vial also contain 40 mg/mL mannitol, USP; 10 mg/mL sucrose, NF; and 1.2 mg/mL tromethamine, USP, as excipients.	0.9% Sodium Chloride IV bags.
Unit dose strength(s)/Dosage level(s):	0.7% cantharidin liquid which will be diluted with acetone to 0.2%	0.75 ng/kg (activity 6 EU/ng)	60μg / m^2	1L
Route of Administration	Topical	IV	IV infusion	IV
Dosing instructions:	Apply 5 µl of 0.2 % Cantharidin solution (diluted in acetone) directly onto skin in area of ~ 1 cm^2.	IV injection of 0.75 ng/kg body weight formulated as suspension in normal saline.	Dose calculated by calculating body surface area to give IV infusion dose given over approximately 2 hours.	Administer intravenously at a rate of 250 mL/hr for 4 hours prior to dosing with LPS and 8 hours after dosing with LPS.

Study Treatment Name:	Cantharone (Cantharidin)	LPS	GM-CSF	Intravenous Hydration with saline solution (for LPS only)
Manufacturer	Dormer Laboratories Inc. ADDRESS: 91 Kelfield St. # 5 Rexdale Ontario Canada M9W 5A3 http://www.dormer.ca/PDF/CanRegMSDS.pdf	List Biological Laboratories, INC 540 Division Street, Campbell California 95008-6906 USA www.listlabs.com	Leukine is a registered trademark licensed to Genzyme Corporation. Manufactured by: sanofi-aventis U.S. LLC Bridgewater, NJ 08807 A SANOFI COMPANY US License No. 1752 © April 2013 sanofi-aventis U.S. LLC Phone: PPD	Baxter Inc. Caxton Way Thetford IP24 3SE

Information regarding the dose of the cantharidin, LPS and GM-CSF challenge agents to be administered in Part A treatment Period 4, and Part C (Cohorts 4 and 8), of the study is described in Section 5.5.

7.2. Dose Modification

Details of all the planned dose levels of GSK3358699, the LPS and GM-CSF challenge agents, and cantharidin are provided in Section 5.5 and Section 7.1. The actual doses of GSK3358699 to be administered in either Part A or Part C may be adjusted based on review of the safety, tolerability, PK and PD data from prior dose levels by the DEC. These dose adjustments may involve either an increase or a decrease in the planned dose but the average exposure in a cohort at any planned dose will not intentionally exceed the C_{max} of 42 ng/ml or total daily AUC of 255 ng/ml.h.

Individuals in each cohort will be monitored throughout the study. If 2 or more participants in a given cohort at the same dose level exceed these PK stopping criteria, dose escalation will be halted.

Furthermore, throughout all parts of the study, either a population PK model or the results of a non-compartmental analysis will be used to help inform the choice of the next dose level as part of dose escalation discussions. For either approach, it is planned that the 95th percentile for the predicted total daily AUC values will not exceed 1/3 of the mean AUC observed at the cynomolgus monkey NOAEL and the 95th percentile of the predicted C_{max} will not exceed 1/3 of the mean C_{max} observed at the cynomolgus monkey NOAEL.

Doses investigated in Part B or Part C will not exceed the magnitude of those investigated in Part A.

The dosing schedule may also be adjusted to address the following:

- Expand a cohort to further evaluate safety, PK or PD findings at a given GSK3358699 dose level.
- To add cohorts to evaluate additional dose levels.

- To change the dosing regimen to less than or more than once daily.

Dosing may also be halted before all planned dose levels have been completed if stopping criteria have been met or if a review of the data determines that evaluation of further dose levels is not necessary to meet study objectives.

In addition, decisions relating to the challenge agent administrations may be taken during the course of the study based on newly available data. This may include:

- The decision to alter the timing of the LPS or GM-CSF challenge agent administrations.
- The decision to evaluate more than one challenge agent administration timing.
- The inclusion of challenge agents in earlier cohorts (Cohorts 5 – 7).
- Expansion of existing cohorts or addition of new cohorts.
- Inclusion of blister induction and blister fluid harvest in cohorts prior to Cohort 8.
- Reduction to fewer than 14 days dosing in the challenge Cohorts.

Alterations may also be made to the randomisation ratio of active to placebo for Cohort 8 and any subsequent additional cohorts based on all available safety, PK and PD data following the conclusion of Cohort 7.

7.3. Method of Treatment Assignment

At Screening a unique Participant Number (case report form (CRF) number) will be assigned to any participant who has at least one Screening procedure performed, other than informed consent. The unique Participant Number will be used to identify individual participants during the course of the study.

Participants who meet the screening eligibility criteria will be randomised to a treatment group through RAMOS NG. RAMOS NG will confirm the participants CRF number (Participant number) and provide the randomisation number, where:

- A randomisation number will be assigned from a randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once assigned, this number must not be reassigned to any other participant in the study.

Therefore, the randomisation is centrally controlled by RAMOS NG.

Part A

Within each cohort, participants will be assigned to one of three dosing sequences in a 1:1:1 ratio for the dose escalation phase, where participants will be randomised to:

	Cohort 1	**Cohort 2**
Sequence	PCE APE ACP	PDF BPF BDP

Where the treatment codes are as follows:

Treatment code	**Treatment Description**
A	1 mg GSK3358699
B	3 mg GSK3358699
C	10 mg GSK3358699
D	20 mg GSK3358699
E	35 mg GSK3358699
F	45 mg GSK3358699
P	Placebo

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. Dose level of GSK3358699 to be determined following the completion of the dose escalation phase.

Part B

Participants will be assigned to one of two dosing sequences in a 1:1 ratio, where participants will be randomised to:

	Cohort 3
Sequence	GH HG

Where the treatment codes are as follows:

Treatment code	**Treatment Description**
G	GSK3358699 Fed
H	GSK3358699 Fasted

The dose level of GSK3358699 will be determined following the completion of Part A.

Part C

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, where the treatment codes will be:

Treatment code	**Treatment Description**
I	Dose 1 GSK3358699 QD
J	Dose 2 GSK3358699 QD
K	Dose 3 GSK3358699 QD
L	Dose 4 GSK3358699 QD
P	Placebo

7.4. Blinding

This will be a double blind (sponsor open) study with respect to allocation of GSK3358699 or placebo to participants. All site staff will be blinded with the exception of unblinded pharmacists and analytical laboratory staff involved with the intracellular PK monocyte isolation process. Investigators will be unblinded with respect to the LPS and GM-CSF allocation. The food effect part of the study (Part B) will be open-label.

The following will apply:

- RAMOS NG will be programmed with blind-breaking instructions. The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK within 24 hours of breaking the blind, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- A participant will be withdrawn if the participant's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- Sponsor open refers only to the GSK DEC members involved in the review of the unblinded safety data on an as required basis and at the dose escalation meetings. No-one outside of this committee will be unblinded to the study data. The investigator (or delegate) will be a member of the DEC, but will review only blinded data. Further details of how this will be managed are included in Section 12.3 and is included in the DEP.

7.5. Preparation/Handling/Storage/Accountability

1. GSK3358699 solutions will be prepared by dissolving drug substance in water for injection at a concentration of 0.2 mg/mL. Solutions will contain doses from 1 mg up to 10 mg. A visually matching placebo solution of water for injection will also be prepared

2. GSK3358699 capsules for oral administration will be prepared by filling capsules with the drug substance only. Capsules will contain doses between 3 mg and a maximum of 70 mg GSK3358699. A visually matching placebo capsule will also be prepared by filling capsules with microcrystalline cellulose.
3. The capsules and solutions will be extemporaneously prepared at the clinical site using a Manufacturing Batch Record which will be reviewed and approved by GSK prior to use. The Manufacturing Batch Record will contain full details of the procedures to be followed.
4. The capsule formulation will be administered within 28 days of preparation.
5. The solution formulation will be administered within 7 days of preparation.
6. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
7. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
8. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
9. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

7.5.1. GSK3358699

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.5.2. Cantharidin

Cantharidin is not expected to pose significant occupational safety risk to site staff under proposed conditions of use and administration. Adequate precautions will be taken to avoid direct eye or skin contact and the generation of aerosols or mists. Precaution will be taken to avoid direct contact with the challenge agent. A MSDS describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure, the monitor, medical monitor and/or study manager will be notified.

One part of Cantharone will be mixed with 2.5 parts of pharmaceutical grade acetone according to standard practice. This reconstituted challenge agent will be used within 4

hours and any residual material will be discarded according to standard GSK waste-streams.

7.5.3. LPS

LPS is not expected to pose significant occupational safety risk to site staff under the proposed conditions of use and administration. Adequate precautions will be taken to avoid direct eye or skin contact and the generation of aerosols or mists. Precaution will be taken to avoid direct contact with the challenge agent. A MSDS describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure, the monitor, medical monitor and/or study manager will be notified.

The dose of LPS will be calculated according to body weight and injected as a bolus over less than 2 minutes. Any residual material will be discarded according to standard GSK waste-streams.

7.5.4. GM-CSF

GM-CSF is not expected to pose significant occupational safety risk to site staff under the proposed conditions of use and administration. Adequate precautions will be taken to avoid direct eye or skin contact and the generation of aerosols or mists. Precaution will be taken to avoid direct contact with the challenge agent. A MSDS describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure the monitor, medical monitor and/or study manager will be notified.

The dose of GM-CSF will be calculated based on body surface area (BSA) (Mosteller formula: BSA = 0.016667 × Weight (kg)$^{0.5}$ × Height (cm)$^{0.5}$ [Mosteller et al 1987] and intravenously infused over approximately a 2 hour period. Any residual material will be discarded according to standard GSK waste-streams.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use.
- dates of administration including start and end dates.
- dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants receiving blister challenges in the study must abstain from use of emollients containing hydrocortisone during their participation in the study and must also abstain from applying topical creams as detailed in Section 6.3.3.

Paracetamol, at doses of ≤ 2 grams/day, is permitted for use any time during the study except for 12 hours before or after intravenous LPS for those participants receiving this challenge. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy participants are eligible for this study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

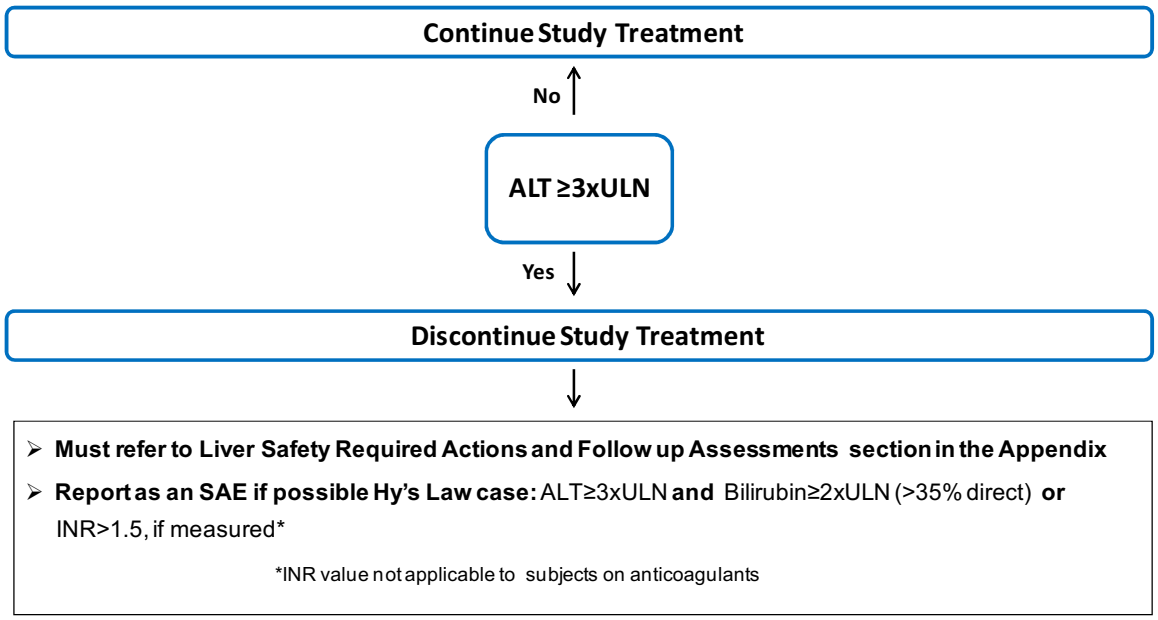
A participant may be discontinued from study treatment according to the protocol stopping criteria.

8.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study treatment for abnormal liver tests is required when a participant meets one of the conditions outlined in the algorithm.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



In addition discontinuation of study treatment will be required if bilirubin is > 2xULN and conjugated (direct) bilirubin >35% and the Liver Stopping Event Algorithm will be followed.

Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.7.

8.1.2. QTc Stopping Criteria

A participant that meets either of the bulleted criteria below will be withdrawn from the study.

- QTcF > 500 msec
- Change from baseline: QTcF > 60 msec
- The QTcF should be based on single or averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

8.1.3. Haematological Stopping Criteria

A participant that meets the criteria below, where the finding is persistent, confirmed on repeat testing and is regarded as clinically significant by the Investigator, will be withdrawn from the study. It should be noted that following acute LPS or GM-CSF challenge transient changes in haematological criteria are expected. Since the challenges are only administered after the final dose of GSK3358699 in any given part of the study, haematological results following challenge administration will be reviewed and any action based on evaluation of results will be at Investigator discretion in conjunction with the Medical Monitor.

- Haemoglobin ≤ 9 g/dL (5.58 mmol/L) or an absolute decrease of ≥3 g/dL from baseline (pre-dose Day 1)
- Neutrophils ≤ 1.0 x 10^9/L, or neutrophils >1.0-1.5 x 10^9/L if the results are deemed clinically significant at the discretion of the Investigator.
- Lymphocytes ≤ 0.5 × 10^9/L
- Platelets ≤ 50,000/mm^3

8.1.4. Lipid Stopping Criteria

A participant that meets the criteria below, where the finding is persistent, confirmed on repeat testing and is regarded as clinically significant by the Investigator, will be withdrawn from the study. Lipid stopping criteria do not apply to the food effect part of the study (Part B) since lipid elevations are expected after a high fat meal.

- Fasted Triglycerides > 5.7 mmol/L
- Fasted Total cholesterol > 10.3 mmol/L

8.1.5. Gastrointestinal Stopping Criteria

If a participant reports any persistent gastrointestinal symptom (i.e., nausea, abdominal pain/discomfort, diarrhea, or vomiting) which causes the participant concern or interferes with daily activities (including eating and sleeping) during any dosing Period, and is considered at least possibly related to the investigational product, then the participant should be withdrawn from the study.

If the participant reports a gastrointestinal AE of concern during dosing or at follow up, the Investigator will complete a clinical assessment of the gastrointestinal adverse event(s) of concern and could consider referral to a Gastroenterologist.

8.1.6. Individual Safety Stopping Criteria

- If a participant experiences a serious or severe clinically significant AE that in the clinical judgement of the Investigator, after consultation with the medical monitor, is possibly, probably or definitely related to investigational product, then the participant should be withdrawn from the study.

8.1.7. Dose Adjustment/Stopping Pharmacokinetic Criteria

The following dose adjustment / PK stopping criteria will apply:

- If mean cohort exposure exceeds or is predicted to exceed the C_{max} of 42 ng/ml or total daily AUC of 255 ng/ml.h, dose escalation will be stopped.
- Individuals in each cohort will be monitored throughout the study. If 2 or more participants in a given cohort at the same dose level exceed these stopping criteria, dose escalation will be halted.
- If the PK stopping criteria is reached with initial doses, the dose escalation will be stopped. The GSK team will decide based on safety, PK and any available PD

information whether to evaluate any lower doses or repeat doses already evaluated in remaining periods to collect additional safety, PK and PD data.

Throughout all parts of the study, either a population PK model or the results of a non-compartmental analysis will be used to help inform the choice of the next dose level as part of dose escalation discussions. For either approach, it is planned that the 95th percentile for the predicted total daily AUC values will not exceed 1/3 of the mean AUC observed at the cynomolgus monkey NOAEL and the 95th percentile of the predicted C_{max} will not exceed 1/3 of the mean C_{max} observed at the cynomolgus monkey NOAEL.

8.1.8. Dose Adjustment/Stopping Pharmacodynamic Criteria

The PD of GSK3358699 will be evaluated throughout the study. The DEC will apply the following PD stopping criteria which are relevant to any cohort evaluated in any part of the study. If these criteria are met before the highest planned dose level or other stopping criteria are reached, the PD data obtained up to the point the PD stopping criteria is met will provide sufficient information to model effective doses in future studies and therefore, the decision will be taken not to proceed with higher dose levels.

- MCP-1 and TNF inhibition in participant blood stimulated *ex vivo* with LPS, where maintenance of ≥ 90% MCP-1 and TNF inhibition for a minimum of 12 hours post dose relative to baseline is achieved.

- Additionally, if the PD effect of GSK3358699 appears to have become saturated over the course of 2 consecutive dose levels, dose escalation will be halted.

8.1.9. Dose Escalation / Study Progression Stopping Safety Criteria

Progression to the next higher dose level will be halted if:

- Two or more participants in the same cohort experience severe non-serious adverse reactions (i.e. severe non-serious adverse events considered as, at least possibly related to the administration of GSK3358699), independent of within or not within the same system-organ-class.

- Any participant experiences a serious adverse reaction (i.e. a serious adverse event considered at least possibly related to the administration of GSK3358699).

- Three or more participants in a cohort experience the same adverse event of moderate severity that can be reasonably attributed to dosing with GSK3358699.

The dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the GSK medical monitor, relevant GSK personnel, and with the IRB / IEC will then take place prior to any resumption of dosing, which may include the evaluation of lower doses.

If dosing is halted, and if deemed acceptable by GSK internal safety review to proceed with or modify dose escalation to further characterize the safety profile of GSK3358699,

a formal request with appropriate data and a substantial amendment will be submitted to the MHRA for approval before further dosing takes place.

An exception will be if taste/smell AEs are reported when a solution formulation of GSK3358699 is being utilised, in which case escalation can continue as planned based on the judgement of the investigator and the GSK medical monitor.

All other stopping criteria will apply even if no PK or PD stopping criteria have been met.

8.1.10. Rechallenge

8.1.10.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after any stopping criteria are met by any participant in this study is not allowed for that individual.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Acceptable time windows around the nominal time points for specific assessments will be included in the SRM and assessments performed within these time windows will not constitute a protocol deviation.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is not planned to exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs will be collected from the start of study treatment until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to

a GSK product will be recorded from the time a participant consents to participate in the study.

- All AEs will be collected from the start of study treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as Medical History in the participant's source notes not the AE section of the CRF.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until the final follow-up visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 12.5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

For this study, any dose of GSK3358699, LPS challenge agent, GM-CSF challenge agent or cantharidin, greater than the protocol planned doses or doses defined as part of dose escalation decisions, will be considered an overdose.

9.3.1. GSK3358699

In the event of an overdose of GSK3358699, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 48 hours).
3. Obtain a plasma sample for PK analysis within 8 hours of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

GSK does not recommend specific treatment for an overdose. The Investigator (or physician in charge of the participant at the time) will use clinical judgment to treat any overdose.

9.3.2. Cantharidin

Participants will not have access to cantharidin and overdose is therefore extremely unlikely. In the event of overdose, the clinical management will be based on symptomatic

treatment and supportive measures as indicated and required according to current UK guidelines.

In case of any overexposure to Cantharone refer to the MSDS.

Inhalation: Remove victim to fresh air. Give oxygen or artificial respiration if necessary.

Skin Contact: Immediately flood affected skin with water while removing and isolating all contaminated clothing. Gently wash all affected skin areas thoroughly with soap and water. Seek medical attention if warranted.

Eye Contact: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control centre. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim after flushing eyes to a hospital even if no symptoms (such as redness or irritation) develop.

Ingestion: Do not induce vomiting. If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and immediately call a hospital or poison control centre. Immediately transport the victim to a hospital. If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open, and lay the victim on his/her side with the head lower than the body. Transport the victim immediately to a hospital.

9.3.3. LPS

LPS dose selection has been made on the basis of a lower dose and potency than is usually reported in the literature, and thus overdose is not anticipated.

Intravenous LPS has the potential to be extremely harmful in overdose and induce symptoms and organ dysfunction in keeping with septic shock. Participants who receive an overdose of intravenous LPS will be hydrated with rapid intravenous fluid boluses. Clinical staff may need to expedite immediate transfer to hospital in the event that volunteers exhibit clinical signs of septic shock. Mild pyrexia and malaise may be observed.

9.3.4. GM-CSF

GM-CSF dose selection has been made on the basis of a lower dose than is usually reported in the literature/given to patients, and thus overdose is not anticipated.

In case of overdose, participant will be carefully monitored for white blood cell (WBC) increase and respiratory symptoms. Symptomatic management will be carried out according to existing guidelines.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Body Weight

Body weight will be measured at the time points in the SoA. In Part A, body weight measured in treatment Period 4 Day -1 will be used to calculate the dose of LPS and GM-CSF to be used. In Part C (Cohort 4 and 8 only) body weight measured on the day prior to challenge administration will be used to calculate the dose of LPS and GM-CSF to be used.

9.4.3. Assessment of blister sites

- Visual assessment of blister site will be carried out at selected visits as detailed in the SoA.

9.4.4. Vital Signs

- Tympanic temperature, heart rate, respiratory rate, and blood pressure will be assessed.
- Vital signs measurements are to be taken before blood collection for laboratory tests.
- Tympanic temperature and respiratory rate will be taken as single measurements at the timepoints detailed in the SoA.
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting, in a semi-supine position, without distractions (eg, television, cell phones).
- In Part A and Part B, blood pressure and pulse measurements will be performed as follows.
  - Day -1, Day 1 pre-dose, 24 h and 48 h post-dose: triplicate measurements
  - Day 1 post-dose: single measurements throughout except for:
    - GSK3358699 C_{max} timepoint; triplicate measurement
    - For 12 hours post-LPS challenge: triplicate measurement

- In Part C (Cohorts 4 and 8), blood pressure and pulse measurements will be performed as follows:
  - Day – 1 to Day 13: triplicate measurements
  - Day 14 pre-dose, Day 15 and Day 16: triplicate measurements
  - Day 14 post-dose: single measurements throughout except for:
    - GSK3358699 approximate C_{max} timepoint; triplicate measurement
    - For 12 hours post-LPS challenge: triplicate measurement
- In Part C (Cohorts 5 - 7), blood pressure and pulse measurements will be performed as follows:
  - Day – 1 to Day 13: triplicate measurements
  - Day 14 pre-dose, Day 15 and Day 16: triplicate measurements
  - Day 14 post-dose: single measurements throughout except for:
    - GSK3358699 approximate Cmax timepoint; triplicate measurement
- At timepoints where triplicate measurements of pulse and blood pressure are required, 3 consecutive readings will be recorded at intervals of at least 1 minute.

9.4.5. Electrocardiograms

- Triplicate 12-lead ECGs will be obtained in the study at the time points detailed in the SoA and at other times in the study if clinically indicated (Section 2.3; single ECGs at all other time points) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 4 minutes apart. The full set of triplicates should be completed in less than 8 minutes.
- Holter monitoring will be performed at screening only. This 24-hour Holter will be performed to eliminate participants with non-clinically overt cardiac arrhythmias or other exclusionary criteria.

9.4.6. Cardiac Telemetry

Continuous cardiac telemetry will be performed in the study at the time points detailed in the SoA and at other times in the study if clinically indicated as detailed in the SoA (Section 2.3).

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7-14 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If a cardiac arrhythmia occurs, a PK sample and drugs of abuse test should be taken as close to the time of the event as possible.
- Laboratory results at Day -1 are for the purposes of providing baseline values prior to dosing. The review of laboratory abnormalities at Day -1 for eligibility will be based on Investigator discretion and clinical judgement.

9.4.8. Participant Diary Card

Participants will be given a diary card for them to record the healing time of the blisters as well as to record any adverse events or medications taken whilst outside of the unit.

9.5. Pharmacokinetics

9.5.1. Blood sample collection and analysis

- Blood will be collected into appropriate tubes (type to be confirmed pending on-going stability investigations) for measurement of GSK3358699 and GSK3206944 concentrations in plasma (approximately 1 mL per time-point up to and including 6 hours post dose and approximately 2 mL per time-point after 6 hours post-dose). **[S1]** and **[S2]**
- Blood (6 mL per time point) will be collected into sodium heparin tubes for the isolation of monocytes and for measurement of GSK3206944 concentrations in monocytes, as specified in the SoA. **[S3]**

- Instructions for the processing, storage and shipping of biological samples will be provided by the sponsor in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK3358699 and GSK3206944 in plasma and GSK3206944 in monocytes. Samples collected for analyses of GSK3358699 and GSK3206944 plasma concentration may also be used to evaluate safety or PD aspects related to concerns arising during or after the study.
- Once the plasma has been analyzed for GSK3358699 and GSK3206944 any remaining plasma will be analyzed qualitatively for other compound-related metabolites and the results reported under a separate protocol. **[E4]**
- Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Drug concentration information that may unblind the study will not be reported to the investigator site or blinded personnel until the study has been unblinded.

9.5.2. Urine Sample Collection and Analysis

- Urine will be collected for qualitative analysis of compound-related metabolites according to the SoA time points. Immediately prior to dosing, each participant will be instructed to void their bladder into a collection container and no more than 20 mL of this urine sample will be retained as a pre-dose control sample. A 0-24 hour urine collection will begin immediately following dose administration. Participants will be instructed to collect all urine voided on each occasion into a collection container and the urine will be transferred / pooled in a 0-24 h storage container for further processing after the end of the collection period, with the exception of the samples required for urinalysis testing during this period which will be collected separately. Further instructions on urine sample processing, storage and shipment will be provided in the SRM. The results of this analysis will be reported under a separate protocol. **[E4]**.

9.6. Pharmacodynamics

There will be several measures of PD taken in the study using whole blood or blood-derived samples, as outlined in the SoA.

9.6.1. Ex vivo PD sample

1 mL whole blood samples will be collected according to the timings specified in the SoA. At each timepoint, one 1mL sample will be drawn into a TruCulture tube containing LPS and a second 1mL sample will be drawn into a 1 “GSK3358699 LPS” TruCulture tube, and incubated for 24 hours. For all samples, cellular and soluble contents will be separated and inflammatory mediators (MCP-1, IL-6 and TNF) analysed in the soluble fraction. **[S4]**

9.6.2. Circulating inflammatory biomarkers / proteins

Approximately 2 mL of blood will be collected into heparin tubes according to the timings on the SoA. This will allow for analysis of plasma to measure inflammatory mediators, such as MCP-1, IL-12p40 and MMP-9. Measurement of soluble inflammatory mediators will be carried out in batch analysis. **[E1a]**

9.6.3. Gene array panel

Approximately 2.5 mL of blood will be collected into PAXgene tubes for gene array analysis according to the timings on the SoA. Samples will be used to extract ribonucleic acid (RNA) and prepare complementary deoxyribonucleic acid (cDNA) which will subsequently be used for analysis by gene array panels. **[E1b]**

Other measures of pharmacodynamics will be measured as part of the in vivo challenges (LPS, GM-CSF or cantharidin) and the measurements are described in Biomarkers in Section 9.8.

9.7. Genetics

All randomized subjects will be required to provide a 2 mL blood sample for potential companion diagnostic development, if test development is required by regulatory authorities to identify subjects who are appropriate for GSK3358699 treatment. This 2 mL blood sample will be stored frozen at the central lab.

All randomized subjects will be required to provide a 6 mL blood sample for investigation of genetic variation of genes that encode carboxyesterase (CES) according to the timings on the SoA **[E5]**. Additionally, this sample will be used for additional genetics research for those participants who have consented in the optional exploratory genetics analysis component of the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 12.6 Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

9.8. Biomarkers

There will be several different types of biomarker samples collected during the study as outlined in the SoA, including biomarkers from blood and blister fluid. The biomarkers will be induced using the inflammatory stimuli (LPS, GM-CSF, cantharidin) as described in Section 5.1. The biomarkers will include cellular and soluble proteins and gene expression, and the effect of GSK3358699 on these measures of inflammation will be determined.

9.8.1. Biomarkers in blood

Biomarkers in blood will be collected pre- and post- challenge (*in vivo* challenge with LPS or GM-CSF). Cellular and soluble activation markers will be determined at several time points as specified in the SoA. Leukocyte counts for each sample will be recorded in the eCRF. **[E2]**

9.8.1.1. Cellular activation markers blood sample (all cohorts in Part C)

Approximately 2 mL of blood will be collected into heparin tubes for measurement of leukocyte number and activation markers by flow cytometry (see indicative list in endpoints) **[E2b]**.

9.8.1.2. Circulating inflammatory biomarkers blood sample (challenge cohorts only)

Approximately 2 mL of blood will be collected into heparin tubes according to the timings on the SoA. This will allow for analysis of plasma to measure inflammatory mediators. Methods of analysis which may be used on these samples are detailed in the SRM. Measurement of soluble inflammatory mediators will be carried out in batch analysis. **[E2a]**

9.8.1.3. Gene array panels (challenge cohorts only)

Approximately 2.5 mL of blood will be collected into PAXgene tubes for gene array analysis according to the timings on the SoA. Samples will be used to extract RNA and prepare cDNA which will subsequently be used for analysis by gene array panels to determine the effects of compound on challenge with LPS or GM-CSF. **[E2d]**

9.8.2. Biomarkers in blisters

Biomarkers in blisters will be collected by piercing the blister with a needle and aspirating the blister contents with a pipette into a polypropylene micro-centrifuge tube. Cellular and soluble contents will be separated. The volume of the blister sample will be calculated and recorded in the eCRF. **[E3]**. 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).

9.8.2.1. Cellular blister sample

Blister sample will be used to measure leukocyte number and activation markers by flow cytometry (see indicative list in Section 4), at times specified in the SoA **[E3].**

9.8.2.2. Soluble blister sample

The soluble fraction from the blister sample will be used to measure inflammatory mediators. Methods of analysis which may be used on these samples are detailed in the SRM **[E3].**

9.8.3. RNA Expression Research of a Subset of RNA Species

As detailed in Section 9.6.3 and Section 9.8.1.3, samples will be used to extract RNA and prepare cDNA which will subsequently be used for analysis by gene array panels. **[E1b, E2d]**

9.9. Health Economics OR Medical Resource Utilization and Health Economics

This is not applicable to this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

As the primary objective of the study is to assess the safety of GSK3358699 in healthy volunteers, there are no formal hypotheses. There are also no formal hypotheses to be tested for the single or repeat dose PK data.

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

10.2. Sample Size Determination

10.2.1. Sample size assumptions

At each dose level studied in Part A there will be approximately nine participants; six randomised to each of the GSK3358699 treatment groups and three receiving placebo in any one period. In Part A, each participant will be randomised to one of three sequences for the dose escalation phase.

In Part B of the study there will be approximately six participants, all receiving GSK3358699 (randomised to either fed or fasted administration), each participant will be randomised to one of two sequences. In Part C approximately fourteen participants in Cohort 4 were planned (ten randomised to the GSK3358699 treatment group and four receiving placebo, in a 5:2 ratio). In Cohorts 5 - 7 approximately eighteen participants are planned (nine randomised to each of the GSK3358699 treatment groups and nine receiving placebo, in a 1:1 ratio) and in Cohort 8 approximately twenty subjects are planned (ten randomised to the GSK3358699 treatment group and ten receiving placebo, in a 1:1 ratio).

Refer to Section 7.2 for further information on sample size and randomisation changes in the event of any dose modifications.

The sample size is based on feasibility.

The primary objective of the study is safety, where the number of safety events would be of interest, for example the number of participants experiencing a particular adverse event. At each dose level in Part A six participants will receive GSK3358699. If 0/6 of a

particular safety event in the GSK3358699 group is observed, using a Bayesian approach to determine the credible interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe 1 safety event in 6 then the posterior distribution would be Beta (2, 6), where we can be 95% certain that the true probability of the safety event lies between 0.04 and 0.58.

Sample size sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates. If the number of subjects who completed each active dose reduces, then the true incidence rates of safety events that could not be ruled out would change. These changes are outlined below:

N on GSK3358699 Completing Cohort	Number of a particular safety event observed with GSK3358699	Upper limit of exact 95%CI indicating that a true incidence rate of x% could not be ruled out
6	2	71%
	3	82%
5	0	46%
	1	64%
	2	78%
4	0	52%
	1	72%
	2	85%

Sample size re-estimation

There is no sample size re-estimation planned.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who are randomised into the study and receive a randomisation number.
Evaluable	A participant is considered evaluable if they complete both screening and all their planned treatment Periods in Part A; both Periods in Part B, or the 14 day treatment Period and subsequent assessment Period in Part C.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
Pharmacokinetic	All participants in the Safety Population who receive an active dose and for whom a PK sample was obtained and analysed.

Population	Description
PK/PD	The Safety Population will be used so that participants receiving placebo can be included.

10.4. Statistical Analyses

Parts A, B and C will be reported separately in the outputs.

10.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library standards.

10.4.2. Pharmacokinetic Analyses

All PK analyses will be performed on the Pharmacokinetic Population.

Endpoint	Statistical Analysis Methods
Secondary	Plasma GSK3358699 and the metabolite GSK3206944 concentration-time data will be analysed by non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study. Concentration-time data will be listed for each participant and treatment and summarized by planned time point and treatment. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve [$AUC_{(0-24)}$, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$], and apparent terminal phase half-life ($t_{1/2}$). PK parameters will be listed for each participant and treatment and summarized descriptively by treatment using the PK population. For each of these parameters, except t_{max}, the following summary statistics will be calculated for the active treatment group at each cohort: median, maximum, minimum, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. For t_{max}, median, maximum, minimum, arithmetic mean and standard deviation will be calculated. The first point, last point and number of points used in the determination of lz will be included on the listing of the derived parameters.

Endpoint	Statistical Analysis Methods
	Part A: Dose proportionality will be assessed by analysis of $\log_e$-transformed parameters $AUC_{(0-\infty)}$ [or if not available $AUC_{(0-t)}$] and C_{max} using the power model. Further details will be included in the RAP. **Part B:** A mixed effects model will be fitted on the $\log_e$-transformed parameters $AUC_{(0-\infty)}$ [or if not available $AUC_{(0-t)}$] and C_{max} with fed status as a fixed effect and participant as a random effect. Point estimates and corresponding 90% CIs will be constructed for GSK3358699 fed - GSK3358699 fasted using the residual variance. These will then be back transformed to provide point estimates and corresponding 90% CIs for the geometric mean ratio GSK3358699 fed to GSK3358699 fasted. **Part C:** The extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) will be determined. The plasma steady state ratio (Rs) and an assessment of plasma steady state across the trough concentrations will also be made. Dose proportionality will be assessed using similar methods to the single dose Part A.

10.4.3. Other Analyses

The intra-cellular acid parameters and PD parameters collected during the study and after each challenge will be listed for each participant and treatment and summarized descriptively by treatment. If deemed appropriate the dose response relationship at each time point for the change from baseline in key PD parameters will be determined.

PD and biomarker exploratory analyses will be described in the RAP.

It is intended that a population PK model will be built to predict the exposures at the next ascending dose from the currently available PK data.

The population PK and PK/PD analyses and exploratory biomarker analyses may be presented separately from the main clinical study report (CSR).

10.4.4. Interim Analyses

If a decision is made to perform challenges on a previously tested dose (i.e. not evaluate a new dose regimen) in the challenge cohort (Cohort 8), a formal interim statistical analysis will be performed on the completed cohorts in Part A, Part B and Part C of the study once all participants complete Cohort 7 of Part C to aid internal decision making. There will be no changes to the study design or planned number of participants in Cohort 8 as a direct result of the interim analysis.

Dose escalation meetings will also occur after each Period in Part A and after the completion of up to 14 days dosing of each cohort in Part C.

The decision to proceed to the next cohort, and next dose strength to be studied, or to the next study Part, will be made by the DEC based on assessment of safety, plasma

GSK3358699 pharmacokinetic concentrations and target engagement data obtained in all participants at the prior dose level. Individual safety data (AEs, laboratory safety tests, ECGs and vital signs) will be reviewed, according to the DEP.

This study is double blind (sponsor open), where the participant, investigator and site staff will remain blinded to the treatment allocation. Sponsor open refers only to those members of the DEC. Note that Part B will be open label.

The RAP will describe the planned interim analyses in greater detail.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations	
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMD	Age-related Macular Degeneration
API	Active Pharmaceutical Ingredient
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BET	Bromodomain and Extra Terminal domain
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CD	Cluster of Differentiation
CDER	Center for Drug Evaluation and Research
cDNA	Complementary DNA
CES	Carboxyesterase
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum Concentration
CK	Creatine Kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
(e)CRF	(electronic) Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DDI	Drug Interaction
DEC	Dose Escalation Committee
DEP	Dose Escalation Plan
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EDTA	Ethylenediaminepentaacetic acid
E_{max}	Maximum Effect Possible
ESM	Esterase Sensitive Motif
EU	European Union

FDA	Food and Drug Administration
FTIH	First Time In Human
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GSK	GlaxoSmithKline
HED	Human Estimated Dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA-DR	Human Leukocyte Antigen - antigen D Related
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IG	Immunoglobulin
IL	Interleukin
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INR	International Normalized Ratio
IP	Interferon gamma-induced Protein
IUD	Intra-Uterine Device
IUS	Intra-Uterine hormone releasing System
IV	Intravenous
IRB/IEC	Institutional Review Boards /Independent Ethics Committees
LDH	Lactose Dehydrogenase
LPS	Lipopolysaccharide
MABEL	Minimum Anticipated Biological Effect Level
MCH	Mean Corpuscular Hemoglobin
MCP	Monocyte chemoattractant protein
MCV	Mean Corpuscular volume
MDC	Macrophage-Derived Chemokine
MHRA	Medicines and Healthcare Products Regulatory Agency
MMP	Matrix Metallopeptidase
MSDS	Material Safety Data Sheet
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PBO	Placebo
PBPK	Physiologically Based Pharmacokinetic
PD	Pharmacodynamics
PK	Pharmacokinetics

PT	Prothrombin Time
QD	Once Daily
QTc	Electrocardiogram QT interval corrected for heart rate
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid Arthritis
RAP	Reporting Analysis Plan
RBC	Red Blood Cell
RDW	Red cell Distribution Width
RNA	Ribo Nucleic Acid
Ro	Accumulation Ration
Rs	Plasma steady state ratio
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SD	Standard Deviation
SoA	Schedule of Activities
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SNP	Single Nucleotide Polymorphism
SPF	Sun Protection Factor
SRM	Study Reference Manual
SST	Serum-Separating Tube
SUSAR	Suspected Unexpected Serious Adverse Reactions
TARC	Thymus and Activation Regulated Chemokine
TBC	To Be Confirmed
TE	Target Engagement
TGF	Transforming Growth Factor
T_{max}	Time to C_{max}
TNF	Tumour Necrosis Factor
ULN	Upper limit of normal
UVA/B	Ultra Violet A/B
WBC	White Blood Cell
WCC	White Cell Count

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Cantharone
Leukine

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-Required Safety Laboratory Assessments

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 transferase (GGT)[4]	Creatine kinase (CK)[4]	
Routine Urinalysis				
• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)				

Laboratory Assessments	Parameters
Other Clinical Laboratory Tests	
• alcohol breath test and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Urine cotinine The results of each test will be loaded electronically into the eCRF.	

NOTES:
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 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

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

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

Data Protection

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

Committees Structure

Dose Escalation Committee

The DEC will make the decision to proceed to the next dose level of GSK3358699 at the end of each single dose (Cohorts 1-2) and repeat dose cohort (Cohorts 4-8); along with making the decision on the dose for Part B of the study and the decision to move into Part C of the study. For details of the information to be considered as part of this decision making process see Section 5.1.

Safety, PK and PD stopping criteria will be strictly applied. Details of these criteria can be found in Section 8. There will be an open and closed part to the dose escalation meeting as required. At the beginning of the meeting blinded data will be discussed in an open forum with the investigator in attendance. If required, the data will then be reviewed in an unblinded fashion by the unblinded members of the DEC. These unblinded members include the Medical Monitor, GSK GCSP representative, GSK

statistician and GSK pharmacokineticist. In instances where the TE data is reviewed the GSK biology representative will also be present at the dose escalation meeting. A DEP will be written outlining in detail how the study team will ensure data integrity used in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions, as well as outlining the responsibilities of the investigators and site staff for reporting safety data, participation during dose escalation meetings, and confirmation that the data used for dose escalation are accurate and complete.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 7 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- In addition, male participants must refrain from donating sperm for duration of study and for 91 days from last dose

Table 7 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment Period and for at least 91 days after the last dose of study treatment

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

12.6. Appendix 6: Genetics

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin et al 2012] with certain variants reported to influence treatment response [Chen et al 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

CES Genotyping

There is known genetic variation [Merali et al 2014] with the potential to impact *CES-1* activity and potentially impact its ability to hydrolyse GSK3358699 to form the active compound GSK3206944. A sample will be collected from all participants to allow mandatory assessment of CES variation **[E5]**. Additionally, that same sample may be used for exploratory genetic analysis in participants who have consented to participate in the genetics analysis component of the study. Participation in the exploratory genetics analysis is optional. Participants who do not wish to participate in the exploratory genetic research may still participate in the study.

Additionally, a blood sample will be collected from all participants will be stored frozen for use in the development of a companion diagnostic in the event of a Regulatory Authority requirement.

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples may be used for research related to GSK3358699 and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GSK3358699 and rheumatoid arthritis plus other potential inflammatory indications such as psoriasis and fibrotic liver disease. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)

- DNA samples will be analysed for CES variation and may be analyzed for genetic variation in additional genes if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3358699 or study treatments of these drug classes. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3358699 or rheumatoid arthritis plus other potential inflammatory indications such as psoriasis and fibrotic liver disease continues but no longer than 15 years after the last participant last visit or other Period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
Bilirubin > 2xULN and conjugated (direct) bilirubin >35%
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 8 hours of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, 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); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

12.8. Appendix 8: Protocol Amendment History

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

Amendment 1 (25th January 2018)

Overall Rationale for the Amendment: Medicines and Healthcare Products Regulatory Agency (MHRA) feedback on the protocol requires wording to be added to the Dose Escalation / Study Progression Stopping Safety Criteria section. Some minor administrative / typographical revisions have also been made within the SoA tables.

Section # and Name	Description of Change	Brief Rationale
Section 2.2 Part B Food Effect Schedule of Activities	Reference to 'agent' and 'placebo' deleted on page 25	Part B of the study does not involve challenge agents or placebo
Section 2.3 Part C General Schedule of Activities	'X' added to 'Visual Forearm Check' on Days 15 and 16.	Updated for consistency with Section 2.3.2 and Section 2.3.3 where this assessment is already included on Days 15 and 16.
Section 8.1.8 Dose Escalation / Study Progression Stopping Safety Criteria	Wording added to indicate that, if any of the dose escalation stopping criteria are met, an application for a substantial amendment with the MHRA must be submitted and approved before further dosing takes place.	Change required by MHRA.

Amendment 2 (21st March 2018)

Overall Rationale for the Amendment: This is a non-substantial amendment primarily to correct a discrepancy in the API storage temperature; the protocol stated temperature is incorrect however the API labelling and other documentation is correct. Some minor administrative / typographical revisions have also been made.

Section # and Name	Description of Change	Brief Rationale
Synopsis and Section 5.5.1.1 Part A Study Schematic; Section 7.3 Method of Treatment Assignment	QD (once daily) removed.	It is clearly described in the text that Parts A and B of the study are single-dose. However to avoid confusion regarding the use of the term QD these sections have been updated.
Section 2.1 Part A Schedule of Activities	Added note to SoA to clarify that 24 and 48 hour safety sampling will be done prior to participants receiving breakfast.	To increase clarity.
Section 2.3 Part C Schedule of Activities Tables	Some minor revisions to the Days referenced in the comments column, (eg Day 4-12 changed to Days 4, 8 and 12)	To increase clarity
Section 2.3 Part C General Schedule of Activities	'X' added to 'Blood sampling for intracellular PK' on Day 16.	Updated for consistency with Section 2.3.1 where this assessment is already included on Day 16.
Section 5.3 Participant and Study Completion	Added '…for which he was eligible' to the end of the first sentence	To increase clarity.
Section 7.5 Preparation/Handling/ Storage/Accountability	Bullet 4 deleted	Bullet 4 described a specific storage temperature for the bulk API which is incorrect and not in line with the storage conditions on other documentation. Since bullet 8 (now bullet 7) contains an acceptable, more general statement on storage conditions, bullet 4 is not required.
Section 2, SoA; Section 3.3.1 Risk Assessment; Section 5.5.1 Part A Dose Justification Section 7.1 (Table 5) Section 8.1.3 Haematological Stopping Criteria Section 10.4.2 Pharmacokinetic Analysis	Minor typographical corrections to include superscripts or subscripts, eg Cmax changed to $C_{max,}$ 106 changed to 10^6	
Section 5.5.4	Updated cross-reference 5.1.1 to 5.5.1.	Correction of cross-reference

Amendment 3 (29 May 2018)

This is a substantial amendment being made primarily for two reasons.

Firstly, capsule formulation development has been ongoing in order to allow doses lower than 10 mg to be administered as a capsule; currently doses from 1 mg up to 10 mg require solution administration. The amendment will allow dose levels from 3 mg to be administered as a capsule formulation, which will be of particular benefit in the repeat dose part of the study (Part C) should administration of lower dose levels be required.

In addition, the flexibility of participation in Part A has been increased to facilitate subject recruitment. The protocol has therefore undergone a thorough review and appropriate changes made in order to increase flexibility for, and to aid recruitment and retention of, participants, while ensuring participant safety is maintained.

Other minor revisions have also been made in response to logistical / operational considerations now that the study is underway, and to provide additional clarification on some points.

The specific revisions are summarised below:

Section # and Name	Description of Change	Brief Rationale
SoA tables (all)	Stipulated fasted screening safety clinical chemistry samples	To ensure exclusion criteria #19 and #20 (now #18 and #19), and on-treatment fasted lipid levels, are compared with fasted lipid levels at screening
2.1, 2.2 and 2.3 SoA General Activities Tables for Parts A, B and C	Clarification of Day -1 Inclusion/Exclusion criteria	To ensure that it is known that this is to recheck eligibility against medical conditions, prior therapy etc and not against Day -1 lab tests such as clinical chemistry and haematology etc.
2.1 SoA Part A	Visual forearm screening clarification	Clarification that a visual forearm check is required in Treatment Period 3 only if the participant is eligible for Treatment Period 4.
2.1.1 SoA. Part A Period 4	Note added to state that participants taking part in treatment Period 4 only will undergo screening prior as detailed in Section 2.1. Day -10 column corrected to '± 3 days'	For clarification Correction – previously said '+/ 3 days'
2.1.1.1., 2.1.1.2 (SoA Part A Period 4 [LPS and GM-CSF]), 2.3.2 and 2.3.3 (SoA Part C [LPS and GM-CSF])	Removed the 10hr column	There are no assessments at the 10 hour timepoint other than vitals where timepoints are already covered in the notes column.
2.3, 2.3.2 and SoA tables Part C	Added coagulation tests on Day 13 (Section 2.3) and Day 13 and 14 (Section 2.3.2) Added Day 16 cellular activation sample (E2b)	To allow post-LPS challenge coagulation to be assessed as already included in Part A Missed in error
2.3 SoA table Part C and 2.3.1 Part C Day 14 SoA	Added S4 sample time points.	Missed in error
2.3.1 Part C Day 14 SoA	Added a note to state that S3 samples only collected until start of challenge administration	Missed in error
2.3.3 Part C Day 14 GM-CSF	Moved 10 h haematology sample to 8 h	Correction
Synopsis and 5.1.1.1 Part A Single Ascending Doses	Paragraph added to increase flexibility of participation in Part A Text regarding: timing of dosing of remainder of cohort after sentinels updated	To increase recruitment / retention potential in Part A. To clarify that the 48 hours is not a specific timepoint.
Synopsis and 5.1.1.3 Part A Total Duration	Study durations added for participants not taking part in all four treatment Periods	Required with text included in Section 5.1.1.1 to add flexibility in Part A participation
Synopsis and 5.2 Number of	Added text to explain that participants randomised to one part of the study	To aid recruitment/retention.

Section # and Name	Description of Change	Brief Rationale
Participants	can enrol on another part, excluding those who have received an LPS challenge. Added text to 'Additional participants / cohorts' paragraph' to state this means as part of a new cohort	 Clarification.
5.2 Number of Participants	Text added to clarify that any new participants taking part in Treatment Period 4 only will be classed as replacement subjects for participants who took part in treatment Periods 1-3.	To allow flexibility within the current cohorts and thus ensuring minimal impact to the randomisation set-up.
5.4 Scientific Rationale	Added text to Part A paragraph to explain why flexibility of participation has been included	To aid recruitment / retention
6.1 Inclusion Criteria #1	Upper age limit has been increased to 55 years for participants having challenge agents. Upper age limit increased to 65 years for participants not having challenge agents.	To aid recruitment/retention. Team agreed this could be increased slightly without impact. No requirement to restrict age range
6.2 Exclusion #3	Added text to clarify this criterion only applies to participants having blister induction	To aid recruitment into parts of the study where no blister induction is required, as this assessment is not necessary.
6.2 Exclusion #7	Changed time period from previous trial from 90 days to 30 days	To aid recruitment / retention. Was 90 days in line with enabling study protocol (Study ID 207654) but 30 days is standard for heathy volunteer studies.
6.2 Exclusion #10	Exclusion 10 has been deleted.	To aid recruitment. Study team have agreed that only prior LPS exposure requires exclusion and not prior blister induction or GM-CSF exposure, therefore no need to exclude all enabling study participants.
6.2 Diagnostic assessments Header	Added 'at screening'	To clarify that the Day -1 tests are not for eligibility.
6.2 Exclusion #16 (now #15)	Added text to clarify CRP abnormalities must be clinically significant	Match exclusion #17 (now #16)
6.2 Exclusion #19 (now #18)	Stipulated fasted levels and increased limit	Fasted triglycerides are appropriate for screening thresholds. Also ensures on-treatment fasted triglyceride levels are compared with fasted triglyceride levels at screening. Criterion changed to reflect CTCAE guidelines
6.2 Exclusion #20 (now #19)	Stipulated fasted levels and increased limit	Fasted total cholesterol is appropriate for screening thresholds. Also ensures

Section # and Name	Description of Change	Brief Rationale
		on-treatment fasted cholesterol levels are compared with fasted cholesterol levels at screening. Criterion changed to reflect CTCAE guidelines
7.1 Treatments Administered; Table 3	Amended capsule unit dose strength to 'from 3 mg to 70 mg' and added note to bottom of table	3 mg capsule formulation being developed to avoid need for a repeat dose solution administration at lower doses. Maximum dose strength updated to be in line with Investigational Medicinal Product Dossier (IMPD) and note added to bottom of table to clarify this is not the maximum planned dose in the study.
7.5 Preparation /Handling /Storage /Accountability	Amended item 2 to include 3 mg capsule strength and maximum 70 mg capsule strength. Amended items 4 and 5	3 mg capsule formulation being developed to avoid need for a repeat dose solution administration at lower doses. Maximum dose strength updated to be in line with IMPD Stability work is now complete therefore the shelf-life information can be confirmed.
7.7 Concomitant Therapy	Wording amended to make it clearer that abstention from emollients containing hydrocortisone and topical creams only applies in parts of the study with blister challenges.	Clarification as blister challenges may not be performed in Part C or for some subjects in Part A.
8.1.3 Haematological stopping criteria	Added that safety stopping criteria are for persistent abnormalities that are confirmed on repeat testing where applicable. Amended to 'neutrophils ≤ 1.0 x 10^9/L or neutrophils >1.0-1.5 x 10^9/L which is clinically significant'	Risk of lab errors or spurious results meeting stopping criteria Neutrophils > 1.0-1.5 have been observed in asymptomatic healthy volunteers
8.1.4. Lipid stopping criteria	Added that safety stopping criteria are for persistent abnormalities that are confirmed on repeat testing where applicable. Stipulated fasted levels. Added text that lipid stopping criteria do not apply to Part B. Increased stopping limits	Risk of lab errors or spurious results meeting stopping criteria. Rationale as described for Section 6.2 To avoid unnecessary withdrawals as lipid elevations are expected after food. In line with CTCAE criteria.
8.1.9.1 Study Treatment Restart or Rechallenge	Clarified this is for that individual's restart or rechallenge	Could be misinterpreted as applying to the whole study

Section # and Name	Description of Change	Brief Rationale
9 Study Assessments	2nd bullet from bottom – changed such that total blood volume is not planned to exceed 500 mL (rather than will not)	Required repeat sampling e.g. for safety monitoring may increase blood volume draw. Language then consistent with ICF
9.2.1 Time Period & Frequency for AE/SAE Info	Updated bullet 3 on medical occurrences to state that these are recorded in source notes	Noted that PIMS does not have a Med History / Current Med conditions page
9.4.4 Vital Signs	Text revised to change some triplicate timepoints to single measurements	To aid with assessment logistics – not deemed essential to have all timepoints as triplicate.
9.4.7 Clinical Safety Laboratory Assessments	Added bullet that Day -1 clinical lab safety samples are for baseline assessment	Clarification that the purpose of the Day -1 samples is not for specific review against eligibility criteria.
9.5.2. Urine Sample Collection and Analysis	Wording added regarding handling of urinalysis samples during the 0-24h urine collection period	To clarify that samples collected for urinalysis will not be part of the overall 0-24h collection.
10.2.1 Sample size assumptions	The word 'approximately' added to Part A, B and C paragraphs.	To align with the minimum evaluable number of subjects required for data analysis
12.2 Appendix 2 Clinical Lab tests	Added clarification on fasting sample requirements	To ensure exclusion criteria #19 and #20 (now #18 and #19), and on-treatment fasted lipid levels, are compared with fasted lipid levels at screening