Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for an open label parallel group study to investigate the optimum methodology for the use of LPS or GM-CSF as challenge agents on healthy participants by assessing inflammatory biomarkers in cantharidin-induced skin blisters, peripheral blood, and urine.
Compound Number	:	No Compound (Study 207654)
Effective Date	:	14-MAY-2018

Description:

- This version of the RAP is intended to describe the safety and biomarker analyses required for dose escalation and planned biomarker analyses required for interim analyses for study 207654. A subsequent version of the RAP will be developed for Final study reporting.
- Only sections related to dose escalation and interim analyses have been described.

RAP Author(s):

Approver	Date	Approval Method
PPD Senior Statistician (Immuno-Inflammation Clinical Statistics)	N/A	N/A

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the safety and biomarker analyses required for dose escalations and planned biomarker analyses required for interim analyses for Protocol:

Revision Chronology:		
2016N309726_00	08-May-2017	Original
2016N309726_01	07-AUG-2017	Change of GM-CSF (LEUKINE) administration from subcutaneous to IV infusion. This is due to liquid LEUKINE no longer being available from the manufacturer Sanofi-Aventis, however lyophilised LEUKINE is available. The guidelines for reconstitution of lyophilised LEUKINE prevent us from administering by subcutaneous as the volume would be too high. In order to remain consistent with clinical practice in dosing GM-CSF therapeutically the dose will be calculated using body surface area.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 08-May-2017) and protocol amendment 1 (Dated: 07-Aug-2017) are outlined in Table 1 for this version of the RAP.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	**Reporting & Analysis Plan**	
Statistical Considerations	**Statistical Analysis Plan**	**Rationale for Changes**
• Sample size re-estimation will be conducted following Part I of the study.	• Sample size re-estimation will not be conducted	• The methodology used for the original sample size calculation is no longer applicable, therefore the sample size re-estimation will not be conducted. Instead a set of criteria outlined in Section 3.2 will be used to decide if additional participants will be enrolled in Part II of the study.
• Randomized Population (All participants who are randomized to receive and are given the treatment (LPS or GM-CSF challenge)) is defined as one of the analysis population.	• Randomized Population will not be used for Analysis	• The randomized and safety populations have the same definitions. Hence only safety population would be used.

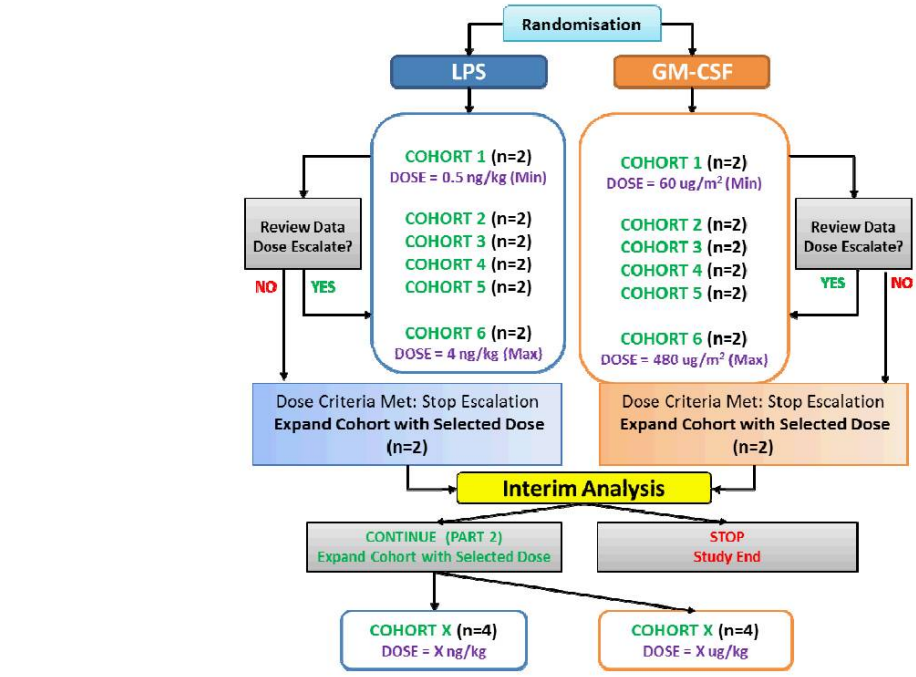
2.2. Study Objective(s) and Endpoint(s)

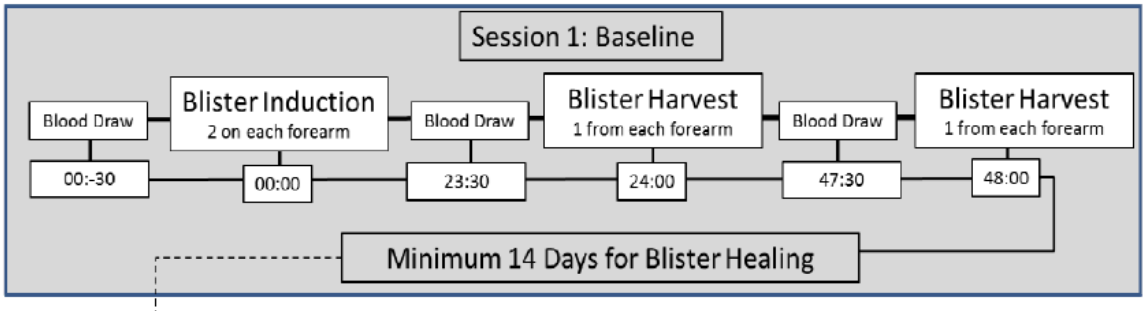
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To compare and define the time course of soluble and cellular inflammatory biomarkers (and urinary prostaglandins for LPS only) following systemic challenge with LPS or GM-CSF in healthy participants	• For LPS only: time course and magnitude of upregulation of circulating TNF-α and IL-6 as well as urinary tetranor PGDM • For GM-CSF only: time course and magnitude of upregulation of circulating total leukocyte numbers.
Secondary Objectives	**Secondary Endpoints**
• To compare soluble and cellular inflammatory biomarkers in cantharidin-induced skin blisters at baseline versus systemic challenge with LPS or GM-CSF in healthy participants	• Soluble inflammatory biomarkers in skin blisters (may include but not limited to IL-1b, IL-2, IL-6, IL-8, IFNg, TNF-α, MCP-1, GM-CSF, CRP). • Blister volumes and differential cell counts (cellular activation markers may include, but not limited to expression of CD16, CD86, CD80, CD163, CD206, CD83, CD40, CD209, HLA-DR in blister leukocytes)
• To define the time course of circulating soluble and cellular inflammatory biomarker upregulation following systemic challenge with LPS or GM-CSF in healthy participants	• Time course of regulation of circulating soluble inflammatory biomarkers (may include but is not limited[1] to IL-1b, IL-2, IL-6, IL-8, IFNg, TNF-α, MCP-1, GM-CSF, CRP). • Time course of regulation of circulating leukocyte numbers and cellular activation markers (may include, but not limited to expression of CD16, CD86, CD80, CD163, CD206, CD83, CD40, CD209, HLA-DR in circulating leukocytes)
Exploratory Objectives	**Exploratory Endpoints**
• To compare suitability of blisters sampled at 24 and 48 hours[2] after induction for maximising observed effects of systemic challenge	• Primary and Secondary endpoints measured in 24 versus 48 hour blisters
• To assess the safety and tolerability profile of the challenge agents and to ensure it is not materially different from previous experience.	• Adverse events, clinical laboratory measures, vital signs, pain scale assessments
• Determining whether carboxyesterase-1 (CES-1) expression is present in monocytes following systemic GM-CSF challenge	• Number of monocytes which are CES-1+ in blood
• To compare prostaglandins in urine, blister fluid and plasma at baseline versus systemic challenge with LPS or GM-CSF	• Quantification of prostaglandins including (but not limited to [3]) tetranor -PGDM, tetranor-PGEM, PGD2 and PGE2
• To assess changes in whole blood transcriptome induced by systemic LPS or GM-CSF	• Analysis of differential gene expression in whole blood taken pre-challenge and at selected times post- challenge
• For LPS challenge only: to assess whether the dose of in -vivo LPS challenge is sufficient to induce innate immune tolerance	• Quantification of inflammatory markers including (but not limited to) TNF-α and IL-6 in blood drawn pre- and 6 hour post-systemic LPS challenge following ex vivo incubation in 'LPS-TruCulture' tubes and LPS-null TruCulture'

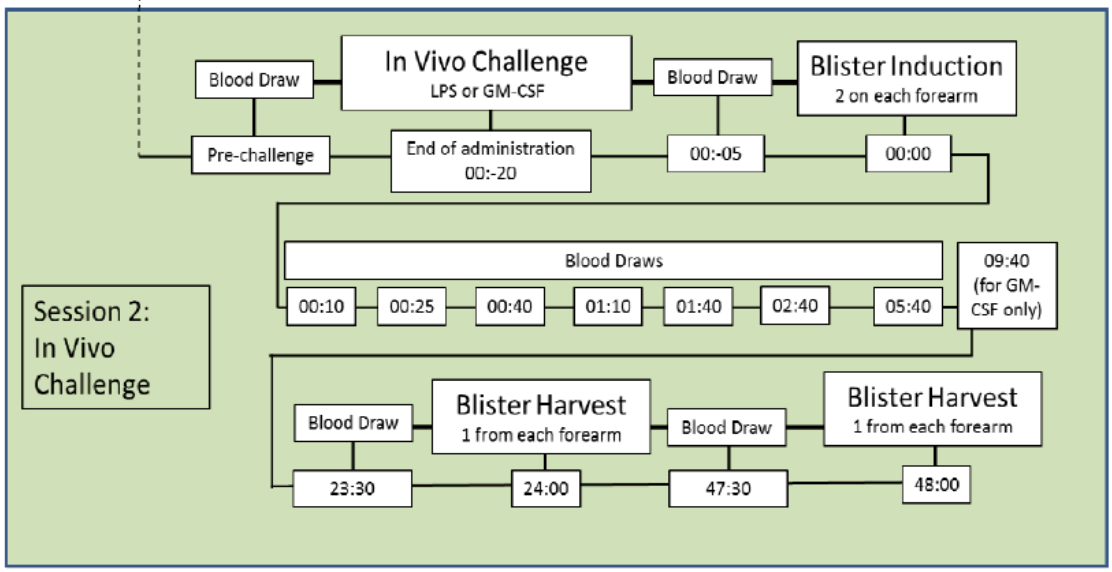
Objectives	Endpoints
	tubes[3]
• To assess the effects of systemic LPS and GM-CSF challenges on blister healing times	• Blister healing times (self-reported in participant diary card)
[1] As an exploratory endpoint, samples will be measured in the Somalogics assay. [2] Blister samples will also be used in the Somalogics assay. [3] Protein panels: IL-6, TNF-α (tolerized proteins), GRO-a (CXCL1) (unchanged) & IL-8 & IL-10 (hyper-responsive)	

2.3. Study Design

Overview of Study Design and Key Features







Design	• Exploratory parallel design study comprising of 2 parts.

Overview of Study Design and Key Features	
Features	• For Part I, a dose exploration design is used to find a dose that provides a robust inflammatory response for both LPS and GM-CSF. • For Part II, an additional cohort of up to 8 participants may be enrolled if an interim analysis indicates that this would provide further precision on estimates of primary endpoints. The same 2-session design, as described above, would be used and participants will be dosed with LPS and GM-CSF at the same dose as the 8 evaluable participants from Part I.
Time & Events	• Refer to Appendix 1: Schedule of Activities
Treatment Assignment	• Participants will be randomised to receive either a LPS or GM-CSF in vivo challenge. The total study duration for each participant is approximately 13 weeks from screening to the final follow-up.
Interim Analysis	• There will be ongoing data reviews conducted by the study team of any available data through the study progression. • For Part I, data reviews will be performed by the study team to support whether to dose escalate to the next cohort for each challenge agent. • At the end of Part 1, an interim analysis will be conducted to decide whether to enrol additional participants in Part II of the study, for the optimum dose selected in Part I.

2.4. Statistical Hypotheses / Statistical Analyses

This is an exploratory enabling study which is primarily designed to estimate the effect of systemic exposure to LPS or GM-CSF challenge on soluble and cellular inflammatory biomarkers in blood, urine and cantharidin-induced skin blisters. There are no formal hypotheses to be tested.

3. PLANNED ANALYSES

Safety and biomarker data were reviewed on an ongoing basis throughout the progression of the study for dose escalation.

3.1. Dose Escalation

Dose Escalation	Details
Study Review Committee (SRC)	Core GSK members included: • Study Physician Lead or their delegate; SERM; Statistician; Operations Study Lead; Epigenetics DPU, MM DPU, Scientific Operations Director, Clinical Development Manager.
Timing	• For each challenge agent, when 2 participants were dosed (n=2 with LPS, n=2 with GM-CSF), a dose escalation meeting was held to make an assessment of tolerability and inflammatory response from Cohort 1. • The dose escalation meeting was held prior to Group A in Cohort 2 being dosed with the challenge agents in Session 2. • The dose escalation procedure was continued until a well-tolerated dose for LPS and GM-CSF showing a robust inflammatory response was identified.
Safety Data Required	• Ongoing safety data was reviewed, these included: o Participant clinical parameters (including pulse, blood pressure, respiratory rate, temperature & ECG) o Adverse events experienced by participants o A physician's clinical assessment of participant's tolerability of the prior dose of GM-CSF or LPS with presence (or absence) of symptomatic tachycardia, symptomatic hypo- or hypertension, pyrexia > 38.5c, vomiting, meningeal symptoms, rigors and any other symptoms of concern o Review of safety blood tests including FBC (and differential), U&E, CRP, LFT, glucose o Other clinical features which in the judgement of the attending physician was pertinent to dose escalation decisions • Safety data was provided from PIMS (i.e. summaries and/or listings).
Biomarker Data Required	Primary endpoints (across all time points) were reviewed: • LPS: Circulating plasma levels of TNF-α and IL-6 as well as urinary tetranor PGDM. • GM-CSF: Circulating total leukocyte numbers. Other available data were also reviewed to support dose escalation, but were not formally included in any dose escalation decision criteria: • MSD & ELISA readouts from plasma, ex-vivo stimulations and blister fluid samples, Flow Cytometry readouts from blood and blister fluid / blister cell counts. • Raw data for biomarkers specified were reviewed (i.e. raw data from GSK CUC

Dose Escalation	Details
	included: MSD/ELISA/Flow & TDL (cell counts) and raw data from GSK BIB group for urinary tetranor PGDM.)
Statistical Analyses	• There were no planned formal statistical analyses of the data. Graphs were created in Excel based on the raw data obtained (nonstandard)
Dose Escalation Criteria	**Below is the Dose Escalation Criteria decided by the study team** If only one participant hits stopping criteria then there will be a presumption of stopping escalation, unless in the judgement of the team further escalation would provide additional scientific value to the study without materially impacting on participant wellbeing. **LPS: STOP dose escalation, IF:** • Peak plasma/serum level of TNF-α ≥ 100 pg/mL (minimum increase of 75 pg/ml from baseline) AND • Peak plasma/serum level of IL-6 ≥ 200 pg/mL (minimum increase of 100 pg/ml from baseline) AND • Urinary tetranor PGDM 3x over baseline in urine OR • Presence of adverse clinical signs (fever, HR + others) which, in the opinion of the investigator, pose an unacceptable risk to participants were dose escalation to proceed. Examples may include, but are not limited to: o Rigors o Meningeal symptoms of moderate severity o Vomiting o Clinically significant hypotension, hypertension, tachycardia or bradycardia **GM-CSF: STOP dose escalation IF:** • Max change of circulating total leukocyte counts increase by 5 giga/L OR • Presence of adverse clinical signs (fever, HR + others) which, in the opinion of the investigator, pose an unacceptable risk to participants were dose escalation to proceed. Examples may include, but are not limited to: o Rigors o Meningeal symptoms of moderate severity o Vomiting o Clinically significant hypotension, hypertension, tachycardia or bradycardia • Elevation of platelet count above 500 x 10^9/L
Dose Escalation Decision	• Following each dose escalation meeting, the decision to STOP or dose escalate for each challenge agent was documented, • An optimum dose of 0.75 ng/kg for LPS and 60 ug/m2 for GM-CSF was identified.

3.2. Interim Analyses

Interim Analysis	Details
Study Review Committee	Core GSK members include: • Study Physician Lead or their delegate; SERM; Statistician; Operations Study Lead; Epigenetics DPU, MM DPU, Scientific Operations Director, Clinical Development Manager.
Timing	• At the end of Part I, an interim analysis will be conducted to decide whether to enrol additional participants in Part II of the study, for the optimum dose of 0.75 ng/kg for LPS and 60 ug / m2 for GM-CSF selected in Part I.
Biomarker Data Required	• Data for Biomarkers listed in Section 10.3.3 will be presented in tabular and graphical format and summarized descriptively according to GSK's IDSL standards.
Statistical Analyses	• There are no planned formal statistical analyses of the data. Descriptive summaries and/or graphical presentations will be presented, including data listings.
Criteria for Part II	If at least one participant meets the criteria below for the optimal dose of 0.75ng/kg for LPS challenge or 60 ug/m2 for GM-CSF challenge, then Part II of the study will be initiated. **Participants will be enrolled to Part II – LPS Challenge at the dose level 0.75 ng/kg if for at least one participant:** • Maximum increase from baseline at any timepoint in plasma level of TNF-α < 50 pg/mL AND • Maximum increase from baseline at any timepoint in plasma level of IL-6 < 50 pg/mL AND • Maximum increase from baseline at any timepoint in urinary tetranor PGDM level < 1.3x **Participants will be enrolled to Part II – GM-CSF Challenge at the dose level 60 ug/m2 if for at least one participant:** • Maximum increase from baseline at any timepoint in total leukocyte counts < 5 giga/L • Note: Available data from all biomarkers will be considered before making the decision to move to Part II – GM-CSF Challenge.
Part II Decision	• The decision to STOP after Part I or CONTINUE to Part II for each challenge agent will be documented, including any supporting data.
Biomarkers for Part II	If a decision is made to continue to Part II of the study, then biomarkers meeting the criteria below will not be assessed in Part II. • RNASeq and Somalogics data will not be collected for participants in Part II. • If any biomarker is not detectable (< LLQ) at all timepoints for all participants

Interim Analysis	Details
	of Part I at the optimal dose, the biomarker will not be assessed in Part II. • If all analytes collected from a single sample type are not detectable (<LLQ) for all participants at all timepoints in Part I at the optimal dose, then this sample will not be collected in Part II. • Additionally, the available data for all biomarkers of Part I will be reviewed to help decide if the biomarkers need to be assessed in Part II.

If the decision is made to Stop after Part I, then the RAP for the Final Reporting will follow and additional displays will be generated as part of the Final Reporting.

3.3. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition /Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Selected Study Population
Enrolled	• All participants who passed screening and entered the study. Included are: Run-in Failures; Randomized Participants; in non-randomized study and participants who were assigned a treatment in a non-randomised study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Selected Study Population
Safety	• All participants who are randomized to receive the treatment (LPS or GM-CSF challenge) and received at least one dose of challenge agent. • This population will be based on the challenge agent participants actually received. • Note: Participants who were not randomized but received at least one dose of challenge agent should be listed.	• Biomarker • Safety

[1] Refer to Appendix 7: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [06Feb2018 V1.1] or higher.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF. For the Interim Analysis, no displays related to protocol deviations and inclusion/exclusion criteria deviations will be generated.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	LPS Dose 1	LPS 0.5 ng/kg	1
B	LPS Dose 2	LPS 1.0 ng/kg	3
C	LPS Dose 3	LPS 0.75 ng/kg	2
D	LPS Dose 4	LPS 0.75 ng/kg	2
G	GM-CSF Dose 1	GM-CSF 60 ug/m2	4
H	GM-CSF Dose 2	GM-CSF 60 ug/m2	4

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose of challenge and used as baseline.

Parameter	Study Assessments Considered as Baseline				Baseline Used in Data Display
	Screening	Session 1 Day 1	Session 1 Day 2	Session 2 Day 1	
Biomarkers					
LPS: TNF-α, IL6 GM-CSF: WBC (Total leukocyte counts)		X	X	X	Session 2 Day 1 (Pre Blister Induction)
Blood		X			Session 1 Day 1 (Pre Blister Induction)
Blister			X		Session 1 Day 2 (24 HR)
Urine			X		Session 1 Day 2 (Pre Fluid Sampling)
In Vivo LPS or GM-CSF				X	Session 2 Day 1 (Pre Blister Induction)
Safety					
Vital Signs & Temperature	X	X			Session 1 Day 1
ECG	X				Screening
Labs	X	X			Session 1 Day 1

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

5.3. Examination of Covariates, Other Strata and Subgroups

5.3.1. Covariates and Other Strata

There are no planned covariates or other strata that will be used in descriptive summaries and statistical analyses, if conducted.

5.3.2. Examination of Subgroups

There are no planned sub-group analyses.

5.4. Multiple Comparisons and Multiplicity

Analyses, if conducted will not be subject to any multiplicity adjustment.

5.5. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
10.2	Appendix 2: Data Display Standards & Handling Conventions
10.3	Appendix 3: Derived and Transformed Data
10.4	Appendix 4: Reporting Standards for Missing Data
10.5	Appendix 5: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the “Enrolled” population, unless otherwise specified. Screen failures will be listed based on the “Screened” population.

Study population analyses including analyses of subject’s disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK IDSL Data Standards. Details of the planned displays are presented in Appendix 7: List of Data Displays.

For the Interim Analysis, only a Summary and Listing of Demographic Characteristics will be presented.

7. EFFICACY ANALYSES

7.1. Primary Biomarker Analyses

Unless otherwise stated, analyses will apply to the interim analyses.

7.1.1. Endpoint / Variables

Challenge	Endpoint
LPS	Time course and magnitude of upregulation of circulating TNF-α and IL-6 as well as urinary tetranor PGDM
GM-CSF	Time course and magnitude of upregulation of circulating total leukocyte numbers.

7.1.2. Summary Measure

Challenge	Endpoint
LPS	Absolute values and change from baseline in TNF-α, IL-6 and PGDM across the time course Baseline: • TNF-α, IL-6: Session 2: Day 1 (Pre Blister Induction) • PGDM: Session 1 Day 2 (Pre Fluid Sampling)
GM-CSF	Absolute values and change from baseline in total leukocyte across the time course • Baseline = Session 2: Day 1 (Pre Blister Induction)

7.1.3. Population of Interest

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

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

No Strategy for Intercurrent (Post-Randomization) Events has been planned for this study.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 7: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2. Secondary Biomarker Analyses

Unless otherwise stated, analyses will apply to the interim analyses.

7.2.1. Endpoint / Variables

There are several different types of biomarker samples collected during the study:

- Biomarkers from skin blister fluid (i.e. mediators and flow cytometry)
- Biomarkers from blood sample (i.e. mediators, flow cytometry, ex vivo stimulation (LPS only) and transcriptome)
- Biomarkers from urine (Primary endpoints)

The secondary endpoints of interest with respect to the biomarkers mentioned above:

Endpoint
Soluble and cellular inflammatory biomarkers in cantharidin-induced skin blisters at baseline versus systemic challenge with LPS or GM-CSF in healthy participants
Time course of circulating soluble and cellular inflammatory biomarker upregulation

7.2.2. Summary Measure

Absolute values and change from baseline of soluble and cellular inflammatory biomarkers across the time course.

Note: In the Interim Analysis, for the biomarkers from skin blister fluid, values will be averaged across arms (left and right) for each participant. These averaged values will be used in tables and figures.

If one of the values is not collected or is missing, then the single value present in the data will be used in tables and figures. Appropriate footnotes will be provided to reflect data are not an average value.

7.2.3. Population of Interest

The secondary biomarker analyses will be based on the “Safety” population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

No Strategy for Intercurrent (Post-Randomization) Events has been planned for this study.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 7: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3. Exploratory Biomarker Analyses

SomaLogic

- The full panel of analytes contains 1305 proteins, and these will be measured from 88 plasma samples and 32 blister samples.
- Data will be delivered as relative fluorescense units, in two batches (one for each sample type).
- Data will be viewed as individual proteins and individual donors. This provides indication of how proteins change within an individual by reviewing the data. However, if effects across participants (i.e. N=4 for LPS or N=4 for GM-CSF) needs to be assessed, data will be normalised prior to analyses.
- Data will only be analysed at the end of the study as part of the Final Reporting. Further considerations for analysis will be detailed in the RAP as part of the Final Reporting.

RNA Seq Data

- RNAseq data will provided by Expression Analysis at Q Squared Solutions in a FASTQ file format. Data in this format will be directly analysed by GSK Computational biology groups. Analysis summary files containing summaries of information such of alignment statistics, mapping quality, base distributions, most frequent gene detected and total number of genes, by sample, will be generated. RNAseq will be analysed outside this reporting effort.

8. SAFETY ANALYSES

The safety analyses will be based on the “Safety” population, unless otherwise specified. There are no Safety Analyses planned for the Interim.

9. REFERENCES

GlaxoSmithKline Document Number 2016N309726_01 Study ID 207654: An open label parallel group study to investigate the optimum methodology for the use of LPS or GM-CSF as challenge agents on healthy participants by assessing inflammatory biomarkers in cantharidin-induced skin blisters, peripheral blood, and urine.
Effective Date: 07-AUG-2017

10. APPENDICES

10.1. Appendix 1: Schedule of Activities

10.1.1. Protocol Defined Schedule of Events

PROCEDURE	Screening	SESSION 1			Interim inspection	SESSION 2				1st follow-up	2nd follow-up
Day:	Within 30 days of Day 1	Day 1	Day 2	Day 3	Minimum 2 wks (max 4 weeks) after end of session 1	Day -1	Day 1	Day 2	Day 3	Minimum 2 wks (max. 4 weeks) after end of session 2	Approx. 5wks after end of session 2
Attend Unit	X	X	X	X	X	X[3]	X[3]	X	X	X	X
Informed Consent	X										
Inclusion/Exclusion checklist	X					X					
Medical /medication history	X										
Demographics	X										
Body weight	X					X					
Drug/alcohol test	X	X				X					
Physical Exam	X	X[1]				X	X[1]			X[1]	
Vital Signs and temperature	X	X[2]				X	X[8]	X		X	X
ECG	X					X	X				
Telemetry							X				
Visual forearm check (including blister healing and cosmetic assessment)	X	X[2]			X	X	X[2]			X	X
Cantharidin application (Session 2 only: 20 minutes post end of LPS or GM-CSF challenge)		X					X				
AE assessment/Con Meds		«----------									----------»
SAE	«----------										----------»
Clinical Chemistry, Haematology, and Urinalysis [4]	X	X	X	X		X	X	X	X		
Mediators blood sample		X[2]	X[5]	X[5]			X[7]	X[5]	X[5]		
Flow cytometry blood sample		X[2]	X[5]	X[5]			X[9]	X[5]	X[5]		
For LPS only: *Ex vivo* stimulation blood sample							X[10]				
Transcriptomic blood sample							X[9]				
Urine sampling for PD			X[11]				X[11]				
For LPS only: Intravenous hydration with normal Saline at a rate of 250 mL / hr							X[12]				
In vivo LPS or GM-CSF challenge							X[2]				
Blister sample for biomarkers			X	X				X	X		
Pain rating[6]				X					X		
Participant diary card given to participant to record blister healing		X					X				

1. Brief physical exam only
2. Within an hour before cantharidin application
3. Overnight stay in the unit
4. Additional clinical lab assessments may be performed, if necessary
5. Before blister fluid sampling
6. After the last blister fluid sampling at each session
7. Multiple blood draws at the following time points: Pre challenge, , 5 mins (i.e. Pre-blister induction), 10 min, 25 min, 40 min, 1hr:10mins, 1hr:40mins, 2hr:40mins, 5hr:40mins with respect to start of blister induction
8. Every half hour for the first 4 hours after challenge, hourly until 8 hours and then 8 hourly until discharge. Frequency can be increased if symptomatic
9. For flow cytometry and transcriptomic blood samples: Multiple blood draws at the following time points: Pre challenge, 40 mins, 2hr:40mins and 5hr:40mins (and 9hr 40mins for GM-CSF for flow cytometry only) with respect to start of blister induction
10. *Ex vivo* stimulation blood sample: 2 samples (one null and one LPS tube) to be taken pre-dose and 2 samples (one null and one LPS tube) to be taken at 5hrs:40mins post blister induction
11. Pre-challenge urine sample will be collected in session 1. For the post-challenge samples in session 2, participants will be encouraged to pass urine immediately before LPS dosing and each urine void will be collected after LPS until 12 hours post-LPS
12. From 4 hours prior to LPS until 8 hours after LPS

10.2. Appendix 2: Data Display Standards & Handling Conventions

10.2.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: NOCOMPOUND\MID207654\Internal_01
Analysis Datasets	
• Analysis datasets will be created per GSK IDSL dataset standards.	
Generation of RTF Files	
• RTF files will be generated for interim reporting effort.	

10.2.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated
(IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• All displays will use the term “Subject”, the term "Subject" is used to refer to a participant in the protocol.
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be in the modular appendices as ICH or non-ICH listings

Formats

• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP’s) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.
• Numeric data will be reported at the precision collected on the eCRF.
• The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP’s.
  • For all Biomarkers, the following DP’s places will be applied:
  • Summary Statistics: Maximum of 4 DP’s for Mean and Median, 5 DP’s for SD, 3 DP’s for Min and Max.
  • Listings: Provide DP’s in BEST. format.

Planned and Actual Time

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

Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.3. Appendix 3: Derived and Transformed Data

10.3.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables. • For the biomarkers from skin blister fluid, values will be averaged across arms (left and right) for each participant. These averaged values will be used in tables and figures. If one of the values is not collected or is missing, then the single value present in the data will be used in tables and figures. Appropriate footnotes will be provided to reflect data are not an average value.
Study Day

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

10.3.2. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: • Any participant with a missing day will have this imputed as day '15'. • Any participant with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • If only birth year is collected, then the birth date and month will be imputed as '30th June' for calculating age. • The reference day for age calculation will be screening visit.

10.3.3. Biomarker

The table below provides the list of Biomarkers needed for Interim.

Biomarker Code (BICATCD), Biomarker Test Code (BITESTCD), Biomarker Testing Method Code (BIMETHCD) and Units of Measurement (BIORRESU) can be referred below.

Name (Analyte)	Biomarker Detailed Name	BICATCD	BITESTCD/ BIMETHCD/ BIORRESU
Soluble Inflammatory Mediators (Blood) Primary	Tumour necrosis factor alpha (TNF-α)	TNFA	CONC/ MSD/ PG/ML
	Interleukin 6	IL6	CONC/ MSD/ PG/ML
Soluble Inflammatory Mediators (Blood) Secondary	C-reactive protein (LAB dataset)	LBTESTCD: CRP_PLC	LBORUNIT: MG/L
	Monocyte chemotactic protein-1	MCP1	CONC/ MSD/ PG/ML
	Monocyte chemotactic protein-4	MCP4	CONC/ MSD/ PG/ML
	Eotaxin	EOTAXIN	CONC/ MSD/ PG/ML
	Inducible protein 10	IP10	CONC/ MSD/ PG/ML
	MDC	MDC	CONC/ MSD/ PG/ML
	Chemokine (C-C motif) ligand 26 gene	CCL26	CONC/ MSD/ PG/ML
	Thymus and activation-regulated chemokine	TARC	CONC/ MSD/ PG/ML
	Macrophage inflammatory protein 1 alpha	MIP1A	CONC/ MSD/ PG/ML
	Macrophage inflammatory protein 1 beta	MIP1B	CONC/ MSD/ PG/ML
	Interferon-gamma	IFNG	CONC/ MSD/ PG/ML
	Interleukin 10	IL10	CONC/ MSD/ PG/ML
	Interleukin 12 p70	IL12P70	CONC/ MSD/ PG/ML

Name (Analyte)	Biomarker Detailed Name	BICATCD	BITESTCD/ BIMETHCD/ BIORRESU
	Interleukin 1 beta	IL1B	CONC/ MSD/ PG/ML
	Interleukin 8	IL8	CONC/ MSD/ PG/ML
	Activin-A	ACTIVA	CONC/ ELISA/ PG/ML
	Matrix metalloproteinase-1 (interstitial collagenase)	MMP1	CONC/ MSD/ PG/ML
	Matrix metalloproteinase 3	MMP3	CONC/ MSD/ PG/ML
	Matrix metalloproteinase 9	MMP9	CONC/ MSD/ PG/ML
	Granulocyte macrophage colony stimulating factor	GMCSF	CONC/ ELISA/ PG/ML
Soluble Inflammatory Mediators (Blood - TruCulture)	Interleukin 10	IL10	CONC/ MSD/ PG/ML
	Interleukin 6	IL6	CONC/ MSD/ PG/ML
	Interleukin 8	IL8	CONC/ MSD/ PG/ML
	Tumour necrosis factor alpha (TNF-α)	TNFA	CONC/ MSD/ PG/ML
	Chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	CXCL1	CONC/ ELISA/ PG/ML
Soluble Inflammatory Mediators (Blister)	Monocyte chemotactic protein-1	MCP1	CONC/ MSD/ PG/ML
	Interleukin 10	IP10	CONC/ MSD/ PG/ML
	Thymus and activation-regulated chemokine	TARC	CONC/ MSD/ PG/ML

Name (Analyte)	Biomarker Detailed Name	BICATCD	BITESTCD/ BIMETHCD/ BIORRESU
	Interleukin 12 p70	IL12P70	CONC/ MSD/ PG/ML
	Activin-A	ACTIVA	CONC/ ELISA/ PG/ML
	Matrix metalloproteinase-1 (interstitial collagenase)	MMP1	CONC/ MSD/ PG/ML
	Matrix metalloproteinase 3	MMP3	CONC/ MSD/ PG/ML
	Matrix metalloproteinase 9	MMP9	CONC/ MSD/ PG/ML
Soluble Inflammatory Mediators (Urine) Primary	Tetranor-Prostaglandin E Metabolite	TETPGDM	CONC/ LCMS/ PG/ML
	Tetranor-Prostaglandin D Metabolite	TETPGEM	CONC/ LCMS/ PG/ML
Cell Numbers (Blood) Primary	White blood cells	WBC	TNCELL/ FLWCY/ CELLS/ML
Blister Volume (Blister)	Blister Fluid	BLISTFL	VOL/ WTDENC/ UL
Flow Cytometry Cell Activation Markers on Monocytes (Blister and Blood)	CD16+	CD16	C6/ FLWCY/ MNFI
	CD86+	CD86	C6/ FLWCY/ MNFI
	CD80 molecule	CD80	C6/ FLWCY/ MNFI
	CD163+	CD163	C6/ FLWCY/ MNFI
	CD206+	CD206	C6/ FLWCY/ MNFI
	CD83 molecule	CD83	C6/ FLWCY/ MNFI

Name (Analyte)	Biomarker Detailed Name	BICATCD	BITESTCD/ BIMETHCD/ BIORRESU
	CD40	CD40	C6/ FLWCY/ MNFI
	CD209+	CD209	C6/ FLWCY/ MNFI
	HLA-DR	HLADR	C6/ FLWCY/ MNFI
	CD40+/CD80+	CDX690	%MONO/ FLWCY/ %
Flow Cytometry Cell Activation Markers on Dendritic Cells (Blister and Blood)	CD16+	CD16	R1/ FLWCY/ MNFI
	CD86+	CD86	R1/ FLWCY/ MNFI
	CD80 molecule	CD80	R1/ FLWCY/ MNFI
	CD163+	CD163	R1/ FLWCY/ MNFI
	CD206+	CD206	R1/ FLWCY/ MNFI
	CD83 molecule	CD83	R1/ FLWCY/ MNFI
	CD40	CD40	R1/ FLWCY/ MNFI
	CD209+	CD209	R1/ FLWCY/ MNFI
	HLA-DR	HLADR	R1/ FLWCY/ MNFI
	CD40+/CD80+	CDX690	%TDC/ FLWCY/ %
Flow Cytometry	Neutrophils	NEUT	TNCELL/ FLWCY/ CELLS/ML

Name (Analyte)	**Biomarker Detailed Name**	**BICATCD**	**BITESTCD/ BIMETHCD/ BIORRESU**
Cell Counts (Blood)	Lymphocytes	LYMPH	TNCELL/ FLWCY/ CELLS/ML
	Monocytes	MONO	TNCELL/ FLWCY/ CELLS/ML
	B Cells	BCELL	TNCELL/ FLWCY/ CELLS/ML
	CD45+ CD3- CD56+ (NK Cells)	CDX223	TNCELL/ FLWCY/ CELLS/ML
	CD45+ CD3+ CD56+ (NKT Cells)	CDX224	TNCELL/ FLWCY/ CELLS/ML
	Total T Cells	TTCELL	TNCELL/ FLWCY/ CELLS/ML
	CD4+	CD4	TNCELL/ FLWCY/ CELLS/ML
	CD8+	CD8	TNCELL/ FLWCY/ CELLS/ML
	CD14+CD16+ Monocytes	CDX469	TNCELL/ FLWCY/ CELLS/ML
	CD14+CD16- Monocytes	CDX471	TNCELL/ FLWCY/ CELLS/ML
	CD14-CD16+ Monocytes	CDX611	TNCELL/ FLWCY/ CELLS/ML
	CD34+	CD34	TNCELL/ FLWCY/ CELLS/ML
Flow Cytometry Cell Counts (Blister) Note: These biomarkers are measured in 2 units –	Neutrophils	NEUT	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	Lymphocytes	LYMPH	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER

Name (Analyte)	Biomarker Detailed Name	BICATCD	BITESTCD/ BIMETHCD/ BIORRESU
Cells/ml and 10^3 Cells/Blister	Monocytes	MONO	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	B Cells	BCELL	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	CD45+ CD3- CD56+ (NK Cells)	CDX223	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	CD45+ CD3+ CD56+ (NKT Cells)	CDX224	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	Total T Cells	TTCELL	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	CD4+	CD4	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	CD8+	CD8	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	CD14+CD16+ Monocytes	CDX469	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER
	CD14+CD16- Monocytes	CDX471	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER

Name (Analyte)	Biomarker Detailed Name	BICATCD	BITESTCD/ BIMETHCD/ BIORRESU
	CD14-CD16+ Monocytes	CDX611	TNCELL/ FLWCY/ CELLS/ML or 10^3 CELLS/BLISTER

10.4. Appendix 4: Reporting Standards for Missing Data

10.4.1. Premature Withdrawals

Element	Reporting Detail
General	• As specified in the protocol (Section 5.3), a participant is considered to have completed the study if he/she has completed up to the end of session 2 of the study. • If a participant withdraws before the end of session 2 they will be encouraged to return for a follow-up visit as per the schedule of activities. • If a participant withdraws before the end of session 2 their data may still be used for analysis, depending on how much data is available. If there is insufficient data for analysis, at the discretion of the study team, this participant will be replaced. • **The end of the study** is defined as the date of the last visit of the last participant in the Study (e.g. the second follow up session for the last participant). • All available data from participants who were withdrawn from the study will be listed.

10.4.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. For Biomarkers, the following will be applied: • If any value is not quantified and the numeric result is absent as the value is below the lower limit of quantification, then values will be imputed as half of the LLQ. • If any value is below the lower limit of quantification but the numeric result is present, then the numeric values will be used in all displays. • If any value is above ULQ, such values will be omitted from summaries/figures even if the numeric result is present. These values will only be listed. • Numeric results of samples which are "Plate failed QC" and "CV>20%" will be used in all displays. • Appropriate footnotes will be provided in Tables and Summaries to indicate that <LLQ, CV>20% and Plate Failed Samples have been used. • The diluted samples of the biomarkers whose value is >ULQ will be re-run and the new reported values will be used in the final analysis.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.4.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.

10.5. Appendix 5: Values of Potential Clinical Importance

10.5.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Relative – Low (Multipliers of LLN)	**Relative – High (Multipliers of ULN)**
Hematocrit	Ratio of 1	Male		1.02
		Female		1.17
		Δ from BL	< -0.075 change from baseline	
Haemoglobin	g/L	Male		1.03
		Female		1.13
		Δ from BL	< -25 change from baseline	
Lymphocytes	$x10^9$/ L		0.81	
Neutrophil Count	$x10^9$/ L		0.83	
Platelet Count	$x10^9$/ L		0.67	
While Blood Cell Count (WBC)	$x10^9$/ L		0.67	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Relative – Low (Multipliers of LLN)	**Relative – High (Multipliers of ULN)**
Albumin	mmol/L		0.86	
Calcium	mmol/L		0.91	1.06
Creatinine	umol/L	Δ from BL		1.25
Glucose	mmol/L		0.71	1.41
Magnesium	mmol/L		0.63	1.03
Phosphorus	mmol/L		0.80	1.14
Potassium	mmol/L		0.86	1.10
Sodium	mmol/L		0.96	1.03
Total CO2	mmol/L		0.86	1.14

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

10.5.2. ECG

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

10.5.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Temperature	degrees C	<35.5	>37.5
Systolic Blood Pressure	mmHg	<85	>160
Diastolic Blood Pressure	mmHg	<45	>100
Heart Rate	bpm	<40	>110

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Temperature	degrees C	Change of 1^0C from baseline within four hours			
Systolic Blood Pressure	mmHg	≥20	≥40	≥20	≥40
Diastolic Blood Pressure	mmHg	≥10	≥20	≥10	≥20
Heart Rate	bpm	≥15	≥30	≥15	≥30

10.6. Appendix 6: Abbreviations & Trade Marks

10.6.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
CI	Confidence Interval
CS	Clinical Statistics
CP	Clinical Programming
CPSSO	Clinical Pharmacology Science and Study Operations
CRP	C-reactive protein
CSR	Clinical Study Report
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
DPU	Discovery Performance Unit
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
ELISA	Enzyme Linked ImmunoSorbent Assay
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IL	Interleukin
LLN	Lower Limit of Normal
LLQ	Lower Limit of Quantification
LPS	Lipopolysaccharide
MCH	Mean Corpuscular Hemoglobin
MCP	Monocyte chemoattractant protein
MM	Muscle Metabolism
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PGD2	Prostaglandin D2
PGE2	Prostaglandin E2
QC	Quality Control
RAP	Reporting & Analysis Plan
RNA	Ribonucleic acid
SAC	Statistical Analysis Complete
TA	Therapeutic Area
TNF	Tumour Necrosis Factor
TFL	Tables, Figures & Listings
ULN	Upper limit of normal

10.6.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.7. Appendix 7: List of Data Displays

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1	N/A
Biomarker	2.1 to 2.24	2.1 to 2.47
Safety	N/A	N/A
Section	**Listings**	
ICH Listings	1	
Other Listings	2 to 14	

10.7.1. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 8: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Biomarker	BIO_Fn	BIO_T1	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

NOTES:

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

10.7.2. Deliverables

Delivery [1]	Description
IA SAC [1]	Interim Analysis Statistical Analysis Complete

NOTES:

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

10.7.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
1.1.	Enrolled	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	IA [1]

10.7.4. Biomarker Tables

Biomarker Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Soluble Inflammatory Mediators					
2.1.	Safety	BIO_T1	Summary of Primary Soluble Inflammatory Mediators in Blood	Page by Treatment and Biomarker	IA [1]
2.2.	Safety	BIO_T1	Summary of Change from Baseline in Primary Soluble Inflammatory Mediators in Blood	Page by Treatment and Biomarker.	IA [1]
2.3.	Safety	BIO_T1	Summary of Secondary Soluble Inflammatory Mediators in Blood	Page by Treatment and Biomarker	IA [1]
2.4.	Safety	BIO_T1	Summary of Change from Baseline in Secondary Soluble Inflammatory Mediators in Blood	Page by Treatment and Biomarker	IA [1]
2.5.	Safety	BIO_T1	Summary of Soluble Inflammatory Mediators from In-Vitro (un)stimulated Blood Pre and Post In-Vivo LPS Challenge	Page by Treatment and Biomarker	IA [1]
2.6.	Safety	BIO_T1	Summary of Soluble Inflammatory Mediators in Blister	Page by Treatment and Biomarker	IA [1]
2.7.	Safety	BIO_T1	Summary of Change from Baseline of Soluble Inflammatory Mediators in Blister	Page by Treatment and Biomarker	IA [1]
2.8.	Safety	BIO_T1	Summary of Soluble Inflammatory Mediators in Urine following LPS Challenge	Page by Treatment and Biomarker	IA [1]
2.9.	Safety	BIO_T1	Summary of Change from Baseline of Soluble Inflammatory Mediators in Urine following LPS Challenge	Page by Treatment and Biomarker	IA [1]
Total Leukocyte Numbers					
2.10.	Safety	BIO_T1	Summary of Cell Numbers in Blood following GM-CSF Challenge	Page by Treatment and Biomarker	IA [1]
2.11.	Safety	BIO_T1	Summary of Change from Baseline in Cell Numbers in Blood	Page by Treatment and	IA [1]

Biomarker Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
			following GM-CSF Challenge	Biomarker	
Blister Volume					
2.12.	Safety	BIO_T1	Summary of Blister Volume	Page by Treatment	IA [1]
Flow Cytometry					
2.13.	Safety	BIO_T1	Summary of Cell Activation Markers by Flow Cytometry on Monocytes in Blood	Page by Treatment and Biomarker	IA [1]
2.14.	Safety	BIO_T1	Summary of Change from Baseline in Cell Activation Markers by Flow Cytometry on Monocytes in Blood	Page by Treatment and Biomarker	IA [1]
2.15.	Safety	BIO_T1	Summary of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blood	Page by Treatment and Biomarker	IA [1]
2.16.	Safety	BIO_T1	Summary of Change from Baseline in Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blood	Page by Treatment and Biomarker	IA [1]
2.17.	Safety	BIO_T1	Summary of Cell Counts by Flow Cytometry in Blood	Page by Treatment and Biomarker	IA [1]
2.18.	Safety	BIO_T1	Summary of Change from Baseline in Cell Counts by Flow Cytometry in Blood	Page by Treatment and Biomarker	IA [1]
2.19.	Safety	BIO_T1	Summary of Cell Activation Markers by Flow Cytometry on Monocytes in Blister	Page by Treatment and Biomarker	IA [1]
2.20.	Safety	BIO_T1	Summary of Change from Baseline in Cell Activation Markers by Flow Cytometry on Monocytes in Blister	Page by Treatment and Biomarker	IA [1]
2.21.	Safety	BIO_T1	Summary of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blister	Page by Treatment and Biomarker	IA [1]
2.22.	Safety	BIO_T1	Summary of Change from Baseline in Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blister	Page by Treatment and Biomarker	IA [1]
2.23.	Safety	BIO_T1	Summary of Cell Counts by Flow Cytometry in Blister	Page by Treatment and	IA [1]

Biomarker Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				Biomarker	
2.24.	Safety	BIO_T1	Summary of Change from Baseline in Cell Counts by Flow Cytometry in Blister	Page by Treatment and Biomarker	IA [1]

10.7.5. Biomarker Figures

Biomarker Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Soluble Inflammatory Mediators					
2.1	Safety	BIO_F1	Individual Plot of Primary Soluble Inflammatory Mediators in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.2.	Safety	BIO_F1	Individual Plot of Change from Baseline in Primary Soluble Inflammatory Mediators in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.3.	Safety	BIO_F2	Mean (+/- SD) Plot of Primary Soluble Inflammatory Mediators in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.4.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Primary Soluble Inflammatory Mediators in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.5.	Safety	BIO_F1	Individual Plot of Secondary Soluble Inflammatory Mediators in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.6.	Safety	BIO_F1	Individual Plot of Change from Baseline in Secondary Soluble Inflammatory Mediators in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.7.	Safety	BIO_F2	Mean (+/- SD) Plot of Secondary Soluble Inflammatory Mediators in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.8.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Secondary Soluble Inflammatory Mediators in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.9.	Safety	BIO_F3	Bar Chart of Soluble Inflammatory Mediators from In-Vitro (un)stimulated Blood Pre and Post In-Vivo LPS Challenge	Generate Bar Chart Page by Treatment and Biomarker	IA [1]
2.10.	Safety	BIO_F4	Box Plot of Soluble Inflammatory Mediators from In-Vitro (un)stimulated Blood Pre and Post In-Vivo LPS Challenge	Generate Box Plot Page by Treatment and Biomarker	IA [1]

Biomarker Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	Safety	BIO_F1	Individual Plot of Soluble Inflammatory Mediators in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.12.	Safety	BIO_F1	Individual Plot of Change from Baseline in Soluble Inflammatory Mediators in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.13.	Safety	BIO_F2	Mean (+/- SD) Plot of Soluble Inflammatory Mediators in Blister Over Time	Page by Challenge and Biomarker	IA [1]
2.14.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Soluble Inflammatory Mediators in Blister Over Time	Page by Challenge and Biomarker	IA [1]
2.15.	Safety	BIO_F1	Individual Plot of Soluble Inflammatory Mediators in Urine Over Time following LPS Challenge	Page by Treatment and Biomarker	IA [1]
2.16.	Safety	BIO_F1	Individual Plot of Change from Baseline in Soluble Inflammatory Mediators in Urine Over Time following LPS Challenge	Page by Treatment and Biomarker	IA [1]
2.17.	Safety	BIO_F2	Mean (+/- SD) Plot of Soluble Inflammatory Mediators in Urine Over Time following LPS Challenge	Page by Challenge and Biomarker	IA [1]
2.18.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Soluble Inflammatory Mediators in Urine Over Time following LPS Challenge	Page by Challenge and Biomarker	IA [1]
Total Leukocyte Numbers					
2.19.	Safety	BIO_F1	Individual Plot of Cell Numbers in Blood Over Time following GM-CSF Challenge	Page by Treatment and Biomarker	IA [1]
2.20.	Safety	BIO_F1	Individual Plot of Change from Baseline in Cell Numbers in Blood Over Time following GM-CSF Challenge	Page by Treatment and Biomarker	IA [1]
2.21.	Safety	BIO_F2	Mean (+/- SD) Plot of Cell Numbers in Blood Over Time following GM-CSF Challenge	Page by Challenge and Biomarker	IA [1]

Biomarker Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.22.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Cell Numbers in Blood Over Time following GM-CSF Challenge	Page by Challenge and Biomarker	IA [1]

Biomarker Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Blister Volume					
2.23.	Safety	BIO_F5	Bar Chart of Blister Volume Over Time	Generate Bar Chart Page by Treatment	IA [1]
Flow Cytometry					
2.24.	Safety	BIO_F1	Individual Plot of Cell Activation Markers by Flow Cytometry on Monocytes in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.25.	Safety	BIO_F1	Individual Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Monocytes in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.26.	Safety	BIO_F2	Mean (+/- SD) Plot of Cell Activation Markers by Flow Cytometry on Monocytes in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.27.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Monocytes in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.28.	Safety	BIO_F1	Individual Plot of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.29.	Safety	BIO_F1	Individual Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.30.	Safety	BIO_F2	Mean (+/- SD) Plot of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.31.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.32.	Safety	BIO_F1	Individual Plot of Cell Counts by Flow Cytometry in Blood Over Time	Page by Treatment and Biomarker	IA [1]

Biomarker Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.33.	Safety	BIO_F1	Individual Plot of Change from Baseline in Cell Counts by Flow Cytometry in Blood Over Time	Page by Treatment and Biomarker	IA [1]
2.34.	Safety	BIO_F2	Mean (+/- SD) Plot of Cell Counts by Flow Cytometry in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.35.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Cell Counts by Flow Cytometry in Blood Over Time	Page by Challenge and Biomarker	IA [1]
2.36.	Safety	BIO_F1	Individual Plot of Cell Activation Markers by Flow Cytometry on Monocytes in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.37.	Safety	BIO_F1	Individual Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Monocytes in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.38.	Safety	BIO_F2	Mean (+/- SD) Plot of Cell Activation Markers by Flow Cytometry on Monocytes in Blister Over Time	Page by Challenge and Biomarker	IA [1]
2.39.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Monocytes in Blister Over Time	Page by Challenge and Biomarker	IA [1]
2.40.	Safety	BIO_F1	Individual Plot of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.41.	Safety	BIO_F1	Individual Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.42.	Safety	BIO_F2	Mean (+/- SD) Plot of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blister Over Time	Page by Challenge and Biomarker	IA [1]
2.43.	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blister Over Time	Page by Challenge and Biomarker	IA [1]

Biomarker Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.44.	Safety	BIO_F1	Individual Plot of Cell Counts by Flow Cytometry in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.45.	Safety	BIO_F1	Individual Plot of Change from Baseline in Cell Counts by Flow Cytometry in Blister Over Time	Page by Treatment and Biomarker	IA [1]
2.46.	Safety	BIO_F2	Mean (+/- SD) Plot of Cell Counts by Flow Cytometry in Blister Over Time	Page by Challenge and Biomarker	IA [1]
2.47	Safety	BIO_F2	Mean (+/- SD) Plot of Change from Baseline in Cell Counts by Flow Cytometry in Blister Over Time	Page by Challenge and Biomarker	IA [1]

10.7.6. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
1.	Enrolled	DM2	Listing of Demographic Characteristics	ICH E3	IA [1]

10.7.7. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Soluble Inflammatory Mediators					
2.	Safety	BIO_L1	Listing of Primary Soluble Inflammatory Mediators in Blood		IA [1]
3.	Safety	BIO_L1	Listing of Secondary Soluble Inflammatory Mediators in Blood		IA [1]
4.	Safety	BIO_L1	Listing of Soluble Inflammatory Mediators from In-Vitro (un)stimulated Blood		IA [1]
5.	Safety	BIO_L2	Listing of Soluble Inflammatory Mediators in Blister		IA [1]
6.	Safety	BIO_L1	Listing of Soluble Inflammatory Mediators in Urine following LPS Challenge		IA [1]
Total Leukocyte Numbers					
7.	Safety	BIO_L1	Listing of Cell Numbers in Blood following GM-CSF Challenge		IA [1]
Blister Volume					
8.	Safety	BIO_L2	Listing of Blister Volume		IA [1]
Flow Cytometry					
9.	Safety	BIO_L1	Listing of Cell Activation Markers by Flow Cytometry on Monocytes in Blood		IA [1]
10.	Safety	BIO_L1	Listing of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blood		IA [1]
11.	Safety	BIO_L1	Listing of Cell Counts by Flow Cytometry in Blood		IA [1]
12.	Safety	BIO_L2	Listing of Cell Activation Markers by Flow Cytometry on Monocytes in Blister		IA [1]
13.	Safety	BIO_L2	Listing of Cell Activation Markers by Flow Cytometry on Dendritic Cells in Blister		IA [1]
14.	Safety	BIO_L2	Listing of Cell Counts by Flow Cytometry in Blister		IA [1]

10.8. Appendix 8: Example Mock Shells for Data Displays

Example: BIO_T1 Page 1 of n
Protocol: 207654
Population: Safety

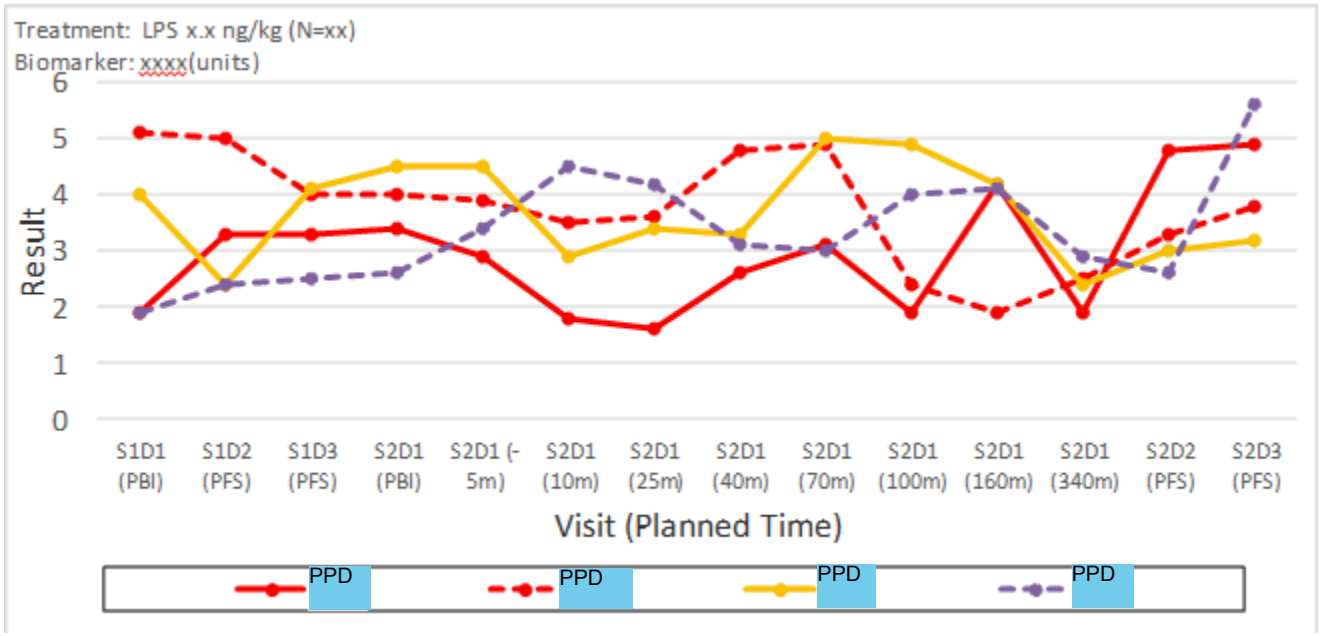
Table 2.1
Summary of Primary Soluble Inflammatory Mediators in Blood

Treatment: LPS x.x ng/kg (N=xx)
Biomarker: xxxx (units)

Visit	Planned Relative Time	n	Mean	SD	Median	Min.	Max.	%CVb
SESSION 1 DAY 1	PRE BLISTER INDUCTION	x	x.xxx	x.xxxx	x.xxx	x.xx	x.xx	xx%
SESSION 1 DAY 2	PRE FLUID SAMPLING	x	x.xxx	x.xxxx	x.xxx	x.xx	x.xx	xx%
SESSION 1 DAY 3	PRE FLUID SAMPLING	x	x.xxx	x.xxxx	x.xxx	x.xx	x.xx	xx%
SESSION 2 DAY 1	PRE BLISTER INDUCTION	x	x.xxx	x.xxxx	x.xxx	x.xx	x.xx	xx%
SESSION 2 DAY 1	-5 MIN	x	x.xxx	x.xxxx	x.xxx	x.xx	x.xx	xx%

Note: Biomarker xxxx includes <LLQ values, Biomarker yyyy includes CV>20% values, Biomarker zzzz includes Plate failed QC values (only if applicable).
Note: Values recorded as '<LLQ' have been imputed as LLQ/2 (only if applicable).
Repeat for all treatments and biomarkers
For all Summaries of Change from baseline, provide the footnote as below:
Note: Session x Day x is considered as Baseline.

Figure 2.1
Individual Plot of Primary Soluble Inflammatory Mediators in Blood Over Time



S1D1=Session 1 Day 1, S1D2=Session 1 Day 2, S1D3=Session 1 Day 3, S2D1=Session 2 Day 1, S2D2=Session 2 Day 2, S2D3=Session 2 Day 3, PBI=Pre Blister Induction, PFS=Pre Fluid Sampling

Note: Biomarker xxxx includes <LLQ values, Biomarker yyyy includes CV>20% values, Biomarker zzzz includes Plate failed QC values (only if applicable).

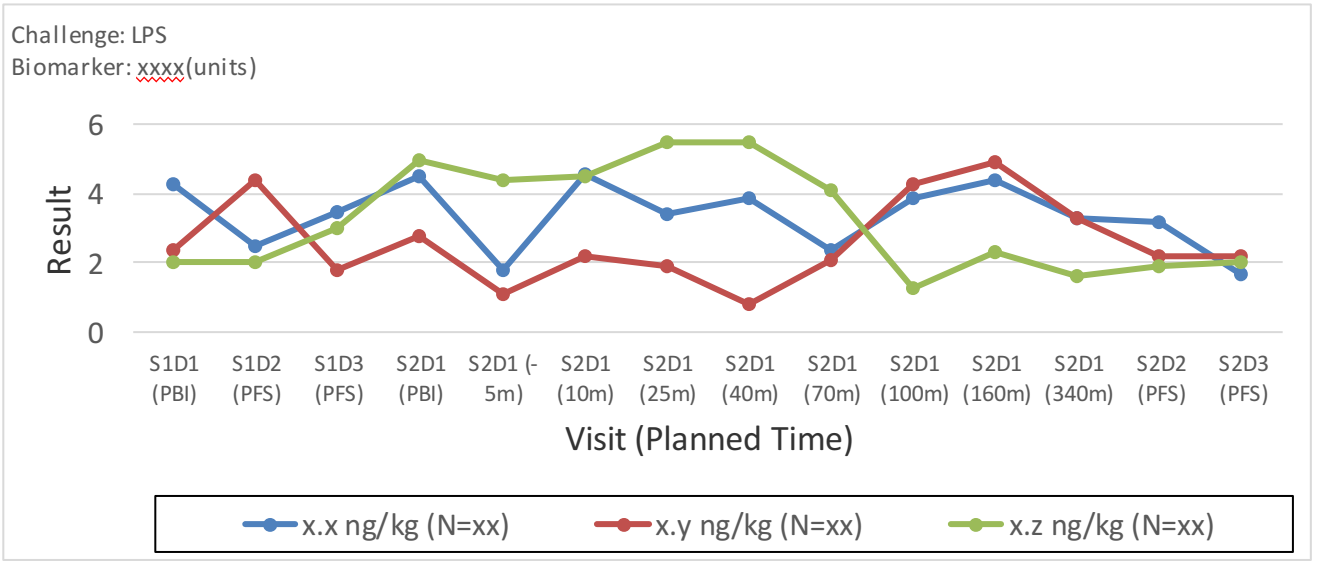
Note: Values recorded as '<LLQ' have been imputed as LLQ/2 (only if applicable).

Repeat for all available treatments and biomarkers.

For Individual Plots of Change from baseline, provide the footnote as below:

Note: Session x Day x is considered as Baseline.

Figure 2.3
Mean (+/- SD) Plot of Primary Soluble Inflammatory Mediators in Blood Over Time

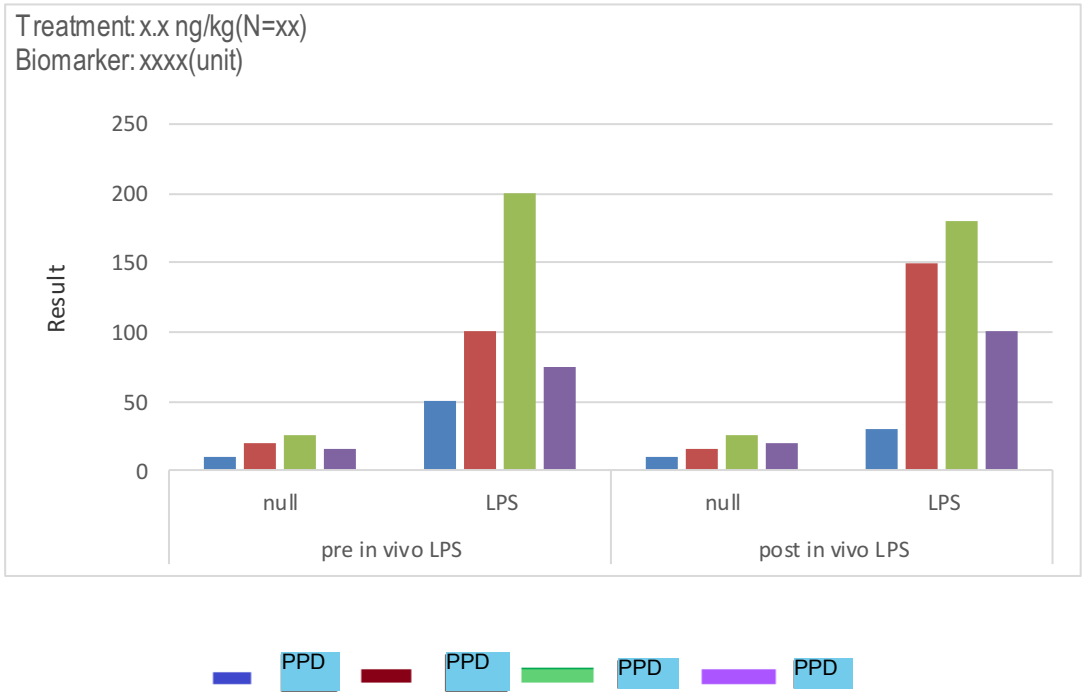


S1D1=Session 1 Day 1, S1D2=Session 1 Day 2, S1D3=Session 1 Day 3, S2D1=Session 2 Day 1, S2D2=Session 2 Day 2, S2D3=Session 2 Day 3, PBI=Pre Blister Induction, PFS=Pre Fluid Sampling

Note: Biomarker xxx includes <LLQ values, Biomarker yyy includes CV>20% values, Biomarker zzzz includes Plate failed QC values (only if applicable).
Note: Values recorded as '<LLQ' have been imputed as LLQ/2 (only if applicable).
Repeat for all available biomarkers and challenges.

For Mean (+/- SD) Plots of Change from baseline, provide the footnote as below:
Note: Session x Day x is considered as Baseline.

Figure 2.9
Bar Chart of Soluble Inflammatory Mediators from In-Vitro (un)stimulated Blood Pre and Post In-Vivo LPS Challenge

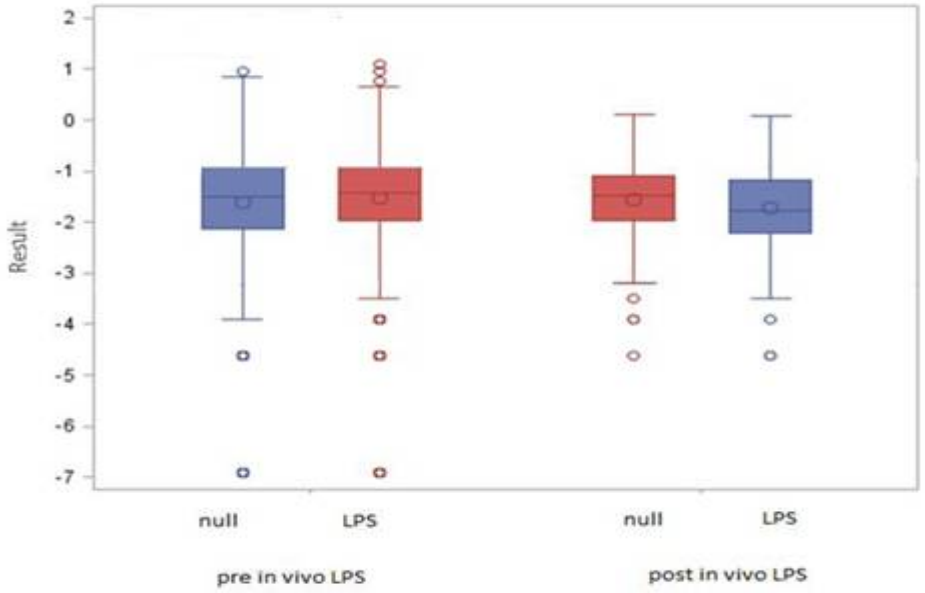


Note: Biomarker xxx includes <LLQ values, Biomarker yyy includes CV>20% values, Biomarker zzzz includes Plate failed QC values (only if applicable).
Note: Values recorded as '<LLQ' have been imputed as LLQ/2 (only if applicable).
Each Bar represents a participant.
Repeat for all available treatments and biomarkers.

Example: BIO_F4
Protocol: 207654
Population: Safety

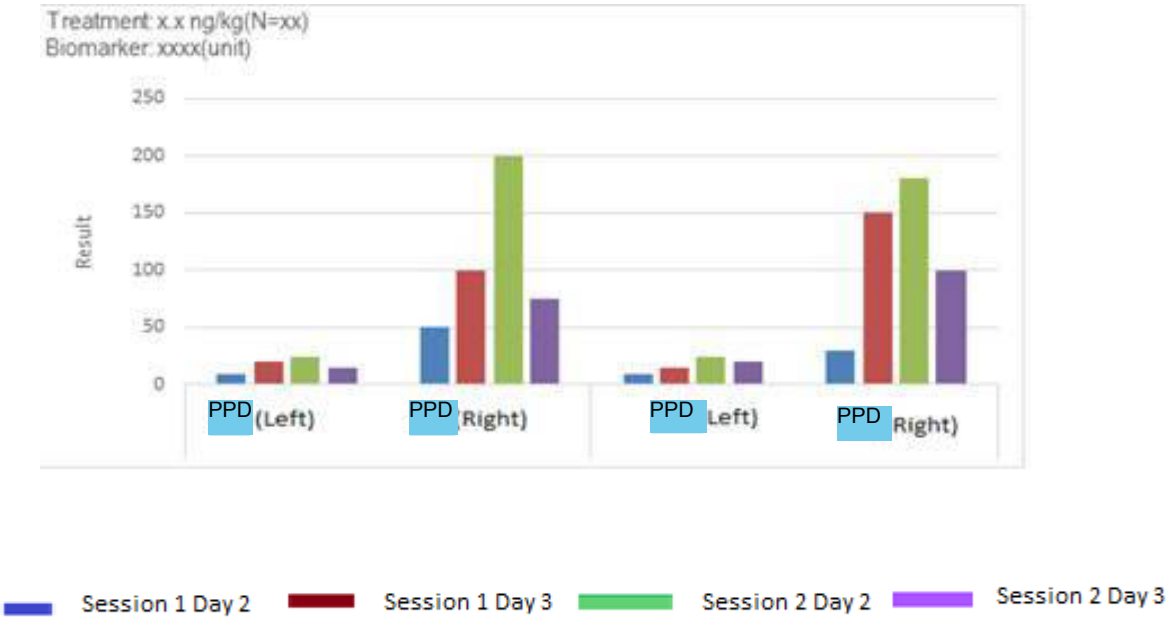
Figure 2.10
Box Plot of Soluble Inflammatory Mediators from In-Vitro (un)stimulated Blood Pre and Post In-Vivo LPS Challenge

Treatment: x.x ng/kg (N=xx)
Biomarker: xxxx(unit)



Note: Biomarker xxx includes <LLQ values, Biomarker yyy includes CV>20% values, Biomarker zzzz includes Plate failed QC values (only if applicable).
Note: Values recorded as '<LLQ' have been imputed as LLQ/2 (only if applicable).
Provide Mean, Median, Inter-quartile ranges, Minimum, Maximum and Outliers in the box plot.
Repeat for all available treatments and biomarkers.

Figure 2.23
Bar Plot of Blister Volume Over Time



Note: Biomarker xxx includes <LLQ values, Biomarker yyy includes CV>20% values, Biomarker zzzz includes Plate failed QC values (only if applicable).
Note: Values recorded as '<LLQ' have been imputed as LLQ/2 (only if applicable).
Repeat for all available treatments

Listing 2
Listing of Primary Soluble Inflammatory Mediators in Blood

Treatment	Biomarker (Unit)	Centre ID/ Subj ID	Visit/ Planned Relative Time	Date/ Time/ Study Day	Result	Change from Baseline	Test Comments
LPS x.x ng/kg	xxxxxxx (unit)	xxxx/ xxxx	xxxxx/ xxx	xxxx/ xxxxx	xxxx	xxxx	<LLQ
			xxxx/ xxxx	xxxx/ xxxx	xxxx	xxxx	
			xxxx/ xxxx	xxxx/ xxxx	xxxx	xxxx	
			xxxx/ xxxx	xxxx/ xxxx	xxxx	xxxx	
	xxxxxxx (unit)	xxxx/ xxxx	xxxx/ xxxx	xxxx/ xxxx	xxxx	xxxx	CV>20%
			xxxx/ xxxx	xxxx/ xxxx	xxxx	xxxx	>ULQ

Note: LLQ=Lower Limit of Quantification, ULQ=Upper Limit of Quantification, CV=Coefficient of Variation.
Note: Repeat for all available treatments and biomarkers.

Example: BIO_L2
Protocol: 207654
Population: Safety

Listing 5
Listing of Soluble Inflammatory Mediators in Blister

Treatment	Biomarker (Unit)	Centre ID/ Subj ID	Visit/ Planned Relative Time	Date/ Time/ Study Day	Arm	Result	Change from Baseline	Test Comments
LPS x.x ng/kg	xxxxxxx (unit)	xxxx/ xxxx	xxxxx/ xxx	xxxx/ xxxx/ xxxxx	Right	xxxx		<LLQ
				xxxx/ xxxx/ xxxxx	Left	xxxx		
				xxxx/ /xxxxx	Average	xxxx	xxxx	
			xxxx/ xxxx	xxxx/ xxxx/ xxxx	Right	xxxx	xxxx	>ULQ
				xxxx/ xxxx/ xxxx	Left	xxxx		
				xxxx/ /xxxxx	Average	xxxx	xxxx	

Note: LLQ=Lower Limit of Quantification, ULQ=Upper Limit of Quantification, CV=Coefficient of Variation.
Note: Repeat for all available treatments and biomarkers.