STATISTICAL ANALYSIS PLAN

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Study Title:	A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Single Center Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide LHD153R Adjuvanted Meningococcal C-CRM197 Conjugate Vaccine compared to an Aluminium Hydroxide Adjuvanted Meningococcal C-CRM197 Conjugate Vaccine in Healthy Adults (18-45 years of age)
Study Number:	V132_01EXP, EUDRACT No. 2014-002430-31
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Phase of Development:	Phase 1
Sponsor:	GlaxoSmithKline Biologicals
Approvers: Supervisory	PPD Biostatistician
	PPD Cluster Head
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ELISA	Enzyme Linked Immunosorbent Assay
ER	Emergency room
EXC	Excluded from analysis set
FAS	Full Analysis Set
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HI	Hemagglutination Inhibition
hSBA	Human complement serum bactericidal assay
ICH	International Conference on Harmonisation

IM	Intramuscular
LLQ	Lower limit of quantification
MAR	Missing at Random
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NOCD	New onset of chronic disease
PD	Protocol Deviation
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFL	Tables, Figures and Listings
TOC	Table of Contents
WHO	World Health Organization
µg	Microgram

1. BACKGROUND AND RATIONALE

The aim of this study is to assess the safety of Aluminium Hydroxide/LHD153R adjuvanted MenC-CRM_{197} conjugate vaccine (MenC-CRM_{197}/Aluminium Hydroxide/LHD153R) and to compare the antibody-mediated immune response elicited by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R with the licensed aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (Menjugate®).

For further details, refer to section 1.0 of the protocol.

2. OBJECTIVES

2.1 Primary Objectives

Primary Safety Objective

To assess the safety of MenC-CRM197/Aluminium Hydroxide/LHD153R as compared to that of aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine.

Primary Immunogenicity Objective

To compare the antibody responses of MenC-CRM197/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal C-CRM197 Conjugate Vaccine at Day 29, as measured by human complement serum bactericidal assay (hSBA) directed against MenC.

2.2 Secondary Objectives

Secondary Immunogenicity Objective(s)

1. To compare the antibody responses of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal $CCRM_{197}$ Conjugate Vaccine at Day 8 and Day 181 after vaccination, as measured by hSBA directed against MenC. Baseline antibody titers will also be measured by hSBA.
2. To compare the antibody responses of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R and aluminium hydroxide adjuvanted Meningococcal $CCRM_{197}$ Conjugate Vaccine, at Day 8, Day 29 and Day 181 after vaccination, as measured by an enzyme-linked immunosorbent assay (ELISA) to MenC. Baseline antibody concentrations will also be measured by ELISA.

2.3 Exploratory Objectives

1. To evaluate the systemic exposure of LHD153 at several early time-points after IM injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or Meningococcal $CCRM_{197}$ Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM_{197} protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine. Subsequently, the B cell

repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.

3. To explore the baseline T cell mediated immunity to CRM_{197} and to evaluate the frequency and quality of CRM_{197} specific T cells induced by MenCCRM$_{197}$/Aluminium Hydroxide/LHD153R compared to aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.

3. STUDY DESIGN

This is a Phase 1, randomized, observer blind, active-controlled, adjuvant dosageescalation study performed at a single center. In total, approximately 80 healthy adults (18-45 years of age) will be enrolled in the study.

Tables 1 and 2 describe the different enrollment groups, cohorts, vaccine formulations as well as the injection schedule and the enrollment stages based on Data Monitoring Committee (DMC) reviews.

Table 1. Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}

All cohorts will have a staggered entry. For each cohort, the first 5 subjects (i.e. the first 1:4 randomization block) to receive either aluminium hydroxide adjuvanted Meningococcal C-CRM_{197} Conjugate Vaccine (n=1) or MenC-CRM_{197}/Aluminium Hydroxide/LHD153R (n=4) will be vaccinated at rate of 1 subject each day.

After entry of the first 5 subjects in each cohort, the enrollment will be paused. The remaining 15 subjects for each cohort will be enrolled only after the review by the DMC of the safety results obtained through Day 14 has been finalized (Table 2). In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed by the

DMC. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC review between the different enrollment stages.

Table 2. Overview of staggered entry of subjects based on DMC reviews

Stage	Dosage Cohort	MenC-CRM$_{197}$/ Aluminium Hydroxide (n)	MenC-CRM$_{197}$/ Aluminium Hydroxide /LHD153R (n)
1	1	1	4
Enrollment pause until DMC review of Stage 1 Day 14 Safety Results			
2	1	3	12
	2	1	4
Enrollment pause until DMC review of Stage 1 Day 29 and Stage 2 Day 14 Safety Results			
3	2	3	12
	3	1	4
Enrollment pause until DMC review of Stage 2 Day 29 and Stage 3 Day 14 Safety Results			
4	3	3	12
	4	1	4
Enrollment pause until DMC review of Stage 3 Day 29 and Stage 4 Day 14 Safety Results			
5	4	3	12

Tables 3 and 4 display the time and events until Day 29 and Day 366 respectively. Sections referred to in these tables are those in the protocol.

Table 3. Times and Events Table (until Day 29)

	Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit
	Study Day	-28 to -3	1	4	8	15	22	29
	Visit Window (Days)	n/a	n/a	n/a	-1/+1	+1	n/a	-2/+2
	Visit Number	Screening	1	2	3	4	5	6
Study Event	Protocol References							
Study Treatment								
Vaccination	Section 5.2		X					
Screening and Safety								
Informed Consent	Section 5.1.1	X						
Demographic Data & Medical History	Sections 5.1.2	X						
Physical Exam	Sections 5.1.2 and 5.2.1	X	X[a]					
Safety Laboratory blood draw (10 mL)	Section 7.1.7	X	X[b]		X			X
Urinalysis	Sections 7.1.7	X	X[b]		X			X
Pregnancy Test	Sections 5.1.2 and 5.2.1	X	X[a]					

Exclusion/Inclusion Criteria	Section 4.0	X	Xa					
Randomization	Section 5.2.3		Xa					
30 min and 24 hr Post Injection Assessment	Section 5.2.5		Xc					
Subject Diary Dispensed with Training	Section 5.2.5		X					
Subject Diary Reminder	Section 5.2.5			X	X			
Subject Diary Reviewed and Collected	Section 5.3.1					X		
Assess all solicited AEs	Section 7.1.1 and 7.1.3					X		
Assess all unsolicited AEs	Sections 7.1.2 and 7.1.3	X	X	X	X	X		

BCDM-14 TEMP 01 / Atlas No. 296412

	Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
Assess SAEs	Section 7.1.4	X	X	X	X	X	X	X
Assess AESIs	Section 7.1.4.1	X	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives								
Serum Blood Draws (Primary/Secondary Objectives; 10 mL)	Section 3.5		Xa		X			X

Serum Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		Xd	X	X			
Whole Blood Draws (Exploratory Objectives; 3 mL)	Section 3.5		Xe	X				
Whole Blood Draws (Exploratory Objectives; 5 mL)	Section 3.5		Xf	X	X			
Whole Blood Draws (Exploratory Objectives; 20 mL)	Section 3.5		Xg	X				
Whole Blood Draws (Exploratory Objectives; 50 mL)	Section 3.5							X
Whole Blood Draws (Exploratory Objectives; 70 mL)	Section 3.5		Xa		X			

Notes:

a Procedure must be performed prior to vaccination.

b Two blood draws (2 x 10 mL) and two urine samples must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 24 h after vaccination.

c Body temperature measurement must be performed at 30 min, 2, 4, 6, 8, 10, 12, 18 and 24 h after vaccination.

d Three Serum Blood Draws (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6 h and at 24 h after vaccination.

e Six Whole Blood Draws (6 x 3 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination) and at 1, 2, 4, 8 and 24 h after vaccination.

f Three Whole Blood Draws (3 x 5 mL) must be taken at Study Day 1, i.e. at baseline (prior to vaccination), at 6h and at 24 h after vaccination.

g Whole Blood Draw (20 mL) at Study Day 1 must be taken at 24 h after vaccination.

BCDM-14 TEMP 01 / Atlas No. 296412

Table 4. Time and Events Table – Follow-up Period (until Day 366)

	Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Phone Call	Clinic Visit
	Study Day	85	113	181	209	271	366

	Visit Window (Days)	-7 to +7	-7 to +7	-7 to +7	-14 to +14	-14 to +14	-14 to +14
	Visit Number	7	8	9	10	11	12
Study Event	Protocol References						
Safety							
Assess SAEs	Section 7.1.4	X	X	X	X	X	X
Assess AESI	Section 7.1.4.1	X	X	X	X	X	X
Assess NOCDs, medically attended AEs, AEs leading to withdrawal	Sections 7.1.3	X	X	X	X	X	X
Assess relevant medications	Sections 5.1.2 and 6.5	X	X	X	X	X	X
Blood draws for Immunogenicity and Exploratory Objectives							
Serum Blood Draw (Secondary Objective; 10 mL)	Section 3.5			X			
Whole Blood Draw (Exploratory Objectives; 50 mL)	Section 3.5			X			
Study Completion Procedures							
Study Termination[a]	Section 5.5						X

Notes:

a. Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5 of the protocol for further details.

4. RANDOMIZATION AND BLINDING

4.1 Method of Group Assignment and Randomization

Subjects will be randomized in a 1:4 ratio to receive a single intramuscular (IM) vaccination of either the licensed aluminium hydroxide adjuvanted Meningococcal CCRM197 Conjugate Vaccine (Menjugate®) or the investigational vaccine, MenCCRM197/Aluminium Hydroxide/LHD153R. Each of the four cohorts will evaluate a different dosage of LHD153R.

For further details, refer to section 5.2.3 of the protocol.

4.1.1 Definition of Vaccination Errors

A vaccine administration error occurs when a subject receives a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration.

An overdose of study vaccine occurs when a dosage higher than the recommended dosage is administered in one dose.

The list below provides some examples of potential errors that may occur during vaccination:

- Subjects got vaccinated with a vaccine different from the one assigned at randomization
- Subjects got vaccinated with the correct vaccine but containing a lower volume

See section 7 of this document for a complete guidance on how vaccination errors are handled in the statistical analysis.

4.1.2 Forced Randomization

Not applicable.

4.2 Blinding and Unblinding

For details, refer to section 3.3 of the protocol.

The unblinding of a subject during the study is reported as a major protocol deviation, except for Pharmacovigilance unblinded suspected unexpected serious adverse reactions (SUSAR). The unblinding will be documented.

The first-line analysis excludes unblinded subject(s) in immunogenicity statistical analyses based on the per-protocol set (PPS). The unblinded subjects will be included in the full analysis set (FAS) and safety sets.

As described in section 3 of PXL SOP-EP.CL-WW-003-01 ('Administration of Investigational Product'), these two steps are taken to ensure blindness in observerblinded studies except in cases where the protocol stipulates otherwise:

- The Principal Investigator, Investigator, Registered Nurse, Licensed Practical Nurse, Pharmacist or other licensed health care provider who assists in the IP preparation will not perform other procedures on that study;
- An independent Principal Investigator, Investigator, Registered Nurse, Licensed Practical Nurse, Pharmacist or other licensed health care provider who performs the dispensing procedures and has therefore been unblinded will not perform any dosing procedures nor will they participate in any assessment procedure or the execution of the study in any other way.

5. SAMPLE SIZE AND POWER CONSIDERATIONS

For details, refer to section 8.5 of the protocol.

Sample size/power considerations are included in the study protocol. Technical details including statistical assumptions and software are given in a separate sample size memo authored by the study Biostatistician. In the same document, a statistical co-reviewer verified and documented the sample size/power considerations. This document was completed prior to finalization of the protocol and stored in Home/analysis/v132/v132_01exp/sample_size/dev/docs.

6. DETERMINATION OF PROTOCOL DEVIATIONS

6.1 Definition of Protocol Deviations

Major (Clinical Study Report (CSR) reportable) protocol deviations (PDs) are defined in accordance with ICH E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial.

All reportable PDs will be evaluated before unblinding and classified according to ICH into the following five categories:

- Subject developed withdrawal criteria during the study but was not withdrawn:
  - Underlying medical condition forbidden by the protocol or which may influence immune response.
  - Subject received wrong vaccine or incorrect dose.
  - Study vaccine was not administered at all.
  - Vaccine administration not according to protocol.
  - Randomization failure.
- Subject took an excluded concomitant medication:
  - Administration of concomitant vaccine(s) forbidden in the protocol.
  - Administration of any medication forbidden by the protocol.
- Subject randomized and did not satisfy the entry criteria:
  - Subject did not meet entry criteria.
- Deviations from key study procedures:
  - Randomization code was broken.
  - Subject did not provide any post-vaccination safety data.
  - Subject did not comply with blood draw schedule.
  - Serological results not available post-vaccination.
  - Obvious incoherence, abnormal serology evolution or error in data.

Major (CSR reportable) PD will lead to exclusion of the subject or part of the subject's data from at least one analysis set.

The number of subjects in any and by PD category will be summarized by dosage and overall and individual subject listings will be provided in an appendix.

Prior to unblinding, designated PXL and Sponsor staff will develop a memo that describes the PDs that lead to exclusions from analysis sets. This memo will be signed off by at least the Biostatistician and the Cluster Physician and will be included in the trial master file.

Prematurely terminating study participation for reasons such as withdrawal of consent or occurrence of adverse events (including death) is not considered as a PD. The missing assessments that should have otherwise been collected for that subject later in the study are also not considered as a PD.

6.2 Determination of Protocol Deviations

Prior to unblinding, a set of listings will be provided to the Cluster Physician and the Clinical Trial Leader (CTL) for review according to PXL SOP-EP.BS-WW-008-01.

The listings will be programmed following the list presented in table in section 7.3.8, and specifically using the PD codes specified in the first column. In addition, PDs will be evaluated during periodic review meetings as described in the Protocol Deviations Manual.

6.3 Exclusions of Individual Values for Safety Analysis

Some local and systemic adverse events will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible. Therefore these implausible measurements will be included in listings but excluded from summary tables. Implausible measurements are summarized in Table 6.3-1:

Table 6.3-1. Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	<=33°C or > =42°C
Erythema	> 900 mm or <0 mm
Induration	> 500 mm or <0 mm
Swelling	>500 mm or < 0 mm

7. ANALYSIS SETS

7.1 All Enrolled Set

All screened subjects who provide informed consent and provide demographic and/or other baseline screening measurements, regardless of the subject's randomization and vaccination status in the trial, and receive a subject ID.

Demography and baseline characteristics tables as well as subject listings will be produced on the All Enrolled Set.

7.2 All Exposed Set

All subjects in the All Enrolled Set who receive a study vaccination.

7.3 Safety Set

Solicited Safety Set

All subjects in the All Exposed Set who:

- Provide post vaccination local or systemic solicited adverse event data. Unsolicited Safety Set

All subjects in the All Exposed Set who:

- Have post-vaccination unsolicited adverse event data.

Overall Safety Set

All subjects who are in the solicited safety set and/or in the unsolicited safety set.

Subjects providing only 30 minutes postvaccination safety data will be reported separately in a 30 minute postvaccination safety analysis and excluded from all other safety analysis.

In case of vaccination error, subjects will be analyzed as "treated" (i.e., according to the vaccine a subject receives, rather than the vaccine to which the subject is randomized).

If a subject is unblinded during the study, he/she will be included in all safety sets.

7.4 Full Analysis Immunogenicity Set (FAS)

All subjects in the All Enrolled Set who are randomized, receive a study vaccination AND provide immunogenicity data at relevant time points

- Days 1 and 29 (Immunogenicity FAS-1).
- Days 1 and Day 8 (Immunogenicity FAS-2), or Day 181 (Immunogenicity FAS-3).

Subjects in the FAS will be analyzed according to the vaccine to which they were randomized. In case of vaccination error, subject in the FAS will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

If a subject is unblinded during the study, he/she will be included in the FAS.

7.5 Per Protocol Immunogenicity Set (PPS)

All subjects in the FAS Immunogenicity who:

- Have serology results available.
- Correctly receive the vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time point Day 1).
- Have no major protocol deviations leading to exclusion (see section 6.2) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis (see section 6.2)

In case of vaccination error, the subject is excluded from the PPS. If a subject receives a vaccine, labeled for another subject but the same as the one the subject was randomized to, the subject will not be removed from the PPS.

If a subject is unblinded during the study, except for SUSAR, he/she will be excluded from the PPS.

7.6 Other Analysis Sets

All subjects in the All Enrolled Set who consent to additional blood draws, receive a study vaccination AND provide exploratory assay data at relevant time points will be included in an exploratory assay subset. The analyses of the exploratory endpoints will be detailed in a separate statistical analysis plan.

7.7 Overview of Analysis Sets by PD Code

Table mock-ups with summaries of the number of available subjects by objective and analysis set are given below.

Table 7.7-1: Safety Sets

PD code	PD Description	All Exposed Set	Overall Safety Set	Unsolicited Safety Set	Solicited Safety Set			
					T30m	D1-D4*	D5-D8	D8-D14
	Exclusion code	EXPFL	SAFFL	SSU10FL	SSS01FL	SSS02FL	SSS03FL	SSS04FL
100	Study vaccine not administered AT ALL	EXC	EXC	EXC	EXC	EXC	EXC	EXC
115	Subject did not provide any post-vaccination unsolicited safety data	None	None	EXC	None	None	None	None
116	Subject did not provide any post-vaccination solicited safety data	None	None	None	EXC	EXC	EXC	EXC

EXC = excluded from this analysis set.

* Without 30 minutes post-vaccination.

All Safety sets and codes correspond to the primary safety objective.

Table 7.7-2: Immunogenicity Sets

PD code	PD Description	PPS	FAS-2		FAS-1			
			D1	D29	D1	D8	D29	D181
	Exclusion code	**PPS01FL**	**FAS01FL**	**FAS02FL**	**FAS03FL**	**FAS04FL**	**FAS05FL**	**FAS06FL**
100	**Study vaccine not administered AT ALL**	EXC	EXC	EXC	EXC	EXC	EXC	EXC
110	**Serological results are not available**	EXC	EXC	EXC	EXC	EXC	EXC	EXC
110.1	**Serological results are not available for hSBA**	EXC	EXC	EXC	EXC	EXC	EXC	EXC
110.2	**Serological results are not available for ELISA**	EXC	None	None	EXC	EXC	EXC	EXC
112	**Obvious deviation from Laboratory Manual or error in laboratory data**	EXC	EXC	EXC	EXC	EXC	EXC	EXC
112.1	**Incoherence between CRF and CLS database in terms of sample availability (e.g. sample not collected but result is available)**	EXC	EXC	EXC	EXC	EXC	EXC	EXC
112.2	**Label error of blood samples that could not be resolved**	EXC	EXC	EXC	EXC	EXC	EXC	EXC
112.3	**Wrong handling of laboratory samples with impact on the results (e.g. critical deviations during storage at sites or shipment but sample was tested)**	EXC	EXC	EXC	EXC	EXC	EXC	EXC

120	**Randomization failure**	EXC	EXC	EXC	EXC	EXC	EXC	EXC
120.1	**Subject randomized to the wrong strata**	EXC	None	None	None	None	None	None

BCDM-14 TEMP 01 / Atlas No. 296412

PD code	**PD Description**	**PPS**	**FAS-2**		**FAS-1**			
			D1	D29	D1	D8	D29	D181
	Exclusion code	**PPS01FL**	**FAS01FL**	**FAS02FL**	**FAS03FL**	**FAS04FL**	**FAS05FL**	**FAS06FL**
120.2	**Subject received another vaccine than allocated (Actual Arm different from Planned Arm)**	EXC	None	None	None	None	None	None
130	**Randomization code was broken**	EXC	None	None	None	None	None	None
140	**Vaccination not according to protocol**	EXC	None	None	None	None	None	None
140.1	**Administration of temperaturedeviated vaccine**	EXC	None	None	None	None	None	None
140.2	**Administration of expired vaccine**	EXC	None	None	None	None	None	None
140.3	**Administration of only part of the study vaccine**	EXC	None	None	None	None	None	None
140.6	**Route of study vaccine administration wrong or unknown**	EXC	None	None	None	None	None	None
140.7	**Site / side of study vaccine administration wrong or unknown**	EXC	None	None	None	None	None	None

140.8	**Administration not according to protocol for other reasons specified by the investigator**	EXC	None	None	None	None	None	None
150	**Administration of forbidden vaccine**	EXC	None	None	None	None	None	None
200	**Subject did not meet entry criteria**	EXC	None	None	None	None	None	None
220	**Subject had contraindication for a subsequent study vaccination but was vaccinated**	EXC	None	None	None	None	None	None

BCDM-14 TEMP 01 / Atlas No. 296412

PD code	**PD Description**	**PPS**	**FAS-2**		**FAS-1**			
			D1	D29	D1	D8	D29	D181
	Exclusion code	**PPS01FL**	**FAS01FL**	**FAS02FL**	**FAS03FL**	**FAS04FL**	**FAS05FL**	**FAS06FL**
230	**Administration of forbidden medication**	EXC	None	None	None	None	None	None
240	**Underlying medical condition forbidden by the protocol**	EXC	None	None	None	None	None	None
250	**Concomitant infection related to the vaccine which may influence immune response**	EXC	None	None	None	None	None	None
260	**Did not comply with study vaccination schedule**	EXC	None	None	None	None	None	None
270	**Did not comply with blood draw schedule**	EXC	None	None	None	None	None	None

270.1	**Day 1 blood draw performed out of planned visit window**	EXC	None	None	None	None	None	None
270.2	**Day 8 blood draw performed out of planned visit window**	EXC	None	None	None	None	None	None
270.3	**Day 29 blood draw performed out of planned visit window**	EXC	None	None	None	None	None	None
270.4	**Day 181 blood draw performed out of planned visit window**	EXC	None	None	None	None	None	None

FAS = Full Analysis Set; PPS=Per Protocol Set; EXC = excluded from this analysis set.

8. GENERAL ISSUES FOR STATISTICAL ANALYSES

8.1 Adjustment for Covariates

Section 11.2 describes the statistical model and all adjustments for covariates.

8.2 Handling of Dropouts, Missing Data

First-line analyses will be without missing values.

8.2.1 Safety Data

To minimize the effect of dropouts and missing data, the study period will be divided into time intervals for statistical analysis of safety.

Unsolicited adverse events: these events will be reported from the date of signed informed consent to Day 14 and from Day 15 to study termination (for SAEs, Medically Attended AEs, NOCDs and AESIs).

Solicited adverse events, the solicited study period (Days 1-14) after vaccination will be divided into these intervals: 30 min, Days 1-4 (without 30 min), Days 5-8, Days 1-8 (without 30 min), Days 8-14 and Days 1-14 (without 30 min).

8.2.2 Immunogenicity Data

Imputation methods will not be used. Primary, secondary, and exploratory objectives will be analyzed using the PPS. The primary objectives will also be analyzed using the FAS as a measurement of the robustness of the findings.

8.2.3 Efficacy Data

Not applicable.

8.3 Multicenter Studies

Not applicable.

8.4 Multiple Comparisons and Multiplicity

No multiple comparison adjustment will be performed.

8.5 Subsets

The B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects. This analysis is described in detail in a separate SAP Addendum for the exploratory endpoints.

8.6 Subgroups

Selected immunogenicity analyses may be provided based on seropositivity status at baseline.

8.7 Derived and Computed Variables

8.7.1 Demographics

Age is calculated in days for subjects using the following formula:

Age = Date of Visit 1 – Date of Birth + 1 (days) and

converted to years by dividing the resulting quantity by 365.25.

Body Mass Index (kg/m^2) will be calculated using the following formula:

BMI = Weight (kg) / Height^2 (m^2).

8.7.2 Immunogenicity

Values below the limit of quantification (recorded as "< LLQ") will be set to half the lowest limit of quantification.

Titer greater or equal to a given threshold is defined as a binary variable for nonmissing values as:

= 1, if the titer is superior or equal to the given threshold (≥4-fold rise in hSBA titer),

= 0, otherwise.

Seroresponse is defined as a binary variable for subjects with non-missing values prevaccination and postvaccination as:

- For subjects with a prevaccination hSBA titer < 4:

= 1, if postvaccination titer ≥ 8

= 0, otherwise.

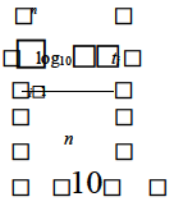
- For subjects with a prevaccination hSBA titer ≥ 4:

= 1, if post-vaccination titer increases at least 4 times the baseline hSBA titer

= 0, otherwise.

Geometric Mean Titer/Concentration

The GMT/GMC will be calculated using the following formula:

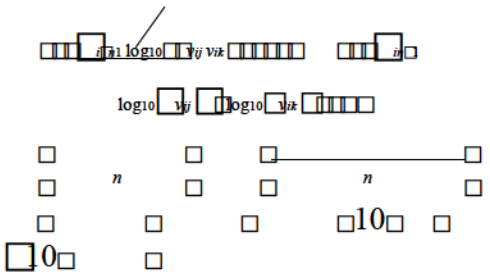


where t t_1 $_2$, ,…,t_n are n observed immunogenicity titers/concentrations.

Geometric Mean Ratio

Geometric mean ratios (GMRs) measure the changes in immunogenicity titers/concentrations *within* subjects.

The GMR will be calculated using the following formula:



where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers/concentrations for subject i at time-points j and k, j k.

8.7.3 Adverse Events

The time of onset of AEs is defined as:

Study day=Date of onset of AE – vaccination date + 1 (days).

Duration in the study is defined in days as:

Last visit date (visit x)[a] – Enrollment date (visit 1) + 1 (days).

[a] or premature discontinuation date (in case of withdrawal from the study) The duration is missing if one of the dates is missing or incomplete.

Solicited Adverse Events

For details see section 13.2.

Unsolicited Adverse Events

All adverse events will be characterized according to the date of occurrence related to the vaccination phase as follows:

- **Emergence before vaccination phase**: start date before the first date of injection of study vaccine.
- **Emergence during vaccination phase**: start date on or after the first date of injection of study vaccine or, adverse event increase in severity including to "serious" adverse event.

If start date is equal to the first date of injection, the "timing" variable ("On injection day, before injection"/"On injection day, after injection") will be used to define whether the adverse event started before or after the injection.

If an adverse event start date is missing or unknown and the end date is not before the injection date, the adverse event will be considered as emergent.

When start and/or end dates of an adverse event are only partially known, adverse events will be categorized as emergent before and during vaccination phase using the following rules:

- If the partial end date is before (<) the first study vaccination (i.e., year or year & month is/are before the first study vaccination year or year & month), the adverse event is emergent before vaccination phase.

- If the partial start date is equal or after (≥) the first study vaccination (i.e., year or year & month is/are after or the same as the first study injection year or year & month), the adverse event is emergent during vaccination phase.

The **maximum event severity** is the greatest severity associated with a system organ class/preferred term combination of an adverse event according to this order: Mild < Moderate < Severe. Unknown/ Missing severity is considered as severe (except for the definition of emergence).

Multiple AEs with the same PT for the same subject are counted only once when counting number of subjects with a given PT.

Vaccination-related Adverse Events are those for which the cause has been evaluated by the investigator, and recorded either as possibly related, probably related or unknown/ missing.

8.7.4 Safety Laboratory Data

The laboratory tests listed in section 7.1.7 of the protocol will be listed and summarized. All laboratory tests including retests and reasons for retests will be included in the subject listings. In case of multiple measurements of a laboratory test at a given time point for a subject only these measurements will be retained for analysis:

1. Before the study vaccination, only the last measurement closest to the study vaccination.
2. After the study vaccination, only the first measurement closest on/or before the planned visit..

The reference ranges to categorize the results as “low” (values below the lower limit of the reference range), “normal” (values within the reference range) or “high” (values above the upper value of the reference range) will be those provided by the laboratory (as specified in the Clinical Specimen Lab Manual), which performed the tests. The corresponding grading scales can be found in Appendices C-E of the protocol.

8.7.5 Prior and Concomitant Medications

A **prior medication** is a medication used before the day of study vaccination (medication end date < study vaccination date).

A **post-vaccination medication** is a medication used only after study termination (i.e. medication start date > study termination date).

All other medications are **concomitant.**

When start and/or end dates of a medication intake are missing, the medication is considered as concomitant with the study vaccination schedule.

If the first study vaccination date is missing then the medication is considered as concomitant with the study vaccination schedule, provided that the study vaccine was administered to the subject.

8.8 Analysis Software

All data processing, summarization, and analyses will be performed using SAS□version 9.2 or higher (SAS Enterprise Guide 4.3).

8.9 Data Transformation

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers or concentrations will be $\log_{10}$-transformed. GMTs and their 95% CIs are computed by exponentiating (base 10) the least squares means and 95% CIs of the $\log_{10}$ titers.

9. STUDY SUBJECTS

9.1 Disposition of Subjects and Withdrawals

The following tables will be created:

- Number of randomized subjects.
- Number of subjects who received study medication.
- Number of randomized subjects who completed the study in each vaccine group.
- Number of subjects who discontinued after randomization, by dosage group and main reason.

The frequencies and percentages of subjects in each analysis set, study withdrawals, subgroups, and major protocol deviations will also be presented.

The time the subjects are under observation will be summarized by dosage group and overall using summary statistics (n, mean, SD, minimum, median, maximum). The number and percent of subjects at each visit will also be summarized.

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

10.1 Demographics

Subjects will be summarized according to the subject's dosage group and overall.

Age, height, weight, and body mass index at enrollment will be summarized by reporting the mean, standard deviation, median, minimum and maximum, and will be calculated by dosage group and overall.

The frequencies and percentages of subjects by sex, race, and entry criteria met will be presented by dosage group and overall. Demographic data will be tabulated for the All Enrolled, All Exposed, Solicited Safety, Unsolicited Safety, Overall Safety, the FAS, and the PPS.

For females, the results of the pregnancy test at Screening and visit 1 will be listed.

10.2 Medical History

The frequencies and percentages of subjects in the All Enrolled Set with medical history will be presented by MedDRA system organ class and preferred term, by dosage group and overall for the All Enrolled Set. The same table will be created for the Overall Safety Set if such a set differs from the All Enrolled Set.

11. IMMUNOGENICITY ANALYSIS

11.1 Blood Samples

The frequencies and percentages of subjects in the All Enrolled Set with blood draws will be summarized overall and by vaccine group. A similar table will be created for the additional blood samples collected at Day 1, Day 4, Day 8, Day 29 and Day 181 in subjects who signed the separate Informed Consent form.

11.2 Primary Objectives Analysis

The primary immunogenicity endpoints are the GMTs measured by hSBA directed against MenC from samples collected on Day 1 (baseline, before vaccination) and Day 29 as well as the GMR of the titers (Day 29 / Day 1).

The primary immunogenicity analyses will be based on the PPS on Day 29. The primary endpoints will also be assessed using the FAS as a sensitivity analysis

Geometric Mean Titers

The logarithmically (base 10) transformed antibody titers will be modeled using an analysis of covariance (ANCOVA) model with a qualitative factor for the dosage of the LHD153R adjuvant (0, 12.5, 25, 50 or 100 µg) and log (base 10) pre-vaccination titer as a covariate. The adjusted GMT and the two-sided, 95% confidence intervals (CIs) of the GMT will be calculated based on this model as will the ratio of GMTs and corresponding CIs.

The adjusted GMT and two-sided 95% CIs will be constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) antibody titer. The ratio of GMTs (LHD153R adjuvant dosage minus Men C control), and corresponding two-sided 95% CIs, will be constructed by exponentiation (base 10) of the least square differences obtained from this model. The model can be written as:

$$\log10\,(y_{ik}) = \mu + \alpha_i + \beta x_{ik} + \varepsilon_{ik}$$

where μ represents a common overall mean, α_i represents the adjuvant dose group i effect, β represents the common slope for the log10 pre-vaccination titer, x_{ik} for subject k in adjuvant dose group i, and ε_{ik} represents random error for subject k in adjuvant dose group i.

The following SAS® code will be used for this ANCOVA model:

```
ODS OUTPUT DIFFS=D_SET
                LSMEANS=L_SET;
PROC MIXED ORDER=data;
   CLASS adj_dosage;
  MODEL log_titer=adj_dosage log_pre/ddfM=KR;
   LSMEANS adj_dosage /DIFF CL;
RUN;
```

where:

ADJ_DOSAGE: adjuvant dosage (0, 12.5, 25, 50 or 100 µg),

D_SET= dataset containing the ratio of LS means of the log10-transformed titers (the ratio of GMTs and the two-sided 95% CIs will be constructed by exponentiation -base 10-, only the values where _adj_dosage=0 will be used),

LOG_PRE=log10-transformed value of pre-vaccination titer,

LOG_TITER=log10-transformed value of titer on Day 29,

L_SET=dataset containing the LS means of the log10-transformed titer for each adjuvant dosage (the adjusted GMT and two-sided 95% CIs will be constructed by exponentiation -base 10-).

Given that ALPHA=0.05 is the default value, there is no need to specify such a value in the LSMEANS statements to calculate the 95% CIs of the ratios of GMTs or the adjusted GMTs.

Geometric Mean Ratios

The logarithmically (base 10) transformed within subject ratio of antibody titers (Day 29/pre-vaccination) will be modeled using an analysis of variance (ANOVA) model with a qualitative factor for LHD153R adjuvant dosage (0, 12.5, 25, 50 or 100 µg). The adjusted GMR and the two-sided, 95% CIs of the GMR will be calculated based on this model. The model can be written as:

$$\log10\ (y_{ik}) = \mu + \alpha_i + \varepsilon_{ik}$$

where µ represents a common overall mean, αi represents the adjuvant dose group i effect and ε_{ik} represents random error for subject k in adjuvant dose group i.

The following SAS code will be used for this ANOVA model:

```
ODS OUTPUT LSMEANS=L_SET;
PROC MIXED;
  CLASS adj_dosage;
   MODEL log_ws_ratio= adj_dosage /ddfM=KR;
   LSMEANS adj_dosage /DIFF CL;
RUN;
```

where:

ADJ_DOSAGE: adjuvant dosage (0, 12.5, 25, 50 or 100 µg),

LOG_WS_RATIO=log10-transformed value of within subject ratio of antibody titers (Day 29/pre-vaccination),

L_SET=dataset containing the LS means of the log10-transformed ratio of antibody titers (the adjusted GMR and two-sided 95% CIs will be constructed for each adjuvant dosage by exponentiation -base 10-).

Given that ALPHA=0.05 is the default value in the LSMEANS statements, there is no need to specify such a value to calculate the 95% CIs of the adjusted GMRs.

11.3 Secondary Objectives Analysis

The secondary immunogenicity endpoints are:

- GMTs and corresponding GMRs measured by hSBA directed against MenC for samples collected at Day 8 and Day181.
- Percentage of subjects with hSBA seroresponse at Days 8, 29, and 181. Seroresponse is defined as a post vaccination hSBA ≥8 for subjects with a baseline hSBA <4 or have an increase of at least 4 times the baseline hSBA level for subjects with prevaccination hSBA ≥4.
- Antibody geometric mean concentrations (GMCs) against MenC measured by ELISA for samples collected on Days 1 (baseline, prior to vaccination), 8, 29, and 181.
- The percentage of subjects with at least a 4-fold increase in antibody concentrations to MenC as measured by ELISA on Day 8, 29, and 181 relative to baseline (Day 1).

These analyses will be based on the PPS.

In the case of the endpoint for the GMTs and corresponding GMRs measured by hSBA directed against MenC, the same statistical models (ANCOVA and ANOVA) as the one used for the primary objective will be applied.

In the case of the endpoint for the GMCs against MenC measured by ELISA, the same ANCOVA statistical model as the one used for the primary objective will be applied.

The percentage of subjects with seroresponse and associated Clopper-Pearson two-sided 95% as well as the percent of subjects with a >8 titer will be computed for each dosage group at Days 8, 29 and 181.

The percentage of subjects with a 4-fold increase in antibody concentrations to MenC from baseline as measured by ELISA and associated Clopper-Pearson two-sided 95% CIs will be computed for each dosage group at Days 8, 29 and 181.

11.4 Exploratory Objectives Analysis

Refer to section 8.1.3 of the protocol for the exploratory immunogenicity endpoints. A separate SAP will be issued specifically for the exploratory objective analysis.

12. EFFICACY ANALYSIS

Not Applicable.

13. SAFETY ANALYSIS

Refer to section 8.1.1.1 of the protocol for the primary safety endpoints.

The safety assessments will include summaries of the following categories of data collected for each subject:

- Vaccine exposure.
- Solicited local and systemic adverse events.
- Unsolicited adverse events.
- Clinical laboratory parameters.

13.1 Analysis of Extent of Exposure

The frequencies and percentages of subjects with vaccination will be summarized overall and by vaccine group. Data will be tabulated for the All Enrolled Set.

13.1.1 Safety Completeness Analysis

Solicited adverse events

The safety completeness analysis on solicited adverse events aims to identify subjects who completed diary cards, irrespective of severity. The analysis will show the number of subjects with *valid data* by solicited adverse event and time point. *Valid data* in the context of the safety completeness analysis are all data entered in the diary card (including implausible values) except "Not done/unknown".

Four summaries will be produced:

1. The frequencies of subjects who provide diary cards by dosage group.
2. For each solicited adverse event, the frequencies of subjects with *valid data* will be presented by dosage group and time point: 30 minutes post-vaccination and by day for Days 1 through 14.
3. For each type of solicited adverse event (local, systemic) and indicators of solicited adverse events, such as analgesic use, the frequencies of subjects *with valid data* by vaccine group, aggregated over time points: Days 1-14 (without 30 minutes).
4. For each solicited adverse event, the frequencies of subjects *with valid data* by vaccine group, aggregated over time points: Days 1-14 (without 30 minutes).

For the corresponding percentages, the denominator will be the respective numbers of exposed subjects, i.e., subjects who received a vaccination and were still in-study for that time point or time interval, irrespective of whether or not a diary card was present.

All analyses will be based on the 'as treated' analysis set.

13.2 Solicited Local and Systemic Adverse Events

For details, refer to section 7.1.1 of the protocol.

Plausible observations are those with non-missing values other than those "Not done/unknown" or implausible values (see section 6.3). Implausible measurements will be excluded from summary tables but included in listings.

Solicited adverse events will be recorded at 30 minutes and Day 1 directly into the clinical database; and, from Day 2 to Day 14 in the subject diaries.

The analyses of solicited adverse events will be performed separately at these intervals: 30 minutes, Days 1-4 (without 30 minutes), Days 5-8, Days 8-14, Days 1-8 (without 30 minutes) and Days 1-14 (without 30 minutes). In addition, solicited AEs ongoing after day 14 will be presented as unsolicited AEs.

In the case of local AEs, for grades 1 to 3 (i.e., Mild to Severe), refer to Appendix A in the protocol. Grade 4 (Potentially Life Threatening) will be defined as follows (see also Appendix 2):

- Pain: Emergency room (ER) visit or hospitalization.
- Tenderness: ER visit or hospitalization.
- Erythema/Redness: Necrosis or exfoliative dermatitis.
- Induration/Swelling: Necrosis.

(Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, USDA, 2007).

All summary tables will include the number and percent of subjects with solicited adverse events by dosage group and time interval as well as overall.

Summary tables of solicited adverse events by severity and maximal severity will be created. Summary tables showing the occurrence of any local or systemic solicited adverse event will also be created.

The solicited local adverse events include these evaluations at the injection site: erythema, induration, swelling and pain. For erythema, induration and swelling recorded originally as diameters (mm), these categories will be used to summarize the data: None (0 mm), Grade 0 (<25 mm), Any (>=25 mm) with subcategories for Mild (25-50 mm), Moderate (51-100 mm) and Severe (>100 mm).

In the case of systemic AEs, for grades 1 to 3 (i.e., Mild to Severe), refer to Appendix B in the protocol. Grade 4 (Potentially Life Threatening) will be defined as follows (see also Appendix 3):

- Fever: >40 C (>104 F)˚
- Chills: ER visit or hospitalization
- Loss of Appetite: ER visit or hospitalization
- Nausea: ER visit or hospitalization for hypotensive shock
- Vomiting: ER visit or hospitalization for hypotensive shock
- Diarrhea: ER visit or hospitalization
- Generalized Myalgia: ER visit or hospitalization
- Generalized Arthralgia: ER visit or hospitalization
- Headache: ER visit or hospitalization,
- Fatigue: ER visit or hospitalization,
- Generalized Rash, ER visit or hospitalization □Urticaria: ER visit or hospitalization.

Body temperature will be broken down by route of measurement according to the recommendations of the Brighton collaboration and will be summarized according to the 3 schemes described below:

- by 0.5 °C increments: <36.0, ≥36.0-<36.5, ≥36.5-<37.0, ≥37.0-<37.5, ≥37.5-<38.0, ≥38.0-<38.5, ≥38.5-<39.0, ≥39.0-<39.5, ≥39.5-<40.0, ≥40.0°C
- by 1.0 °C increments: <36.0, ≥36.0-<37.0, ≥37.0-<38.0, ≥ 38.0-<39.0, ≥39.0-<40, ≥40°C

- <38.0, ≥38.0 °C

Fever, defined as a body temperature of ≥38°C irrespective of route of measurement, will be considered a systemic adverse event.

The analyses will encompass summaries of the data on five levels:

1. Daily reports of subjects with solicited adverse events.
2. Time of first onset of solicited adverse events (excluding 30 min post-vaccination).
3. Solicited adverse events, maximum event severity by event and time interval.
4. Number of days with solicited adverse events.
5. Solicited adverse events and indicators of solicited adverse events, occurrence of at least one event by category (local, systemic) and time interval.

For each of the time intervals presented in the summaries, only subjects with at least one plausible observation for the solicited adverse events will be included.

Level 1: Daily reports of solicited adverse event

For each time interval, only subjects with at least one plausible observation for the solicited adverse event will be included in the analysis. For each time interval, the number and percent of subjects will be presented by dosage group, solicited adverse event and overall.

Level 2: Time of first onset of solicited adverse events

The **time of first onset** of a solicited adverse event experienced by each subject is the time point at which the event first occurred. For erythema, induration and swelling, a threshold of ≥ 25 mm will be used. The summary will provide the frequencies and percentages of subjects with first onset of each solicited adverse events by dosage group and time point.

For each dosage group, the first onset of the adverse event will be used for each subject.

Level 3: Solicited adverse events, maximum event severity by event and interval

The **maximum event severity** will be defined if there is at least one plausible observation within the time interval. Each subject's data will be aggregated across the time intervals and summarized according to the maximal severity observed for each adverse event,

followed by a summary across subjects for each dosage group. Subjects without any solicited adverse event data in the interval will be excluded from the analysis.

Level 4: Number of days with solicited adverse events

The number of days with the adverse event is defined irrespective of severity. This means at least 'mild' solicited adverse event that are assessed qualitatively and ≥ 25 mm for erythema, induration and swelling. If a solicited adverse event continues beyond day 14 the period after day 14 is added.

The frequency distribution of the number of days will be provided in a summary table by dosage group and adverse event.

Level 5: Solicited adverse events, occurrence of at least one event by category (local, systemic) and interval.

The **occurrence of at least one solicited adverse event** is defined as "any" for a subject who reports greater than "Grade 0" (≥25 mm for erythema, swelling and induration) for the respective event and "Grade 0" otherwise. The occurrence of at least one solicited adverse event (i.e., none versus any) will be summarized by category (i.e., local, systemic, any), by dosage group, and by time interval.

Medications to treat or prevent pain or fever will be summarized by frequencies and percentages of subjects reporting use of the medications by interval: 30 min, Days 1-4 (without 30 min), Days 5-8, Days 1-8 (without 30 min), Day 8-14, Days 1-14 (without 30 min).

13.3 Unsolicited Adverse Events

All the unsolicited adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, will be recorded.

The original verbatim terms used by investigators to identify adverse events in the Case Report Forms (CRFs) will be mapped to preferred terms using the MedDRA dictionary. The unsolicited adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized by dosage group, according to system organ class and preferred term within system organ class. When an unsolicited adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the dosage group will be counted.

Only treatment-emergent adverse events will be analyzed, i.e., excluding those after a subject has given informed consent but before vaccination. The selection of unsolicited adverse events and the assignment to time intervals (Days 1-14 after vaccination, and from Day 15 post vaccination until study termination) will be done by day of onset and not by days ongoing/persisting.

The analysis of unsolicited adverse events comprises the following categories:

- Any unsolicited adverse event.
- Possibly or probably related unsolicited adverse events.
- Unsolicited adverse events leading to death.
- Serious adverse events.
- Possibly or probably related serious adverse event.
- Unsolicited adverse events leading to premature withdrawal from study.
- Medically attended adverse events.
- Adverse events of special interest (AESI).
- New onset of chronic disease (NOCD).

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

13.4 Combined Solicited and Unsolicited Adverse Events

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events will be coded by MedDRA. For clintrial.gov posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced. A further differentiation of combined adverse events according to seriousness, severity, or relationship is not possible.

13.5 Clinical Safety Laboratory Investigations

Baseline will be defined as the last non-missing assessment prior to vaccination.

Clinical safety laboratory values, and change-from-baseline values (baseline to 24 hours, to Day 8 and to Day 29), will be summarized (mean, standard deviation, median, minimum, and maximum) at each time-point of assessment, by dosage group, for the subset of subjects in the Safety Set with available laboratory data.

The frequencies of subjects with clinical laboratory values below, within, or above normal ranges will be tabulated for each clinical laboratory variable by dosage group and time-point of assessment (3 x 3 shift tables).

The percentages of subjects that show a 'range change abnormal high' (RCAH) or a 'range change abnormal low' (RCAL) are to be tabulated for each clinical laboratory variable by dosage group and time point of assessment. A RCAH is a laboratory value that is low or normal at baseline but high post-baseline. A RCAL is a laboratory value that is normal or high at baseline but low post-baseline.

Laboratory values will also be classified and tabulated according to Center for Biologics Evaluation, Research and Review (CBER) toxicity criteria (CBER 2007b). Refer to appendices C, D and E for the toxicity scales (grades 1 to 4) for laboratory abnormalities of the clinical chemistry, hematology and urine tests respectively.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges, toxicity grade, and assessment of clinical significance.

For subjects presenting at least one clinically significant value, an additional listing will be provided of all laboratory results by vaccine group, by subject, and by relevant parameter. Clinical significance assessed by the investigator will be presented.

13.6 Concomitant Medication

The frequencies and percentages of subjects reporting concomitant medications will be tabulated overall and by dosage group. Medications (generic drug name) will be coded using the WHODRUG dictionary (section 8.7.5 defines prior and concomitant medications).

14. INTERIM ANALYSIS

14.1 Interim Analysis

A safety and immunogenicity interim analysis for the selection of an LHD153R adjuvant dosage will be performed based on the data collected through Day 29 from subjects enrolled in all cohorts. This analysis will be performed by personnel not involved in study decisions. The results will be unblinded at the group level thereby preserving the blind for individual subjects. No adjustment to the overall alpha will be performed as the data collected subsequent to this analysis involve secondary and exploratory endpoints.

The interim analysis is to be considered final with regards to the Immunogenicity and Safety Tables up to Day 29.

14.1.1 Futility Analysis

Not applicable.

15. DATA MONITORING COMMITTEES

An independent DMC will be implemented to review safety data during scheduled periodic reviews. The DMC will review safety data collected until Day 14, as described in the DMC charter, after enrollment of the first 5 subjects in each cohort, before proceeding with enrollment of the remaining 15 subjects in each cohort.

In addition, enrollment of the first 5 subjects of the next cohort will only proceed after the Day 14 safety results of the first 5 subjects of the previous cohort have been reviewed. Furthermore, all available Day 14 and Day 29 safety results will be included in DMC reviews between the different enrollment stages.

16. PEER REVIEW

Analyses/Outputs requiring statistical peer review correspond usually to the analyses of the primary and secondary objectives, and data conversion programs. Peer review of these analyses should be performed in accordance with the applicable procedures for validation of SAS programs used in clinical data analysis.

These analyses will be peer reviewed by a biostatistician independent from the study:

- Primary safety analysis.
- Primary immunogenicity analyses.
- Secondary immunogenicity analyses.
- Statistical models.

Programming will be validated by an independent programmer. Statistical models and populations employed will be checked by an independent biostatistician.

17. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

For the complete list of tables, listings and figures, please refer to the Table of Contents (TOC) stored in [Enterprise/eTMF Repository/V132_01EXP/Cluster Documents/Statistical analysis/Statistical analysis Plan.]

These names will be used in the tables and listings for the vaccine groups:

Vaccine Group	Table Column Titles
A	MenC
B	LHD153R 12.5
C	LHD153R 25
D	LHD153R 50
E	LHD153R 100

Columns headings can be split after the plus sign.

In all tables, listings and figures, vaccine groups will be labeled as “MenC”, “LHD153R 12.5”, “LHD153R 25.0”, “LHD153R 50.0” and “LHD153R 100.0”.

18. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

All TLFs will include this header:

GSK	Vaccine: LHD153R and MenC
Final Report: Study V132_01EXP	Single Dose, Healthy Adults

Since all TLFs will be produced using SAS®, the output actually generated may slightly differ from the mock-ups presented in the study specific Mock-up catalogue.

19. REFERENCES

Nauta J. *Statistics in Clinical Vaccine Trials*. 2010. Heidelberg: Springer.

U.S. Department of Health and Human Services, Food and Drug Administration, CBER (2007): *Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*

Clopper CJ, Pearson ES. *The use of confidential or fiducial limits illustrated in the case of the binomial*. Biometrika 1934; 26:404-413.

Miettinen O., Nurminen M. *Comparative analysis of two rates. Statistics in Medicine* 1985; 4(2):213-226.

APPENDIX 1: TABLES, LISTINGS AND FIGURES

A table of contents and example shells for the tables, listings and figures to be provided will be given in a separate document.

APPENDIX 2: GRADING SCALES FOR SOLICITED LOCAL ADVERSE EVENTS*

(Adapted from CBER 2007b)

Adverse event Following Administration of Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	present but does not interfere with activity	interferes with activity	prevents daily activity
Induration / Swelling / Erythema	25 – 50 mm	51 – 100 mm	> 100 mm

*Adapted from CBER 2007 to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. This toxicity grading scale is a Novartis standard that is used for patient reporting.

Grade 4 (Potentially life-threatening):

- Pain: Emergency room (ER) visit or hospitalization.
- Tenderness: ER visit or hospitalization.
- Erythema/Redness: Necrosis or exfoliative dermatitis.
- Induration/Swelling: Necrosis.

APPENDIX 3: GRADING SCALES FOR SOLICITED SYSTEMIC ADVERSE EVENTS*

(Adapted from CBER 2007b)

Systemic Adverse event		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	**°C**	38.0 – 38.4	38.5 – 38.9	39.0 – 40
	°F	100.4 – 101.1	101.2 - 102	102.1 - 104
Chills		present but does not interfere with activity	interferes with activity	prevents daily activity

Loss of Appetite	Loss of appetite without decreased oral intake	decreased oral intake without weight loss	decreased oral intake with weight loss
Nausea	Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal to no oral intake
Vomiting	1-2 episodes/24 hours	>2 episodes/24 hours	requires outpatient hydratation
Diarrhea	2-3 loose stools /24 hours	4-5 loose stools /24 hours	6 or more watery stools /24 hours or requires outpatient IV hydration
Generalized Myalgia	present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Arthralgia	present but does not interfere with activity	interferes with activity	prevents daily activity
Headache	present but does not interfere with activity	interferes with activity	prevents daily activity
Fatigue	present but does not interfere with activity	interferes with activity	prevents daily activity
Generalized Rash	localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin
Urticaria	localized area of the skin (1 extremity only)	moderate area of the skin (2 or more body regions without whole body involvement)	most of the skin

*Adapted from CBER 2007b to enable ease of reporting by Subjects in the source documents for 'patient reported' solicited adverse events. This toxicity grading scale is a Novartis standard that is used for patient reporting. 'Grade 4' is not listed here but will be defined in the statistical analysis plan as necessary

Grade 4 (Potentially Life Threatening) will be defined as follows:

- Fever: >40℃ (>104 F)
- Chills: ER visit or hospitalization
- Loss of Appetite: ER visit or hospitalization
- Nausea: ER visit or hospitalization for hypotensive shock

- Vomiting: ER visit or hospitalization for hypotensive shock
- Diarrhea: ER visit or hospitalization
- Generalized Myalgia: ER visit or hospitalization
- Generalized Arthralgia: ER visit or hospitalization
- Headache: ER visit or hospitalization,
- Fatigue: ER visit or hospitalization,
- Generalized Rash, ER visit or hospitalization □Urticaria: ER visit or hospitalization.

APPENDIX 4: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (SERUM CLINICAL CHEMISTRY)

Serum*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)***
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

***The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value. "ULN" = the upper limit of the normal range.

APPENDIX 5: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (HEMATOLOGY)

Hematology*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)

Hemoglobin (Female) gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Platelets Decreased cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

APPENDIX 6: TOXICITY SCALES FOR LABORATORY ABNORMALITIES (URINE)

Urine*,**	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**Laboratory values that fall in the normal range may be assigned a category of "Grade 0."

Novartis

Document Approval Certificate /

PPD

The individuals listed have approved this document for implementation using an electronic signature in the
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STATISTICAL ANALYSIS PLAN ADDENDUM

Addendum Number 1

Study Title:	**A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)**
Study Number/Product:	V132_01EXP/LHD153R Adjuvant
Phase of Development:	Phase 1
Sponsor:	GlaxoSmithKline Biologicals
Plan Prepared by:	PPD
Version and Date:	Version 2.0: Date (06 Oct 17)
Reviewers:	PPD PPD PPD
Approvers:	Supervisory PPD Statistician CRDL Not PPD PPD PPD Applicable, CEPL SDL Medical Writer

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
$AlHO_3$	Aluminium Hydroxide
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASC	Antibody Secreting Cells
BTM	Blood Transcriptional Module
CD4	Cluster of Differentiation 4
cDNA	Complementary Deoxyribonucleic Acid
CI	Confidence Interval
cmDC	Conventional Myeloid Dendritic Cells
CMo	Classical Monocytes
CRM_{197}	Cross Reacting Material 197
CRP	C-Reactive Protein
CSF	Colony Stimulating Factor
DC	Dendritic Cells
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immunospot
FACS	Fluorescence-Activated Cell Sorting
FAS	Full Analysis Set
FDR	False Discovery Rate
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GMC	Geometric Mean Concentration
HL	Hodges Lehmann
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IM	Intra-Muscular
IMo	Intermediate Monocytes
IP-10	IFN-Γ – Inducible 10-Kilodalton (Kda) Protein
kDa	Kilodalton
LC-MS/MS	Liquid Chromatography-Mass Spectrometry
LLQ	Lower Limit of Quantitation
LOD	Limit of Detection
MBC	Memory B Cells
MCP	Monocyte Chemo-Attractant Protein
MDC	Macrophage-Derived Chemokine

MenC Meningococcal Type C
MFI Median Flourescence Intensity MIP
Macrophage Inflammatory Protein mRNA
Messenger Ribonucleic Acid NCMo Non-
Classical Monocytes NK Natural Killer Cells
PBMC Peripheral Blood Monoculear Cells
pDC Plasmacytoid Dendritic Cells
Ps Polysaccharide RNA Ribonucleic
Acid
SAP Statistical Analysis Plan SAS Statistical
Analysis System
SBA Serum Bactericidal Assay SP Statistical
Programmer
TARC Thymus And Activation-Regulated Chemokine
Tfh T Follicular Helper Cells
Th T-Helper
TLF Table, Listing and Figure TNF Tumor
Necrosis Factor
TOC Table of Contents
VEGF-A Vascular Endothelial Growth Factor - A

1. BACKGROUND AND RATIONALE

This is a Phase 1, randomized, observer blind, active-controlled, adjuvant dosage-escalation study performed at a single center. In total, approximately 80 healthy adults (18-45 years of age) will be enrolled in the study.

Table 1 describes the different enrollment groups, cohorts, and vaccine formulations. **Table 1 Subjects Randomized per Cohort and Treatment Dose Group**

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20
	D	16	10	1	50	0.5 mL	

4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}, MenC = Meningococcal Type C.

A comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. These objectives are:

1. To evaluate the systemic exposure of LHD153 at several early time-points after intramuscular (IM) injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM_{197} protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM_{197} and to evaluate the frequency and quality of CRM_{197} specific T cells induced by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R compared to aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.
5. To evaluate the functionality of MenC-specific antibodies to fix complement, promote antibody-dependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro at Day 1 (baseline), Day 8, Day 29, and Day 181. (Protocol amended: 19 June 2017)

Please see section 7.4 of the protocol for more details on the exploratory measurements.

The exploratory endpoints in order of priority are:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by liquid chromatography-mass spectrometry (LC-MS/MS).
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by flow cytometry analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.
- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by Enzyme-Linked Immunospot (ELISPOT).

- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by ribonucleic acid (RNA) microarray analysis.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.
- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin complementary deoxyribonucleic acid (cDNA) sequencing.
- Functionality of MenC-specific antibodies to fix complement, promote antibodydependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro at Day 1 (baseline), Day 8, Day 29, and Day 181.
- Integrated analysis to identify biomarkers predictive of immunogenicity and/or explanatory of the mode of action of LHD153.

The purpose of this statistical analysis plan addendum is to *a priori* describe the planned analyses for these exploratory objectives.

Please note that the diversity of MenC polysaccharide-specific B-cell repertoire will not be determined and thus, the analyses related to this endpoint should be ignored. As this endpoint

is still listed in the protocol; the description of the originally planned analyses will not be removed from this document

2. STATISTICAL CONSIDERATIONS

2.1 General

Because a maximum of 16 subjects per dosage group will participate in the exploratory endpoint analyses, sample sizes of 12 and 16 were considered. The table below provides the probability to observe at least 1 subject with an event for several presumed true frequencies within an individual dosage group (MenC-CRM_{197} or MenC-CRM_{197} plus an assigned-level of LHD153R/$Al(OH)_3$).

Table 2 Probability of Observing at Least 1 Subject with an Event

Frequency of Event	Probability to Observe at Least 1 Subject with an Event Given N	
	N=12	N=16
0.001	0.0119	0.0159
0.005	0.0584	0.0771
0.01	0.1136	0.1485
0.025	0.2620	0.3331
0.05	0.4596	0.5599
0.10	0.7176	0.8147
0.15	0.8577	0.9257
0.20	0.9313	0.9718
0.30	0.9862	0.9967
0.40	0.9978	0.9997

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers or concentrations will be log_{10}-transformed.

Concentrations and titers below the lower limit of quantitation (LLQ; limit of detection, LOD) will be set to half the LLQ for inclusion in summaries requiring a value.

Many analyses will be performed using SAS® Software version 9.1 or higher. Other software packages such as those available in R may also be used to perform analyses. Specifically, R version 3.1 or higher will be used; and, functionality will be extended through the use of the Bioconductor, and other packages (e.g., GO, plotrix, etc.).

2.2 Exploratory Endpoint Analysis Population (Exploratory FAS)

To be included in the exploratory endpoint analyses, a subject must have signed a separate informed consent form. Thus, the number of subjects included in the exploratory endpoint

analyses may differ from those included in the primary and secondary immunogenicity analyses.

Additionally, to be included in a specific analysis, a result must be valid and evaluable. Examples of reasons for not being valid and evaluable are:

- Sample received hemolyzed
- Insufficient sample for analysis based on volume, quantity and quality
- Assay controls not within expected parameters (ie, assay invalid)

Analyses will be performed in the Exploratory Full Analysis Set (FAS) unless specified otherwise.

The frequencies and percentages of subjects in the exploratory full analysis set, with available data at each blood draw time point, and reasons for exclusion will be presented overall and by dosage group ("MenC", "LHD153R 12.5", "LHD153R 25.0", "LHD153R 50.0" and "LHD153R 100.0").

2.3 Demographics

Age, height, weight, and body mass index at enrollment will be summarized by reporting the mean, standard deviation, median, minimum and maximum, and will be calculated by dosage group and overall for the Exploratory FAS.

The frequencies and percentages of subjects by sex and race, will be presented by dosage group and overall for the Exploratory FAS.

2.4 Laboratory Parameters

C-reactive protein (CRP) will be measured from serum samples obtained during screening (Day -28 to Day -3, at baseline (prior to vaccination), 24 hours after vaccination, on Day 8, and on Day 29.

CRP will be summarized by reporting the mean, standard deviation, median, minimum and maximum, and will be calculated by dosage group and overall for the Exploratory FAS.

2.5 Adjuvant Levels: LHD153 Systemic Exposure

Objective: The primary exploratory objective is to evaluate the extent of systemic exposure of LHD153 after intramuscular (IM) administration of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R).

Systemic exposure of LHD153 will be measured from plasma samples collected at 7 time points: baseline (prior to vaccination), 1, 2, 4, and 8 hours after vaccination on Day 1, 24 hours after vaccination, and on Day 4 (72 hours after vaccination).

There is no formal statistical hypothesis associated with this objective. However, based on pre-clinical studies in rats and dogs, there should be little or no systemic exposure of LHD153 after IM administration of Aluminium Hydroxide/LHD153R and no LHD153 at Day 4.

Endpoint(s):

a. The number and percentage of subjects with evaluable concentrations at or above the lower limit of quantitation (LLQ; LOD) as well as below the LLQ for each blood sampling time point.

b. LHD153 geometric mean concentrations (GMCs) for each blood sampling time point. Values below the LLQ will be arbitrarily set to one-half the LLQ for the calculation of GMCs.

Analysis Method:

a. The percentage of subjects above and below LLQ and associated two-sided 95% Clopper-Pearson CIs (Clopper, 1934) will be summarized by dosage group for each blood sampling time point.

b. LHD153 GMCs will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

c. Difference in percentage of subjects above the LLQ between the LHD153R dosage groups and the MenC group; and, associated two-sided 95% CIs for the difference.

Criteria for Assessment: An initial assessment of little to no systemic exposure will be based on the number of subjects above the LLQ. If at least one subject has an evaluable level above the LLQ, then it will be concluded that LHD153 does not have little or no systemic exposure.

Possible additional exploratory analyses: If concentrations of LHD153 are observed, then the difference in GMCs between the LHD153R dosage groups and the MenC group; and, associated two-sided 95% CIs for the difference will be summarized.

Also, the relationship between LHD153 concentrations and solicited adverse events (AEs) may be performed by plotting the severity of the event (x-axis) against the concentration of LHD153 (y-axis) with vaccine dosage groups differentiated by symbol, color or grouping. A

similar graphical display will be produced to describe the relationship between LHD153 concentrations and CRP levels.

Additionally, if the number of observations with measurable levels permit, then a pharmacokinetic analysis may be performed and reported.

2.6 CRM-Specific CD4 T cell Profile

Objective: To explore the baseline T cell mediated immunity to CRM_{197} and to evaluate the frequency and quality (T helper, activation, and memory profiles) of CRM_{197} specific T cells induced by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R compared to aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine at Day 8 and Day 29.

The frequency of T cells specific for the CRM_{197} protein will be determined by FACS analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations. Blood samples will be collected at 3 time points: at baseline (Day 1, pre-vaccination) and at Day 8 and Day 29 after vaccination.

The expectation is that there will be an increase in cytokine producing T cells with LHD153, in particular in the IFN-γ producing T cells. Table 3 lists the markers and combinations of interest for this study.

Table 3 Markers of T Cell Read-outs in PBMCs

CMI (exploratory endpoints)	List of markers and combinations[1]	
Functional markers (frequency in % of total CD4+ T-cells)	**Markers:**	CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17
	Combinations:	at least one marker (any immune marker) among CD3+CD4+CD45RA- cells
T helper type 0 (Th0) (number per million of total CD4+ Tcells)	**Markers:**	CD40L, IL-2, TNF
	Combinations:	CD40L+ IL-2-TNF- CD40L+IL-2+TNF- CD40L+IL-2-TNF+ CD40L+IL-2+TNF+ among CD3+CD4+CD45RA- cells
T helper type 1 (Th1) (number per million of total CD4+ Tcells)	**Markers:**	CD40L, IFN-γ, IL-2, TNF
	Combinations:	CD40L+IFN-γ+IL-2-TNF- CD40L+IFN-γ+IL-2+TNF- CD40L+IFN-γ+IL-2-TNF+ CD40L+IFN-γ+IL-2+TNF+ among CD3+CD4+CD45RA- cells
T helper type 2 (Th2) (number per million of total CD4+ Tcells)	**Markers:**	CD40L, IL-13, IL-2, TNF
	Combinations:	CD40L+IL-13+IL-2-TNF- CD40L+IL-13+IL-2+TNF- CD40L+IL-13+IL-2-TNF+ CD40L+IL-13+IL-2+TNF+ among CD3+CD4+CD45RA- cells
T helper type 17 (Th17) (number per million of total CD4+ Tcells)	**Markers:**	CD40L, IL-17, IL-2, TNF, IFN-γ
	Combinations:	CD40L+IL-17+IL-2-TNF- IFN-γ− CD40L+IL-17+IL-2+TNF- IFN-γ− CD40L+IL-17+IL-2-TNF+ IFN-γ− CD40L+IL-17+IL-2-TNF-IFN-γ+ CD40L+IL-17+IL-2+TNF+IFN-γ− CD40L+IL-17+IL-2+TNF-IFN-γ+ CD40L+IL-17+IL-2-TNF+IFN-γ+ CD40L+IL-17+IL-2+TNF+IFN-γ+ among CD3+CD4+CD45RA- cells
T follicular helper cells (Tfh)(1) (number per million of total CD4+ T-cells)	**Markers:**	ICOS, CXCR5
	Combinations:	ICOS+CXCR5+ ICOS+CXCR5- ICOS-CXCR5+ ICOS-CXCR5- among CD3+CD4+ CD45RA-CD40L+IL-21+ cells

CMI (exploratory endpoints)	List of markers and combinations[1]	
T follicular helper cells (Tfh)(2) (number per million of total CD4+ T-cells)	**Markers:**	CD45RA, CXCR5, CXCR3, CCR6, ICOS, PD1
	Combinations:	CXCR3+CCR6-ICOS+PD1- CXCR3+CCR6-ICOS-PD1+ CXCR3-CCR6+ICOS+PD1- CXCR3-CCR6+ICOS-PD1+ CXCR3-CCR6-ICOS+PD1- CXCR3-CCR6-ICOS-PD1+ among CD3+CD4+CD45RA-CXCR5+ cells
Differentiation (frequency in % of antigen-specific CD4+ T-cells)	**Markers:**	CD40L, IL-2, IFN-γ, TNF, IL-17, IL-13, IL-21
	Combinations:	at least one marker (any immune marker) among CD4+: Naïve (CD45RA+CD27+CCR7+) TCM (CD45RA-CD27+CCR7+) TEM27+ (CD45RA-CD27+CCR7-) TEM27- (CD45RA-CD27-CCR7-) TEMRA (CD45RA+CD27- CCR7-)

1 For the different markers and combinations, the "CD3+" is omitted from the laboratory test description in the datasets.

Endpoints:

a. The number and percentage of subjects with CRM197-specific CD4+ T-cells at each blood sampling time point.

T-cell functionality

b. For each functional marker, the number of cells expressing the given marker at each blood sampling time point. The number of cells will be obtained by calculating the sum of the cytokine combinations for each subject first.

c. The number of cells expressing at least one functional marker (among CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21) expressed per million total CD4+ T cells at each blood sampling time point. The number of cells will be obtained by calculating the sum of the cytokine combinations for each subject first.

d. The number and percentage of subjects with a given polyfunctional CD4+ profile.

e. The number of CRM197-specific CD4+ T-cells, expressed per million of total CD4+ T cells, in each Th subset (Th0, Th1, Th2, Th17, Tfh). The number of cells will be obtained by calculating the sum of the cytokine combinations for each subject first.

T follicular helper cells

f. Number of CD4+CXCR5+ T-cells expressing chemokine receptors (CXCR3, CCR6) and activation markers (ICOS, PD1), expressed per million of PBMCs

Antigen-specific T follicular helper cells

g. Number of CRM197-specific CD4+ IL-21+ ICOS+ T-cells expressed per million of CD4+ T cells

h. Number of CRM197-specific CD4+ IL-21+ T-cells expressing activation markers (ICOS, CXCR5), expressed per million of CD4 T cells

T-cell differentiation

i. Number of CRM197-specific CD4+ T-cells expressing at least one functional marker (among CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21) in each differentiation subset (naïve, TCM, TEM27+, TEM27-, TEMRA), expressed per million of CD4+ T cells. Analysis Method:

a. The percentage of subjects with CRM197-specific CD4+ T-cells and associated twosided 95% Clopper-Pearson CIs will be summarized by vaccine dosage group for each blood sampling time point.

b. The number of cells (per million of total CD4+ T-cells) expressing at least one functional marker will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

c. The change from baseline in number of cells (per million of total CD4+ T-cells) expressing at least one functional marker will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

d. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of cells (per million of total CD4+ T-cells) expressing at least one functional marker and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

e. The number of cells (per million of total CD4+ T-cells) expressing a given marker will be summarized using medians and corresponding two-sided, 95% CIs around the

median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

f. The change from baseline in number of cells (per million of total CD4+ T-cells) expressing a given marker will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

g. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of cells (per million of total CD4+ T-cells) expressing a given marker and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

h. The percentage of subjects with a given polyfunctional CD4+ profiles will be tabulated and presented graphically by vaccine dosage group for each blood sampling time point.

i. The number of CRM197-specific CD4+ T-cells in each Th subset (Th0, Th1, Th2, Th17, Tfh) expressed per million of total CD4+ T cells will be tabulated and presented by vaccine dosage group for each blood sampling time point.

j. The change from baseline in number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each Th subset (Th0, Th1, Th2, Th17, Tfh) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

k. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each Th subset (Th0, Th1, Th2, Th17, Tfh) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

l. Number of CD4+CXCR5+ T-cells (per million PBMCs) expressing follicular markers (CXCR3, CCR6) and activation markers (ICOS, PD1) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

m. The change from baseline in number of CD4+ CXCR5+ T-cells (per million PBMCs) expressing follicular markers (CXCR3, CCR6) and activation markers (ICOS, PD1) will be calculated per subject and summarized using medians and corresponding twosided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

n. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CD4+ CXCR5+ T-cells (per million PBMCs) expressing

follicular markers (CXCR3, CCR6) and activation markers (ICOS, PD1) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

o. Number of CRM197-specific CD4+ IL-21+ ICOS+ T-cells (per million CD4+ T cells) will be calculated by adding the CXCR5+ and CXCR5- subpopulations for each subject, and summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

p. The change from baseline in number of CRM197-specific CD4+ IL-21+ ICOS+ T cells (per million CD4+ T cells) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

q. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ IL-21+ ICOS+ T-cells (per million CD4+ T cells) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

r. Number of CRM197-specific CD4+ IL-21+ T-cells (per million CD4+ T-cells) expressing activation markers (ICOS, CXCR5) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

s. The change from baseline in number of CRM197-specific CD4+ IL-21+ T-cells (per million CD4+ T cells) expressing activation markers (ICOS, CXCR5) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

t. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ IL-21+ T-cells (per million CD4+ T cells) expressing activation markers (ICOS, CXCR5) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

u. The number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each differentiation subset (naïve, TCM, TEM27+, TEM27-, TEMRA) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

v. The change from baseline in number CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each differentiation substet (naïve, TCM, TEM27+, TEM27-, TEMRA) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

w. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each differentiation subset (naïve, TCM, TEM27+, TEM27-, TEMRA) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

x. To test for differences in the proportion of expressing cells among the dose groups, a Kruskal-Wallis test will be performed for each cytokine/surface marker for each time point. If significant, then pairwise testing of the dose groups will be performed using the Hodges Lehmann (HL) approach which provides the median of the pairwise difference of the dose groups along with its 95% CI. The Kruskal-Wallis test will be repeated on the Day 8 and Day 29 values after adjusting for Day 1 baseline (i.e, Day 8 - Day 1 baseline and Day 29 - Day 1 baseline), followed by pairwise testing.

Graphical Displays: To better illustrate the differences between the dosage groups, the number of T cells expressing specific immune markers may be graphically displayed as a box plot or bar chart with the dosage groups differentiated by symbol, color, or grouping.

Criteria for Assessment: The impact of vaccination on frequency of T cell populations will be described by dosage group using the change from baseline in number of cells expressing specific immune markers.

a. The impact of LHD153R on frequency of T cell populations will be described using the differences between the LHD153R groups and the MenC control group.

b. To describe the impact of the dosage of LHD153R on frequency of T cell populations, the pairwise differences among the LHD153R groups will be used.

Possible additional exploratory analyses: The relationship between antibody response (ELISA and SBA; y-axis) and the T-cell percentages for selected cytokines/surface markers may be plotted differentiating the dose groups by symbol, color or grouping.

2.7 MenC Polysaccharide and CRM-specific B-cells

Objective: The objective is to assess the frequency of antigen specific B cells and long lasting memory B cells (MBCs) induced by LHD153R. The expectation is that there will be increases in the plasma and memory B-cells with LHD153R and that the increases will be dosage-dependent.

The frequency of B cells specific for MenC polysaccharide (Ps) and CRM_{197} will be determined by ELISPOT at Day 1 baseline (prior to vaccination), Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1 baseline), the peak of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Endpoints:

a. The frequency of circulating MenC Ps and CRM-specific plasmablasts at Day 8 (expressed as Antibody Secreting Cells (ASC) IgG+/million PBMC and Antibody Secreting Cells (ASC) IgM+/million PBMC)

b. The number and percentage of subjects with detectable frequencies of MenC Ps-MBC and CRM-MBC at Day 1, Day 29, and Day 181.

c. The frequency of circulating MenC Ps-MBC and CRM-MBC (expressed as percentage of antigen-specific MBC/Total IgG and antigen-specific MBC/Total IgM) at Day 1, Day 29, and Day 181.

d. Within subject fold change of circulating MenC PS-MBC and CRM-MBC from baseline Day 1 to Day 29 and to Day 181.

e. Within subject fold change of circulating MenC PS-MBC and CRM-MBC from Day 29 to Day 181.

Analysis Method:

a. The number of circulating IgG+ and IgM+ MenC Ps and CRM-specific plasmablasts at Day 8 (expressed as ASC/million PBMC) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

b. The percentage of subjects with detectable frequencies of IgG+ and IgM+ MenC PsMBC and CRM-MBC will be summarized using two-sided 95% Clopper-Pearson CIs by vaccine dosage group for samples taken at days 1, 29 and 181.

c. The frequencies of circulating IgG+ and IgM+ MenC Ps-MBC and CRM-MBC will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for samples taken at days 1, 29 and 181. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

d. When baseline day 1 values are non-zero, the fold changes of circulating MBC between Day 29 and baseline Day 1, and Day 181 and baseline Day 1, will be summarized using medians and corresponding two-sided, 95% CIs around the median

by vaccine dosage group. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

Graphical Displays:

a. The number of IgG+ and IgM+ MenC Ps and CRM-specific plasmablasts induced by each dosage of LHD153R at Day 8 will be explored by plotting the median number of IgG+ and IgM+ plasmablasts per million PBMC (y-axis) against LHD153 dose (xaxis) differentiating each dosage group by symbol or color.

b. A graphical display will be generated for the Day 1, Day 29 and Day 181 median frequencies of IgG+ and IgM+ MenC Ps and CRM-specific memory B-cells of different vaccination groups differentiating each dosage group by symbol, color or line type.

Criteria for Assessment:

a. To test for differences in the number of circulating IgG+ and IgM+ MenC Ps and CRM-specific plasmablasts at Day 8, the Kruskal-Wallis test will be performed. If the overall test is significant, then pairwise testing of the dose groups will be performed using the HL approach which provides the median of the pairwise difference of the dose groups along with its 95% CI.

b. To test for the percentage of subjects with detectable frequencies of MenC Ps-MBC and CRM-MBC at days 1, 29 and 181, a test will be performed at each time point. If significant, then pairwise comparisons of the dose groups will be performed with no adjustment for multiplicity.

c. To test for the frequencies of circulating MenC Ps-MBC and CRM-MBC at days 1, 29 and 181, the Kruskal-Wallis test will be performed. If the overall test is significant, then pairwise testing of the dose groups will be performed using the HL approach which provides the median of the pairwise difference of the dose groups along with its 95% CI. The Kruskal-Wallis test will be repeated on the fold changes, followed by pairwise testing.

d. To evaluate differences among the dosage groups in the eCDFs of frequencies of IgG+ and IgM+ MenC Ps and CRM-specific memory B-cells, the Kolmogorov-Smirnov test will be performed (Brittain, 1984 and 1987). If significant, then pairwise comparisons of the eCDFs will be performed.

Possible additional exploratory analyses: The relationship between antibody response (ELISA and SBA; y-axis) and the B-cell percentages for selected markers may be plotted differentiating the dose groups by symbol, color or grouping. Additionally, the Spearman correlation coefficients will be provided.

2.8 Early Biomarkers of Safety and Innate Immune Response

2.8.1 Microarrays

Objective: The objective is to evaluate the vaccine-induced modulation of transcriptome responses in blood transcriptional modules (BTMs), specifically the interferon and inflammatory BTMs.

The vaccine-induced modulation of transcriptome responses will be evaluated on whole blood samples collected at 5 time points: Day 1 (pre-vaccination and 6h after vaccination), Day 2 (24h after vaccination), Day 4 and Day 8. Base analysis will be performed using sets of coordinately regulated genes, or BTMs), as defined by Obermoser, G. *et al.* (2013).

Previously conducted analyses in a non-human primate model have shown that the inclusion of LDH153R in the formulation produces a significant upregulation of 3 BTMs (M1.2, M3.4 and M5.12) containing interferon stimulated genes at 24 hours after vaccine administration. Furthermore, the addition of LDH153R did not upregulate any of the BTMs containing proinflammatory genes (M3.2, M4.2, M4.6, M4.13, M5.1, M5.7 and M7.1).

Specifically, the aim is to show that the LHD153R adjuvant significantly upregulates the response of the interferon BTMs (M1.2, M3.4 and M5.12) but not the pro-inflammatory BTMs (M3.2, M4.2, M4.6, M4.13, M5.1, M5.7 and M7.1) in at least one LHD153R dosage group compared to the MenC control group at 24 hours post-vaccination.

Endpoints:

Vaccine Induced Modulation of Interferon and Pro-Inflammatory Transcriptional Modules

a. The module-specific geometric mean response for each blood sampling time point. For each of the 10 BTMs (3 interferon, 7 pro-inflammatory), the subject level module response will be determined by computing the average log2 fluorescence intensity of genes belonging to the module at each blood sampling time point.

b. The module-specific geometric mean fold change from baseline Day 1 to each postvaccination sampling time point. For each BTM, the subject-level fold change from pre-vaccination to each post-vaccination time point will be computed (ie, postvaccination value / pre-vaccination value). Module level responses will be computed by averaging the log2 scaled, subject-level fold-changes for each dosage group and blood sampling time point.

Vaccine Induced Transcriptome Responses

c. Gene level fold change from baseline in transcriptome response for each gene at each post-vaccination blood sampling time point. In order to reduce the false discovery rate, the

initial set of genes will be reduced by applying a non-specific filtering to the pooled samples coming from all available dosage groups, including the control group. Only those genes showing a between subject interquartile range, in the log2transformed fold change from baseline, ≥ 0.5 will be retained. Analysis Methods:

a. To evaluate the LHD153R ability to upregulate the expression level of a given BTM at a specified time point the following hypothesis needs to be tested for each BTM:
H_0: $(\mu_{LHD153-12.5} \leq \mu_{MenC})$ and $(\mu_{LHD153-25} \leq \mu_{MenC})$ and $(\mu_{LHD153-50} \leq \mu_{MenC})$
and $(\mu_{LHD153-100} \leq \mu_{MenC})$

H_a: $(\mu_{LHD153-12.5} > \mu_{MenC})$ or $(\mu_{LHD153-25} > \mu_{MenC})$ or $(\mu_{LHD153-50} > \mu_{MenC})$
or $(\mu_{LHD153-100} > \mu_{MenC})$

The module response, fold change from baseline at the 24 hour time point, will be analyzed using analysis of variance (ANOVA) with the module response as the dependent variable and a fixed effect for dosage group. The adjusted (model-based) geometric mean fold changes, adjusted ratios of geometric mean responses between vaccine dosage groups and the corresponding two-sided, 95%, confidence intervals will be calculated based on this model. Should the data violate the normality assumption, then a Kruskal-Wallis test will be performed instead, followed by pairwise testing of the dosage groups in the same manner as previously described.

All 10 BTMs will be evaluated and the p-values adjusted using the BenjaminiHochberg False Discovery Rate (FDR) control procedure. BTMs with an adjusted pvalue ≤ 0.05 will be examined further.

b. The module-specific geometric mean fold changes will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

c. To identify transcriptional signatures which are correlated to serum bactericidal assay (SBA) titers, Spearman's rank correlation coefficients will be determined for each gene using the log2 gene-level fold change from baseline and the log2 transformed SBA titer at each post-vaccination time point. Genes will be ranked from largest magnitude to smallest magnitude of the correlation coefficient (ie, by the absolute value of the coefficient) and presented in rank order with the upper 10-th percentile identified for each post-vaccination time point.

Graphical Displays: The upregulation, or lack thereof, will be presented graphically for the modules being examined by dosage group.

Criteria for Assessment: This exploratory endpoint will be verified if the overall null hypotheses are rejected for at least 2 of the 3 interferon BTMs (M1.2, M3.4 and M5.12) and rejected for at most 2 of the 7 pro-inflammatory BTMs (M3.2, M4.2, M4.6, M4.13, M5.1, M5.7 and M7.1), with significance level $\alpha \leq 0.05$ (after correction for multiple testing), at the 24 hour post-vaccination time point.

As a hypothesis generating exercise, the same procedure will also be used for the other time points [Day 1 (6 hours), Day 4 and Day 8], in order to evaluate LHD153R effects at time points different from the 24 hours.

For innate transcriptome response predictive of hSBA, genes with a correlation coefficient above the 90-th percentile (as defined earlier) will be considered the most correlated genes, either positively or negatively. Possible additional exploratory analyses:

Additionally, the relationship between significant BTMs and solicited AEs may be evaluated by plotting the fold-change (y-axis) for subjects with a given severity of the solicited adverse event (x-axis) with vaccine group differentiated by symbol, color or grouping.

Functional enrichment analysis for those genes identified as correlated, or inversely correlated, to hSBA titers will be performed by testing all gene ontology terms and testing whether any category terms are over represented using the hypergeometric test.

2.8.2 Cytokines and Chemokines

Objective: To evaluate biomarkers that may be predictive of safety and/ or innate immune activation.

The vaccine-induced production of inflammatory cytokines and chemokines will be evaluated on serum samples using a commercially available multiplex enzyme-linked immunosorbent assay (ELISA) for a panel of pro-inflammatory cytokines and chemokines. Cytokines and chemokines will be measured from serum collected at 5 time points: Day 1 (pre-vaccination and 6h after vaccination), 24h after vaccination (Day 2), Day 4 and Day 8.

There is no formal statistical hypothesis associated with this objective. However, based on pre-clinical results in non-human primates, inducible 10-kilodalton (kDa) protein (IP-10) concentrations at early time points may be detected at higher levels compared to baseline values of each subject. Further, different levels of serum chemokines and cytokines are expected in human healthy donors (Biancotto, et al, 2013). The kinetics of soluble mediators will be evaluated from baseline to early time points (up to Day 8) in serum. In each subject, cytokine and chemokine concentrations measured at different time points after vaccination will be compared to their baseline levels.

Table 4 List of Cytokines and Chemokines in Plasma by Multiplex (pg/mL)

Assays (units)	List of soluble mediators or markers of cellular effectors
Chemokines indicating activation of immune response which stimulate cell recruitment	
Eotaxin, Eotaxin-3 MCP-1; MCP-4 MDC MIP-1α; MIP-1β TARC IP-10 IL-8	
Cytokines indicating a general activation of the immune system	
	GM-CSF IL-1α; IL-2; IL-5; IL-7; IL-12/IL-23p40; IL-15; IL-16 TNF- β VEGF-A
Proinflammatory c	**tokines indicating activation of the innate immune system**
	IFN-γ IL-1β; IL-4; IL-6; IL-8; IL-10; IL-12 p70; IL-13; IL-17A TNF-α

MCP-1 = monocyte chemo-attractant protein – 1; MIP-1α = macrophage inflammatory protein – 1α; MDC = macrophage-derived chemokine; TARC = thymus and activation-regulated chemokine; IP-10 = inducible 10kilodalton (kDa) protein; IL-8 = interleukin – 8; IFN-γ = interferon gamma; GM-CSF = granulocyte macrophage colony stimulating factor; TNF-β = tumor necrosis factor – beta; VEGF-A = vascular endothelial growth factor – A.

Endpoint(s):

a. The number and percentage of subjects with evaluable concentrations at or above the lower limit of quantitation (LLQ; LOD), as well as below the LLQ for each cytokine/chemokine for each dosage group and blood sampling time point.

b. Cytokine and chemokine geometric mean concentrations for each dosage group and blood sampling time point.

c. Subject level fold change from baseline in the concentration for each cytokine/chemokine for each post-vaccination blood sampling time point.

Analysis Method:

a. The percentage of subjects above and below LLQ and associated two-sided 95% Clopper-Pearson CIs will be summarized by dosage group for each cytokine/chemokine at each blood sampling time point.

b. Cytokine and chemokine geometric mean concentrations will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

c. Change from baseline in the concentration of each cytokine and chemokine (subjectlevel fold change) will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by vaccine dosage group for each post-vaccination blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

Graphical Displays: For each cytokine or chemokine with detectable levels, plot the mean concentration level over time for each group, indicating each dosage group with a symbol, color, or line type.

Additionally, for each cytokine or chemokine with detectable levels, plot the cumulative percentage of subjects with at least an *n*-fold change over baseline (n ranges from the minimum to maximum fold change across all time points) for each time point, indicating each dosage group with a symbol, color or line type.

Criteria for Assessment:

a. Geometric mean fold rises and corresponding CIs will be used to determine which cytokines and chemokines have higher concentrations as compared to baseline concentrations.

b. To evaluate differences in geometric mean ratios (GMRs) among the dosage groups, a Kruskal-Wallis test will be performed for each time point. If significant, then pairwise comparisons of the dosage groups will be performed with no adjustment for multiple comparisons. This is to identify any chemokines or cytokines that may be predictive of safety and/or innate immune activation.

c. To evaluate differences in proportions of subjects with at least a two-fold change from baseline among the dosage groups, a test will be performed for each postvaccination time point. If significant, then pairwise comparisons of the dosage groups will be performed with no adjustment for multiple comparisons.

d. To evaluate differences among the dosage groups in the empirical cumulative distribution functions (eCDFs) of the proportions of subjects with at least an *n*-fold change over baseline, the Kolmogorov-Smirnov test will be performed. If significant,

then pairwise comparisons of the eCDFs will be performed using the two-sample Kolmogorov-Smirnov test.

Possible additional exploratory analyses:

If the number of observations with measurable levels permit, the kinetics of the soluble mediator(s) will be evaluated from baseline up to day 8 post-vaccination in serum.

Should LHD153 have detectable levels also, a graphical representation of the correlation between the any cytokine/chemokine with measurable levels and the LHD153 concentration will be generated with dosage group differentiated by symbol, color or line type.

If differences or trends in solicited AEs between vaccine dosage groups are observed, then the relationship between chemokine/cytokine concentrations and solicited AEs at a given time point may be evaluated by plotting the concentrations of the chemokine/cytokine (yaxis) with the severity of the solicited adverse event (x-axis) with vaccine dosage group differentiated by symbol, color or grouping.

2.8.3 Activation Status of Myeloid and Lymphoid Cells

Objective: The objective is to understand the impact of LHD153R adjuvant on the frequency and activation status of myeloid and lymphoid cells induced by vaccination. Peripheral blood mononuclear cells (PBMCs) will be obtained from blood obtained at baseline (prior to vaccination), 24 hours after vaccination, on Day 4 (72 hours after vaccination) and on Day 8.

Table 5 List of Markers of Cellular Effectors – Innate Cells in PBMCs by Flow Cytometry

Myeloid cells		
	Phenotyping (number of cells per million PBMCs)	
	Classical monocytes (CMo):	Lin- HLADR+ CD14++ CD16-
	Intermediate monocytes (IMo):	Lin- HLADR+ CD14+ CD16+
	Non-classical monocytes (NCMo):	Lin- HLADR+ CD14dim CD16+
	Conventional myeloid DC (cmDC):	Lin- HLADR+ CD14- CD11c+ CD123- CD1c+
		Lin- HLADR+ CD14- CD11c+ CD123- CD1c-
	Plasmacytoid DC (pDC):	Lin- HLADR+ CD14- CD11c- CD123+

	Activation (MFI of activation markers on the different cell subsets)	
	Classical monocytes (CMo):	CMo/HLADR
		CMo/CD40
		CMo/CD86
		CMo/CD32

	CMo/CD64
Intermediate monocytes (IMo):	IMo/HLADR
	IMo/CD40
	IMo/CD86
	IMo/CD32
	IMo/CD64
Non-classical monocytes (NCMo):	NCMo/HLADR
	NCMo/CD40
	NCMo/CD86
	NCMo/CD32
	NCMo/CD64
Conventional myeloid DC (cmDC):	cmDC CD1c+ /HLADR
	cmDC CD1c- /HLADR
	cmDC CD1c+ /CD40
	cmDC CD1c- /CD40
	cmDC CD1c+ /CD86
	cmDC CD1c- /CD86
	cmDC CD1c+ /CD32
	cmDC CD1c- /CD32
	cmDC CD1c+ /CD64
	cmDC CD1c- /CD64
Plasmacytoid DC (pDC):	pDC /HLADR
	pDC /CD40
	pDC /CD86
	pDC /CD32
	pDC /CD64
Lymphoid cells	
Phenotyping (number of cells per million PBMCs)[1]	
γδT:	CD3+ CD19- TCRγδ+

	Natural Killer (NK) cells subtype 1 (NK1):	CD3- CD19- CD16+ CD56dim
	NK cell subtype 2 (NK2):	CD3- CD19- CD16- CD56+
	Activation (MFI of activation markers on the different cell subsets)	
	γδT:	γδT/HLADR+
	NK cells subtype 1:	NK1/HLADR+
	NK cell subtype 2:	NK2/HLADR+

1. Both CD19 and CD20 markers identify the same B-cells population; the only difference between the two markers is that CD20 is downregulated in particular subsets of B-cells under particular conditions while CD19 expression is not modulated. Therefore, we decided to use CD19 as a marker to catch all the B-cells instead of the originally planned CD20.

Endpoint(s): Cellular effectors from the innate/early immune response:

- Innate cell phenotyping at each sampling time:
  (1): Number per million PBMCs of innate cells including myeloid cells (e.g. dendritic cells [DC], monocytes) showing a particular phenotype characterized by a combination of specific surface markers (e.g. HLA-DR, CD14, CD123, CD16), as measured by flow cytometry.
  (2): Number per million PBMCs of innate cells including lymphoid cells (e.g. natural killer [NK], γδT cells) showing a particular phenotype characterized by a combination of specific surface markers (e.g. CD3, CD16, CD56), as measured by flow cytometry.
- Innate cells activation at each sampling time:
  (1): Level of expression (median fluorescence intensity, MFI) of activation markers (e.g., HLA-DR, CD86, CD40, CD32, CD64) on myeloid cells (DC, monocytes) as measured by flow cytometry using PBMC.
  (2): Level of expression (MFI) of activation markers (e.g. HLA-DR) on lymphoid cells (γδ T cells, NK cells) as measured by flow cytometry using PBMC.

Analysis Methods:

a. The number and percentage of subjects with each type of effector cell as listed in Table 5 and associated two-sided 95% Clopper-Pearson CIs will be computed by vaccine dosage group for each blood sampling time point.

b. The number of innate cells expressing specific immune markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

c. The level of expression of activation markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

d. The change from baseline in number of innate cells expressing specific immune markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

e. The change from baseline in level of expression of activation markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

f. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of innate cells expressing specific surface markers and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately.

g. Differences between dosage groups (all pairwise differences) in the change from baseline in the level of expression of activation markers and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately.

h. To test for differences in the proportion of expressing cells among the dose groups, a Kruskal-Wallis test will be performed for each surface marker for each time point. If significant, then pairwise testing of the dose groups will be performed using the Hodges Lehmann (HL) approach which provides the median of the pairwise difference of the dose groups along with its 95% CI. The Kruskal-Wallis test will be repeated on the Day 1 (24h), Day 4, and Day 8 values after adjusting for Day 1 (baseline) (i.e., Day 8 - Day 1 baseline, Day 4 – Day 1 baseline, and Day 1 24 h - Day 1 baseline), followed by pairwise testing.

Criteria for Assessment:

a. The impact of vaccination on frequency and activation status of myeloid and lymphoid cells will be described by dosage group using the change from baseline in number of innate cells expressing specific immune markers and the change from baseline in the level of expression of activation markers.

b. The impact of LHD153R on frequency and activation status of myeloid and lymphoid cells will be described using the differences between the LHD153R groups and the MenC control group.

c. To describe the impact of the dosage of LHD153R on frequency and activation status of the myeloid and lymphoid cells, the pairwise differences among the LHD153R groups will be used.

Possible additional exploratory analyses: Graphical displays of the number of innate cells expressing specific immune marker or the level of expression of activation markers may be produced to better illustrate the differences between the dosage groups.

2.9 Conditional Exploratory Data Analysis

The analyses described in this section depend on the outcomes of prior analyses, including the primary and secondary study endpoints as well as the exploratory endpoints described in previous sections. These analyses may be done in a time-frame different from the other analyses proposed in this statistical analysis plan (SAP) and may be reported separately.

2.9.1 MenC polysaccharide and CRM specific B cell repertoire

Objective: The objective is to understand the impact of LHD153R adjuvant on the B cell repertoire. The expectation is that the B cell diversity (i.e., "antibody signature" and clonotypes) will differ between at least one LHD153R dosage group and the MenC control group. Specifically, it is expected that LHD153R will induce more clonal response (a different size distribution of clones) and have a longer average length of the phylogenetic trees within the clones.

The diversity of the antigen specific B-cell repertoire will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment. Subjects with too few cells recovered or with very low frequencies of MenC Polysaccharide-specific B cells (as assessed by ELISpot) will be excluded.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of cDNA generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B-cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8.

The following analyses were planned but will not be performed due to a decision to not perform the required assay procedures.

Endpoints:

a. Size of the clones at each sampling time point

b. Length of the phylogenetic trees within the clones at each sampling time point

Analysis Method:

a. The size of the clones will be summarized using arithmetic means and corresponding two-sided, 95% CIs around the mean by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

b. The length of the phylogenetic trees within the clones will be summarized using arithmetic means and corresponding two-sided, 95% CIs around the mean by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

Graphical Displays:

The distribution of clonal sizes will be graphically displayed by dosage group at each measurement time.

Criteria for Assessment:

The Kruskal-Wallis test will be performed to compare the vaccine groups overall. If the overall test is significant, then the Dunnett multiple comparison procedure will be used to control the overall significance level to compare the LHD153 groups to the Menjugate control group.

Possible additional exploratory analyses:

For clones and phylogenetic trees significantly different between the LHD153R and Men-C control groups, the correlation with SBA levels will be explored. Additionally, the correlation with SBA levels will be displayed graphically by clonal size (x-axis) using symbols and/or color to differentiate vaccine groups.

2.9.2 Functionality of MenC-specific Antibodies

Objective: The objective is to evaluate the functionality of MenC-specific antibodies to fix complement, promote antibody-dependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro at Day 1 (baseline), Day 8, Day 29, and Day 181.

2.9.3 Integrated Analysis

The different immunological readouts collected in this trial may be integrated with the primary and secondary readouts collected to identify specific combinations of immune signals that are associated with the administered adjuvant dosage or that can predict immunogenicity or safety outcomes. This integration may be performed in three steps:

1. Methods from signal detection theory will be applied to single readouts to: a) identify novel patterns and dimensionality-reduction approaches (e.g., trends in readouts not clinically relevant per se but significantly stratified by treatment group, gene expression patterns not already defined as transcriptional modules) and b) search for correlations between single readouts and safety or immunogenicity outcomes using the improved patterns identified.
2. Unsupervised Machine Learning methodologies will be applied to integrate the multiscale data available (possibly dimensionally-reduced as in step 1 and identify combinations of immune signals that a) predict the clinical outcome, and b) are associated with the treatment administered (e.g., combinations of body-temperature trends, transcriptional responses and cytokine/chemokine concentrations predictive of local solicited AEs, some dependent on the adjuvant dosage, some independent).
3. Causal inference models will be explored to identify associations among the data, assumed from scientific knowledge or inferred by the two previous analyses, supported by a causal relationship and influencing directly the final outcome (e.g., contrasting the influence on immunogenicity of pre-vaccination immunity, vaccine administered, early transcriptional responses, B and T cellular frequencies and functional antibody profiles).

3. PEER REVIEW

The type of peer review required for each output is to be identified by the study Biostatistician and Statistical Programmer (SP) in the Table of Contents (TOC, see BCDM14 TEMP 04). Analyses/Outputs requiring statistical peer review correspond usually to the analyses of the primary and secondary objectives, and data conversion programs. Peer review of these analyses should be performed in accordance with the applicable procedures for validation of SAS programs used in clinical data analysis.

The following analyses are identified as analyses to be peer reviewed by a biostatistician independent from the study:

- None

The following programs are identified as programs to be peer reviewed by a second SP:

- The mapping of the phenotypes
- Checking of the distribution free analysis by running a Proc Means and calculating the confidence intervals

4. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

For the complete list of tables, listings and figures (TLFs), please refer to the TOC.

5. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

All TLFs are to include the following header:

GlaxoSmithKline Biologicals, S.A.	Adjuvant: LHD153R
Additional Analysis: Study V132_01EXP	Exploratory Endpoints

In all tables, listings and figures, vaccine groups will be labeled as "MenC", "LHD153R 12.5", "LHD153R 25.0", "LHD153R 50.0" and "LHD153R 100.0".

For the mock-up catalogue to be used during programming, please refer to the document stored in /GSKVX/Files/NVX/analysis/v132/v132_01exp/ within the SAS Drug Development (SDD) server.

Since tables and listings will be produced using SAS® as well as R, the output actually generated may slightly differ from the mock-ups presented in the study specific mock-up catalogue. Graphical figures of study data will be produced using graphical software, such as SAS and R, in a validated, controlled environment.

6. REFERENCES

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7. APPENDICES

Below is the CV% for each of the cytokine and chemokine assays.

Assay	CV%
IFN-γ	12.6
IL-10	10.0
IL-12p70	6.5
IL-13	16.4
IL-1β	24.2
IL-2	16.4
IL-4	15.9
IL-6	6.7
IL-8	3.6
TNF-α	14.7
Eotaxin	8.5

Assay	CV%
MCP-4	9.0
MDC	9.5
MIP-1α	8.7
MIP-1β	12.8
TARC	8.4
GM-CSF	16.1
IL-12/IL-23p40	7.9
IL-15	6.1
IL-16	5.4
IL-17A	13.9
IL-1α	16.0

Eotaxin-3	18.5		IL-5	32.4
IL-8 (HA)	11.5		IL-7	6.6
IP-10	10.9		TNF-β	15.7
MCP-1	11.2		VEGF	5.1

IFN = interferon; IL = interleukin; TNF-α = tumor necrosis factor – alpha; IP-10 = inducible 10-kilodalton (kDa) protein; MCP-1 = monocyte chemo-attractant protein – 1; MDC = macrophage-derived chemokine; MIP-1α = macrophage inflammatory protein – 1α; TARC = thymus and activation-regulated chemokine; GM-CSF = granulocyte macrophage colony stimulating factor; TNF-β = tumor necrosis factor – beta; VEGF = vascular endothelial growth factor.

This section contains additional information related to weighting for summaries of innate cell phenotyping and activation. The expression of specific immune markers and co-stimulatory molecules of interest can be obtained from the weighting in these tables.

Myeloid and Lymphoid Phenotyping and Lymphoid Activation Weights

	HLADR	CD14	CD16	CD11c	CD123	CD1c	CD3	CD56	TCRγδ	Any
Myeloid Phenotyping										
Lin- HLADR+ CD14++ CD16	1	1								1
Lin- HLADR+ CD14+ CD16+	1	1	1							1
Lin- HLADR+ CD14dim CD16+	1		1							1
Lin- HLADR+ CD14- CD11c+ CD123- CD1c+	1			1		1				1
Lin- HLADR+ CD14- CD11c+ CD123- CD1c-	1			1						1
Lin- HLADR+ CD14- CD11c- CD123+	1				1					1
Lymphoid Phenotyping										
CD3+ CD20- $TCR_{\gamma\delta}$+							1		1	1
CD3- CD20- CD16+ CD56dim			1					1		1
CD3- CD20- CD16- CD56+								1		1
Lymphoid Activation										
γδT/HLADR+	1									
NK1/HLADR+	1									
NK2/HLADR+	1									

Myeloid Activation Weights

	HLADR	CD40	CD86	CD32	CD64	CD1c
Myeloid Activation						
CMo/HLADR+	1					
CMo/CD40+		1				
CMo/CD86+			1			
CMo/CD32+				1		
CMo/CD64+					1	
IMo/HLADR+	1					
IMo/CD40+		1				
IMo/CD86+			1			
IMo/CD32+				1		
IMo/CD64+					1	
NCMo/HLADR+	1					
NCMo/CD40+		1				
NCMo/CD86+			1			
NCMo/CD32+				1		
NCMo/CD64+					1	
cmDC CD1c+ /HLADR+	1					1

cmDC CD1c- /HLADR+	1					
cmDC CD1c+ /CD40+		1				1
	HLADR	**CD40**	**CD86**	**CD32**	**CD64**	**CD1c**
cmDC CD1c- /CD40+		1				
cmDC CD1c+ /CD86+			1			1
cmDC CD1c- /CD86+			1			
cmDC CD1c+ /CD32+				1		1
cmDC CD1c- /CD32+				1		
cmDC CD1c+ /CD64+					1	1
cmDC CD1c- /CD64+					1	
pDC /HLADR+	1					
pDC /CD40+		1				
pDC /CD86+			1			
pDC /CD32+				1		
pDC /CD64+					1	

Laboratory Tests (LBTEST) for Cytokine Combinations	
CD4 CRM19740L+G+2+13+17+21+T+/CD4	CD4 SEB40L+G+2+13+17+21+T+/CD4
CD4 CRM19740L+G+2+13+17+21+T-/CD4	CD4 SEB40L+G+2+13+17+21+T-/CD4
CD4 CRM19740L+G+2+13+17+21-T+/CD4	CD4 SEB40L+G+2+13+17+21-T+/CD4
CD4 CRM19740L+G+2+13+17+21-T-/CD4	CD4 SEB40L+G+2+13+17+21-T-/CD4
CD4 CRM19740L+G+2+13+17-21+T+/CD4	CD4 SEB40L+G+2+13+17-21+T+/CD4
CD4 CRM19740L+G+2+13+17-21+T-/CD4	CD4 SEB40L+G+2+13+17-21+T-/CD4
CD4 CRM19740L+G+2+13+17-21-T+/CD4	CD4 SEB40L+G+2+13+17-21-T+/CD4
CD4 CRM19740L+G+2+13+17-21-T-/CD4	CD4 SEB40L+G+2+13+17-21-T-/CD4
CD4 CRM19740L+G+2+13-17+21+T+/CD4	CD4 SEB40L+G+2+13-17+21+T+/CD4
CD4 CRM19740L+G+2+13-17+21+T-/CD4	CD4 SEB40L+G+2+13-17+21+T-/CD4
CD4 CRM19740L+G+2+13-17+21-T+/CD4	CD4 SEB40L+G+2+13-17+21-T+/CD4
CD4 CRM19740L+G+2+13-17+21-T-/CD4	CD4 SEB40L+G+2+13-17+21-T-/CD4
CD4 CRM19740L+G+2+13-17-21+T+/CD4	CD4 SEB40L+G+2+13-17-21+T+/CD4
CD4 CRM19740L+G+2+13-17-21+T-/CD4	CD4 SEB40L+G+2+13-17-21+T-/CD4
CD4 CRM19740L+G+2+13-17-21-T+/CD4	CD4 SEB40L+G+2+13-17-21-T+/CD4
CD4 CRM19740L+G+2+13-17-21-T-/CD4	CD4 SEB40L+G+2+13-17-21-T-/CD4
CD4 CRM19740L+G+2-13+17+21+T+/CD4	CD4 SEB40L+G+2-13+17+21+T+/CD4
CD4 CRM19740L+G+2-13+17+21+T-/CD4	CD4 SEB40L+G+2-13+17+21+T-/CD4
CD4 CRM19740L+G+2-13+17+21-T+/CD4	CD4 SEB40L+G+2-13+17+21-T+/CD4
CD4 CRM19740L+G+2-13+17+21-T-/CD4	CD4 SEB40L+G+2-13+17+21-T-/CD4
CD4 CRM19740L+G+2-13+17-21+T+/CD4	CD4 SEB40L+G+2-13+17-21+T+/CD4
CD4 CRM19740L+G+2-13+17-21+T-/CD4	CD4 SEB40L+G+2-13+17-21+T-/CD4
CD4 CRM19740L+G+2-13+17-21-T+/CD4	CD4 SEB40L+G+2-13+17-21-T+/CD4
CD4 CRM19740L+G+2-13+17-21-T-/CD4	CD4 SEB40L+G+2-13+17-21-T-/CD4
CD4 CRM19740L+G+2-13-17+21+T+/CD4	CD4 SEB40L+G+2-13-17+21+T+/CD4
CD4 CRM19740L+G+2-13-17+21+T-/CD4	CD4 SEB40L+G+2-13-17+21+T-/CD4
CD4 CRM19740L+G+2-13-17+21-T+/CD4	CD4 SEB40L+G+2-13-17+21-T+/CD4
CD4 CRM19740L+G+2-13-17+21-T-/CD4	CD4 SEB40L+G+2-13-17+21-T-/CD4
CD4 CRM19740L+G+2-13-17-21+T+/CD4	CD4 SEB40L+G+2-13-17-21+T+/CD4
CD4 CRM19740L+G+2-13-17-21+T-/CD4	CD4 SEB40L+G+2-13-17-21+T-/CD4
CD4 CRM19740L+G+2-13-17-21-T+/CD4	CD4 SEB40L+G+2-13-17-21-T+/CD4

CD4 CRM19740L+G+2-13-17-21-T-/CD4	CD4 SEB40L+G+2-13-17-21-T-/CD4
CD4 CRM19740L+G-2+13+17+21+T+/CD4	CD4 SEB40L+G-2+13+17+21+T+/CD4
CD4 CRM19740L+G-2+13+17+21+T-/CD4	CD4 SEB40L+G-2+13+17+21+T-/CD4
CD4 CRM19740L+G-2+13+17+21-T+/CD4	CD4 SEB40L+G-2+13+17+21-T+/CD4
Laboratory Tests (LBTEST) for Cytokine Combinations	
CD4 CRM19740L+G-2+13+17+21-T-/CD4	CD4 SEB40L+G-2+13+17+21-T-/CD4
CD4 CRM19740L+G-2+13+17-21+T+/CD4	CD4 SEB40L+G-2+13+17-21+T+/CD4
CD4 CRM19740L+G-2+13+17-21+T-/CD4	CD4 SEB40L+G-2+13+17-21+T-/CD4
CD4 CRM19740L+G-2+13+17-21-T+/CD4	CD4 SEB40L+G-2+13+17-21-T+/CD4
CD4 CRM19740L+G-2+13+17-21-T-/CD4	CD4 SEB40L+G-2+13+17-21-T-/CD4
CD4 CRM19740L+G-2+13-17+21+T+/CD4	CD4 SEB40L+G-2+13-17+21+T+/CD4
CD4 CRM19740L+G-2+13-17+21+T-/CD4	CD4 SEB40L+G-2+13-17+21+T-/CD4
CD4 CRM19740L+G-2+13-17+21-T+/CD4	CD4 SEB40L+G-2+13-17+21-T+/CD4
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CD4 CRM19740L+G-2+13-17-21+T+/CD4	CD4 SEB40L+G-2+13-17-21+T+/CD4
CD4 CRM19740L+G-2+13-17-21+T-/CD4	CD4 SEB40L+G-2+13-17-21+T-/CD4
CD4 CRM19740L+G-2+13-17-21-T+/CD4	CD4 SEB40L+G-2+13-17-21-T+/CD4
CD4 CRM19740L+G-2+13-17-21-T-/CD4	CD4 SEB40L+G-2+13-17-21-T-/CD4
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CD4 CRM19740L+G-2-13+17+21+T-/CD4	CD4 SEB40L+G-2-13+17+21+T-/CD4
CD4 CRM19740L+G-2-13+17+21-T+/CD4	CD4 SEB40L+G-2-13+17+21-T+/CD4
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CD4 CRM19740L+G-2-13+17-21+T+/CD4	CD4 SEB40L+G-2-13+17-21+T+/CD4
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CD4 CRM19740L+G-2-13-17-21-T-/CD4	CD4 SEB40L+G-2-13-17-21-T-/CD4

The following tables present the genes that are included in the interferon and inflammation modules being considered for this study.

Ge es Included in Module M1.1 - Interferon		
LY6E	OAS1	FLJ20035
IFIT1	MX1	IFITM3
OAS1	BATF2	IFIT3
IFIT1	LAMP3	CXCL10
IFIT3	IFI44L	EPSTI1
OAS3	XAF1	SERPING1
IFIT3	OASL	LOC26010
OAS1	IFI44	OAS2
OASL	OAS2	RSAD2
LOC129607	TRIM6	RTP4
ISG15	HES4	
HERC5	OTOF	

Genes Included in Module M3.2 - Inflammation		
BCL6	SLC37A3	LOC643313
BASP1	LOC642816	FLJ20273
PBEF1	REPS2	MRVI1
KLHL2	F5	CEBPB
SLC2A3	SLA	TSHZ3
SULT1B1	LOC255809	SRPK1
PROK2	ETS2	NCF4
LIN7A	MEGF9	ST3GAL4
ROPN1L	PHTF1	GCA
PYGL	MME	S100A9
SLC11A1	BST1	FAM129A
LOC728417	TLR8	REPS2
LOC641710	GNG10	SEPX1

TGFA	FPRL1	LOC653610
GPR97	SIGLEC5	SLC11A1
KCNJ15	FLJ22662	C16orf57
LOC399744	TLR4	RAB31
TLR6	TLR8	GPR97
ITGAM	MANSC1	CYP4F3
FCGR2A	ALOX5	LTB4R
LOC728417	PFKFB3	STX3
ABHD2	TRIB1	FLOT2
DYSF	FUT7	ZNF438
MLSTD1	SIRPA	MMP25
HCK	Rgr	PHC2
LOC642780	AQP9	CREB5
QPCT	PADI4	IL1RN
CEACAM4	CKAP4	LOC729021
PPP1R3D	TIMP2	FOLR3
CST7	SLC26A8	SERPINA1
LOC641996	EPAS1	CSF3R
LILRA3	SEMA4A	RNF24
PBEF1	TRIM9	C20orf3
STEAP4	LOC399715	LOC642334
LOC728054	RNF149	RFX2

Genes Included in Module M3.2 - Inflammation		
ZNF467	VNN2	ACSL1
FLOT1	DGAT2	OR10G3
ACSL4	GPR160	PLXNC1
DHRS13	SOD2	LOC552891
DUSP1	LOC642267	CRISPLD2
EXOC6	NFIL3	GLT1D1
CD63	LY96	CEBPD
IL1RAP	CDA	SLC22A4
ANKRD33	CCPG1	PGD

HMGB2	GPR97	LOC646434
C14orf94	MKNK1	OSCAR
S100A11	IL17RA	LOC641693
CD55	GNG10	LOC441124
B4GALT5	PDLIM7	

Genes Included in Module M3.4 - Interferon		
IFIH1	ZBP1	CEACAM1
IRF7	WARS	APOL6
PARP14	LAP3	SOCS1
IFIT2	GBP5	LGALS3BP
IFI35	TNFSF10	SCO2
SAMD9L	GBP1	DDX58
STAT1	STAT1	UBE2L6
OAS2	FBXO6	PML
IFIT5	PARP10	TNFAIP6
ATF3	OAS2	INDO
SEPT4	TRIM22	MT2A
HERC6	PARP10	GBP6
IFITM1	GBP3	STAT2
TRIMP1	ZNF684	TIMM10
EIF2AK2	INCA	STAT1
AIM2	GALM	PARP12
MT1A	DHX58	PLSCR1
MOV10	CEACAM1	PARP9
CCL8	UBE2L6	LOC400759
PRIC285	PML	GBP4

Genes Included in Module M4.2 - Inflammation		
LOC728519	IRAK3	WDFY3
ANXA3	CLEC4D	CASP5
TLR5	LMNB1	SIPA1L2
KREMEN1	SAMSN1	S100P
CR1	LOC648984	LIMK2
BMX	LOC391045	S100A12
LRG1	MCTP2	MMP9
OPLAH	VNN2	IL1R2
ALPL	IL1R2	IL18RAP

C19orf59	GRB10	VNN1
LOC642112	CR1	KIAA1881
PGLYRP1	FCAR	PSG3
CA4	IL18R1	KREMEN1
LOC642684	SLPI	MAPK14
MGAM	OSM	C5orf32
SOCS3	NSUN7	SERPINA1
FKBP5	GPR141	SLC2A14

Genes Included in Module M4.6 - Inflammation		
ZFP36	ATF6	CKLF
LOC440093	MGC4093	LOC728069
SLC25A44	DNTTIP1	SBNO2
YIPF1	MSRB2	LSP1
IFITM2	HTATIP2	CHIC2
C6orf166	PIM3	DDAH2
STAT3	NCSTN	PDK3
RNF13	LAMP2	FCGR2A
PHF21A	NFKBIZ	RAB24
PRKCD	CHSY1	GNG5
LOC651143	SELL	C6orf32
MTX1	CTNNA1	RHOT1
C9orf66	STX10	CLIC1
PCNX	CD97	CASP4
SNX27	LRRK2	VAMP3
PLOD1	ATP6V0D1	CYBA
FTH1	CFLAR	IRF2
NT5C2	KIAA1754	CBARA1
GMPR2	STAT5B	TMEM188
APBB1IP	SAT1	MEFV
SNX10	MIDN	USP15
ZCCHC6	SLCO3A1	PSCD4

AXUD1	ENTPD1	LYRM1
LITAF	MTX1	APAF1
MYD88	IFNGR1	MLKL
BRI3	IFNGR2	APH1B
TCIRG1	HEBP2	RALB
ZYX	RIT1	ETV6
MAPK3	C9orf19	PIM3
S100A6	ATG7	NAGK
ERO1L	STK17B	IL10RB
MLKL	P2RY13	RNASEL
KIAA1600	FBXL5	LAT2
GRN	SQRDL	ALOX5AP
THOC5	SNX11	DIP2B
Genes Included in Module M4.6 - Inflammation		
SSFA2	RAB24	MVP
IFNAR1	LYN	GLA
PELO	PFTK1	CHMP2A
C16orf72	JDP2	CSNK1D

Genes Included in Module M4.13 - Inflammation		
LENG4	FAM53C	MTHFS
FRAT1	NINJ1	NLRP12
SIRPB1	TLE3	USP10
DOCK5	SPI1	RAB6IP1
XPO6	CTBS	FRAT1
ACOX1	VNN3	MAG1
GALNAC4S-6ST	CXCL1	SMAP1L
ST6GALNAC2	C1orf24	LOC283547
TREML2	MTMR3	PFKFB4
TSEN34	SKAP2	IL1B
IL8RA	EMR2	C5AR1

ACTN1	NLRP12	NCF4
SSH2	DENND3	IL8RB
SDCBP	SLC19A1	C1RL
LRP10	SLC6A6	CSF2RA
FOS	ZDHHC18	TNFRSF10C
TMEM71	PELI1	PTEN
HLX	CD58	TNFRSF1A
P2RY13	DDEF1	UBTD1
C3orf34	ELF2	RRAGD
TLR6	LPPR2	PDLIM7
PANX2	MXD1	GAB2
TBC1D14	FPR1	IL13RA1
NUMB	FLJ10357	SIRPD
PACSIN2	C7orf53	IFRD1
TNFRSF10B	SVIL	LAMP2
FRAT2	MOSPD2	RNF141

Genes Included in Module M5.1 - Inflammation		
GNAI3	UBE2J1	RAB5A
SLK	PXN	CASP9
HIATL1	RPS6KA1	ATP6V0B
SNX13	HHEX	ROD1
MAP3K8	FLJ10986	CLIP1
LBR	EDEM2	CCND3
SPPL2A	GADD45G	ARHGAP19
FEM1C	OSTM1	GSTO1
KIAA0040	LOC645058	LRRFIP2
CHUK	C1orf25	GRB2
SAP30L	TMEM2	NARF
SFT2D1	TOLLIP	MS4A6A
TOR1AIP1	CTDP1	ZNF281
CAST	INSIG2	GSK3B

ATP6V1D	ZFP106	TMLHE
MAP1LC3B	EHD1	FBXO30
ATG3	PPP2R3C	FOSL2
C1GALT1C1	PTAFR	MAPK1
BAT5	PTPN1	PSMB3
LAPTM5	C20orf24	ARFGAP3
ANXA5	PPP1R10	ACAA1
CAPZA2	SLC15A3	LOC647195
LOC653972	RBMS1	TMEM149
FAM49B	PRCP	NANS
LTA4H	RAB7A	MAPKAPK2
TBXAS1	ME2	FYB
IGSF6	RENBP	C2orf25
SNX16	PHF20L1	PTTG1IP
GBE1	C9orf89	DUSP18
DNAJB6	NDEL1	CRADD
ATP6V0E1	WSB1	SDF2
FOXN2	PGM2	KIAA1434
FKBP15	CHMP2B	GNAI2
PGK1	NEU1	CNN2
LRRFIP2	GRN	RASSF3

Genes Included in Module M5.1 - Inflammation		
E2F3	CFP	PARP4
FBXO38	SRGN	TBXAS1
ARID3A	NOLA3	TPM3
PCMT1	BNIP2	HOXA9
ARPC3	KLHL8	ARPC5
PRKAA1	CTNNB1	CD53
C1orf119	OSTF1	FLII
ILK	DPH3	ZNF319
RAP2C	SCYL2	CHMP2A
KIAA0241	EFHD2	OTUD1

CMTM3	TKT	ACTB
VIM	PSENEN	ATP6AP1
PHF20L1	URP2	GLT25D1
GRB2	NIN	CMTM6
SERPINB8	PLA2G4A	PHKA2
CSNK1D	HK2	MSL3L1
ANKS1A	KCTD21	CD44
LOXL3	CCR1	MFAP3
USP3	LPGAT1	RABAC1
ZNF787	AGPAT2	UBQLN2
ELMOD2	DTX2	UBE2W
SLC30A1	GNA13	LACTB
CAB39	C14orf4	DSE
PTPRC	ZMPSTE24	ALDOA
AZI2	RAB10	GALNT4
TRIOBP	OS9	CSF2RA
SLC12A6	FNDC3A	TMEM50A
MIER1	PRKAR1A	PIK3CB
TM9SF2	BTBD10	FKBP1A
TMEM185B	TMUB2	NIN
ZSWIM6	TMEM180	RANBP9
RBPJ	LOC642489	KLHL6
GMFG	RHOG	ATP6V1C1
NDRG1	ACSS2	TNFSF13B
MAPK1	DHRS7B	ATP6V1B2

Genes Included in Module M5.1 - Inflammation		
TXN	ZDHHC3	NRD1
SELT	RTN4	NDUFB3
HCLS1	MBOAT5	GNA15
TUBA1A	MON1B	DIRC2
RAC2	YIPF4	RB1CC1
USP9X	FKBP1A	LOC648605

MAP2K1IP1	AGPAT2	RAB2A
GNS	ARIH1	TMOD3
PRR13	RAB1A	BIN2
TBK1	KIDINS220	NFE2L2
PPP2R5A	TYROBP	CYB5R4
TMEM97	HEXB	ANTXR2

Genes Included in Module M5.7 - Inflammation		
MAP2K4	TMEM43	HBP1
CHMP1B	PGCP	ZDHHC7
HSD17B11	CARD8	LMBRD1
STXBP5	SERINC1	MAP3K2
IDS	HLA-E	ERGIC1
H3F3B	CTSS	MANBA
KIAA0232	STAT6	CASC4
FAM49A	RGL2	HPSE
TNRC5	RNASET2	MYO5A
ATP6V1A	SPATA2L	KIAA0247
MBP	C14orf138	SUPT4H1
HSPA1L	INPP5A	FCGRT
CD46	RNF130	INPP5A
PGM1	TOPORS	RAF1
PBX2	FAM79A	RAB27A
KLHL21	LONRF1	VAV3
STXBP3	TGFBR2	CORO1C
MARCH7	EGLN1	CPD
ELF1	KBTBD7	CRK
C9orf72	DDX3X	ZBTB34
HSDL2	IDS	GOLGA7
NSMAF	LOC644935	LOC339745
SLC15A4	ATXN1	PYCARD
CD93	ITM2B	IMPA2
TMF1	TMCO3	MAP4K4
MBOAT1	PTPRE	CXCL16
HMGCR	TRIM8	S100A4
VPS24	DHRS7	NUP50
PIK3CD	BICD2	CUGBP2
APPL2	AMICA1	KIAA0513
C7orf25	CDK5R1	TMCC3

PRMT5	SULT1A1	OSBPL8
KIAA0701	LEPROT	EXTL3
FNIP1	MFSD1	PPP3CA
NCOA1	NUP214	FCGR2B

Genes Included in Module M5.7 - Inflammation		
RGS18	ADAM19	CENTB2
UBR2	IGF2R	CLEC4A
CYBRD1	PHF2	CBL
PISD	TBL1X	PPT1
ZNF238	UBE4B	ARHGAP9
NCOA1	SLC44A2	DHRS12
ZNF217	ZNF746	PRDM8
IQGAP1	RRM2B	SPAG9
TXNDC13	EVA1	JARID1B
RFWD2	BID	ICAM3
PLXDC2	CAMK2G	RBPJ

Genes Included in Module M5.12 - Interferon		
RBCK1	GBP2	TRIM5
TRAFD1	TRIM5	NT5C3
TRIM21	RHBDF2	SASP
LOC401433	TMEM140	ISGF3G
COP1	ADAR	REC8
CHMP5	BTN3A1	KIAA1618
TAP2	PARP10	ISG20
SP110	LGALS9	DYNLT1
GADD45B	NBN	LHFPL2
IFI16	ECGF1	TRIM56
TAP1	SAMD9	SP140
ZNFX1	SRBD1	TRIM25
PHF11	NCOA7	TRIM38
ACTA2	DRAP1	ETV7
C1QA	UNC93B1	PSMB9
SP140	SP100	CPT1B
ABCA1	NTNG2	BST2
TCN2	DHRS9	CASP1
ZC3HAV1	TDRD7	NMI
HSH2D	LBA1	
LOC554203	MDK	

Genes Included in Module M7.1 - Inflammation		
MYADM	ACPP	ARHGAP26
ALDH3B1	RIPK3	RIN3
TMEM8	CHKA	CTSA
SUMF1	GSN	DCTN2
TNIP1	DENND1A	PPP4C
RASGEF1A	CDC42EP4	RAB5C
RGS19	DBNL	SERTAD3
SEMA4B	ARF5	MSRA

TADA3L	APOB48R	ZNF213
KCTD2	ZDHHC17	PTPN6
METRNL	RAB1B	ATP13A3
GAPDH	RHOU	MAP3K5
TALDO1	ZDHHC12	PPP1R15A
C9orf72	SH3PXD2B	MOSPD3
TLN1	ULK1	LRPAP1
CAPN1	PLEKHM1	LOC440525
TMEM127	WDR13	GLRX
G6PD	ARHGAP30	UBE1
GPSM3	BLOC1S1	TMLHE
C22orf9	CPNE1	IL2RG
CYB5R1	METRNL	TANK
XRN2	HYAL2	PREX1
CAPZB	KIAA1602	IIP45
TWF2	IRAK4	RARA
GRK6	LOC644964	TIMP1
LOC653888	EIF2C4	LTBR
TK2	MED12	SH2B2
PKM2	AGXT2L2	CDKN2C
STEAP3	GMIP	DEDD
PLD1	RAB4B	JMJD2B
TMEM119	PLEC1	TXNDC3
CYB5R3	HRH2	TGFBR1
OTUD1	ATXN7L3	GBGT1
CHP	DNM2	RAB38
TESK2	SLC16A5	TNPO3
Genes Included in Module M7.1 - Inflammation		
LSP1	FAM70B	RTN2
CDKN2D	H2AFY	LOC652675
KPNA4	AMPH	MYH9
CAP1	DPYD	WAS
ULK1	RNF135	MFN2

C20orf177	CAT	ACTR1A
BCORL1	COQ2	MBD6
ADCK4	CD300LF	RUNX1
METRNL	ECOP	TAZ
FKSG30	RAB3D	FAM20C
PJA2	TIMP2	SSH1
PPP1R12A	NCF2	CUTL1
FAM45A	PICALM	RHBDD2
MLX	ANXA1	MLF2
NFKBIB	PLP2	RASSF2
SLC9A8	LOC648605	CHD7
CORO2A	SYK	GLTP
KIAA1539	TMBIM1	CDC123
SIRPB2	MYL6	TSC22D3
AGXT2L2	PTEN	AP3S2
SCOTIN	SH3BP5L	TMEM142B
CALML4	PAM	C9orf167
PLEKHQ1	MAP1S	IMPDH1
CCDC128	MSN	CPNE3
LOC651524	CARS	MTMR6
C17orf62	ARHGEF11	
EDG6	PNRC1	

STATISTICAL ANALYSIS PLAN ADDENDUM

Addendum Number 2

Study Title: **A Phase 1, Randomized, Observer-Blind, Dosage-Escalation Study to Evaluate the Safety and Immunogenicity of an Aluminium Hydroxide/LHD153R Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine Compared to Aluminium Hydroxide Adjuvanted Meningococcal C-CRM$_{197}$ Conjugate Vaccine in Healthy Adults (18-45 years of age)**

Study Number/Product: V132_01EXP/LHD153R Adjuvant

Phase of Development: Phase 1

Sponsor: GlaxoSmithKline Biologicals

Plan Prepared by: Plan Amended by: PPD
PPD

Version and Date: Final Version 1.0: 19 Jun 18

Reviewers: PPD
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Approvers: Supervisory PPD Statistician
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
$AlHO_3$	Aluminium Hydroxide
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASC	Antibody Secreting Cells
BTM	Blood Transcriptional Module
CD4	Cluster of Differentiation 4
cDNA	Complementary Deoxyribonucleic Acid
CI	Confidence Interval
cmDC	Conventional Myeloid Dendritic Cells
CMo	Classical Monocytes
CRM_{197}	Cross Reacting Material 197
CRP	C-Reactive Protein
CSF	Colony Stimulating Factor
DC	Dendritic Cells
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immunospot
FACS	Fluorescence-Activated Cell Sorting
FAS	Full Analysis Set
FDR	False Discovery Rate
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GMC	Geometric Mean Concentration
HL	Hodges Lehmann
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IM	Intra-Muscular
IMo	Intermediate Monocytes
IP-10	IFN-Γ – Inducible 10-Kilodalton (Kda) Protein
kDa	Kilodalton
LC-MS/MS	Liquid Chromatography-Mass Spectrometry
LLQ	Lower Limit of Quantitation
LOD	Limit of Detection
MBC	Memory B Cells
MCP	Monocyte Chemo-Attractant Protein

MDC Macrophage-Derived Chemokine
MenC Meningococcal Type C
MFI Median Flourescence Intensity MIP
Macrophage Inflammatory Protein mRNA
Messenger Ribonucleic Acid NCMo Non-
Classical Monocytes NK Natural Killer Cells
PBMC Peripheral Blood Monoculear Cells
pDC Plasmacytoid Dendritic Cells
Ps Polysaccharide RNA Ribonucleic
Acid
SAP Statistical Analysis Plan SAS Statistical
Analysis System SBA Serum Bactericidal Assay SP
Statistical Programmer
TARC Thymus And Activation-Regulated Chemokine
Tfh T Follicular Helper Cells
Th T-Helper
TLF Table, Listing and Figure
TNF Tumor Necrosis Factor
TOC Table of Contents
VEGF-A Vascular Endothelial Growth Factor - A

1. BACKGROUND AND RATIONALE

This is a Phase 1, randomized, observer blind, active-controlled, adjuvant dosage-escalation study performed at a single center. In total, approximately 80 healthy adults (18-45 years of age) will be enrolled in the study.

Table 1 describes the different enrollment groups, cohorts, and vaccine formulations.

Table 1 Subjects Randomized per Cohort and Treatment Dose Group

Cohort	Group	Subjects/ Group	MenC Dosage* (µg)	Adjuvant Dosages		Total Volume/Dose	Total Subjects/Group
				Aluminium Hydroxide (mg)	LHD153R (µg)		
1	A	4	10	1	0	0.5 mL	20
	B	16	10	1	12.5	0.5 mL	
2	A	4	10	1	0	0.5 mL	20
	C	16	10	1	25	0.5 mL	
3	A	4	10	1	0	0.5 mL	20

	D	16	10	1	50	0.5 mL	
4	A	4	10	1	0	0.5 mL	20
	E	16	10	1	100	0.5 mL	

*Conjugated to 12.5-25 µg CRM_{197}, MenC = Meningococcal Type C.

A comprehensive set of exploratory objectives has been selected to assess the systemic exposure of LHD153 after intramuscular injection and to evaluate the quality of the specific immune response against MenC-CRM_{197} in detail and to evaluate biomarkers that may be predictive of safety and/or innate immune activation. These objectives are:

1. To evaluate the systemic exposure of LHD153 at several early time-points after intramuscular (IM) injection of MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine.
2. To explore the frequency of B cells specific for MenC polysaccharide and CRM_{197} protein at baseline (Day 1) and at Day 8, Day 29 and Day 181 after vaccination with MenC-CRM_{197}/Aluminium Hydroxide/LHD153R or the aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine. Subsequently, the B cell repertoire of the antigen specific B cells will be analyzed in a selected subset of subjects.
3. To explore the baseline T cell mediated immunity to CRM_{197} and to evaluate the frequency and quality of CRM_{197} specific T cells induced by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R compared to aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine at Day 8 and Day 29.
4. To evaluate biomarkers that may be predictive for safety and/or innate immune activation.
5. To evaluate the functionality of MenC-specific antibodies to fix complement, promote antibody-dependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro at Day 1 (baseline), Day 8, Day 29, and Day 181. (Protocol amended: 19 June 2017)

Please see section 7.4 of the protocol for more details on the exploratory measurements.

The exploratory endpoints in order of priority are:

- Serum concentration of LHD153 at Day 1 baseline (prior to vaccination), Day 1 (1h , 2h, 4h, 8h, and 24h after vaccination), Day 4 by liquid chromatography-mass spectrometry (LC-MS/MS).
- Frequency and quality of T cells specific for CRM_{197} at Day 1 (baseline), Day 8, and Day 29 by flow cytometry analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations.

- Frequency of MenC polysaccharide-specific and CRM_{197}-specific B cells at Day 1 (baseline), Day 8, Day 29, and Day 181 by Enzyme-Linked Immunospot (ELISPOT).
- Gene expression profile in whole blood at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by ribonucleic acid (RNA) microarray analysis.
- Serum concentrations of a panel of 30 chemokines and cytokines at Day 1 baseline (prior to vaccination), Day 1 (6h and 24h after vaccination), Day 4, and Day 8 by multiplex Electro-chemo-luminescence based assay.
- Number and activation status of myeloid and lymphoid cell populations at Day 1 baseline (prior to vaccination), Day 1 (24h after vaccination), Day 4 and Day 8 by flow cytometry.
- Diversity of MenC polysaccharide-specific B-cell repertoire at Day 1 (baseline), Day 8, Day 29, and Day 181 by immunoglobulin complementary deoxyribonucleic acid (cDNA) sequencing.
- Functionality of MenC-specific antibodies to fix complement, promote antibodydependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro at Day 1 (baseline), Day 8, Day 29, and Day 181.
- Integrated analysis to identify biomarkers predictive of immunogenicity and/or explanatory of the mode of action of LHD153.

The purpose of this statistical analysis plan addendum is to *a priori* describe the planned analyses for these exploratory objectives.

Please note that the diversity of MenC polysaccharide-specific B-cell repertoire will not be determined and thus, the analyses related to this endpoint should be ignored. As this endpoint

is still listed in the protocol; the description of the originally planned analyses will not be removed from this document

2. STATISTICAL CONSIDERATIONS

2.1 General

Because a maximum of 16 subjects per dosage group will participate in the exploratory endpoint analyses, sample sizes of 12 and 16 were considered. The table below provides the probability to observe at least 1 subject with an event for several presumed true frequencies within an individual dosage group (MenC-CRM_{197} or MenC-CRM_{197} plus an assigned-level of LHD153R/$Al(OH)_3$).

Table 2 Probability of Observing at Least 1 Subject with an Event

Frequency of Event	Probability to Observe at Least 1 Subject with an Event Given N	
	N=12	N=16
0.001	0.0119	0.0159
0.005	0.0584	0.0771
0.01	0.1136	0.1485
0.025	0.2620	0.3331
0.05	0.4596	0.5599
0.10	0.7176	0.8147
0.15	0.8577	0.9257
0.20	0.9313	0.9718
0.30	0.9862	0.9967
0.40	0.9978	0.9997

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers or concentrations will be log_{10}-transformed.

Concentrations and titers below the lower limit of detection (LLOD) will be set to half the LLOD for inclusion in summaries requiring a value.

Many analyses will be performed using SAS® Software version 9.1 or higher. Other software packages such as those available in R may also be used to perform analyses. Specifically, R version 3.1 or higher will be used; and, functionality will be extended through the use of the Bioconductor, and other packages (e.g., GO, plotrix, etc.).

2.2 Exploratory Endpoint Analysis Population (Exploratory FAS)

To be included in the exploratory endpoint analyses, a subject must have signed a separate informed consent form. Thus, the number of subjects included in the exploratory endpoint

analyses may differ from those included in the primary and secondary immunogenicity analyses.

Additionally, to be included in a specific analysis, a result must be valid and evaluable. Examples of reasons for not being valid and evaluable are:

- Sample received hemolyzed
- Insufficient sample for analysis based on volume, quantity and quality
- Assay controls not within expected parameters (ie, assay invalid)

Analyses will be performed in the Exploratory Full Analysis Set (FAS) unless specified otherwise.

The frequencies and percentages of subjects in the exploratory full analysis set, with available data at each blood draw time point, and reasons for exclusion will be presented overall and by dosage group ("MenC", "LHD153R 12.5", "LHD153R 25.0", "LHD153R 50.0" and "LHD153R 100.0").

2.3 Demographics

Age, height, weight, and body mass index at enrollment will be summarized by reporting the mean, standard deviation, median, minimum and maximum, and will be calculated by dosage group and overall for the Exploratory FAS.

The frequencies and percentages of subjects by sex and race, will be presented by dosage group and overall for the Exploratory FAS.

2.4 Laboratory Parameters

C-reactive protein (CRP) will be measured from serum samples obtained during screening (Day -28 to Day -3, at baseline (prior to vaccination), 24 hours after vaccination, on Day 8, and on Day 29.

CRP will be summarized by reporting the mean, standard deviation, median, minimum and maximum, and will be calculated by dosage group and overall for the Exploratory FAS.

2.5 Adjuvant Levels: LHD153 Systemic Exposure

Objective: The primary exploratory objective is to evaluate the extent of systemic exposure of LHD153 after intramuscular (IM) administration of LHD153R adsorbed to aluminium hydroxide (Aluminium Hydroxide/LHD153R).

Systemic exposure of LHD153 will be measured from plasma samples collected at 7 time points: baseline (prior to vaccination), 1, 2, 4, and 8 hours after vaccination on Day 1, 24 hours after vaccination, and on Day 4 (72 hours after vaccination).

There is no formal statistical hypothesis associated with this objective. However, based on pre-clinical studies in rats and dogs, there should be little or no systemic exposure of LHD153 after IM administration of Aluminium Hydroxide/LHD153R and no LHD153 at Day 4.

Endpoint(s):

a. The number and percentage of subjects with evaluable concentrations at or above the lower limit of quantitation (LLQ; LOD) as well as below the LLQ for each blood sampling time point.

b. LHD153 geometric mean concentrations (GMCs) for each blood sampling time point. Values below the LLQ will be arbitrarily set to one-half the LLQ for the calculation of GMCs.

Analysis Method:

a. The percentage of subjects above and below LLQ and associated two-sided 95% Clopper-Pearson CIs (Clopper, 1934) will be summarized by dosage group for each blood sampling time point.

b. LHD153 GMCs will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

c. Difference in percentage of subjects above the LLQ between the LHD153R dosage groups and the MenC group; and, associated two-sided 95% CIs for the difference.

Criteria for Assessment: An initial assessment of little to no systemic exposure will be based on the number of subjects above the LLQ. If at least one subject has an evaluable level above the LLQ, then it will be concluded that LHD153 does not have little or no systemic exposure.

Possible additional exploratory analyses: If concentrations of LHD153 are observed, then the difference in GMCs between the LHD153R dosage groups and the MenC group; and, associated two-sided 95% CIs for the difference will be summarized.

Also, the relationship between LHD153 concentrations and solicited adverse events (AEs) may be performed by plotting the severity of the event (x-axis) against the concentration of LHD153 (y-axis) with vaccine dosage groups differentiated by symbol, color or grouping. A

similar graphical display will be produced to describe the relationship between LHD153 concentrations and CRP levels.

Additionally, if the number of observations with measurable levels permit, then a pharmacokinetic analysis may be performed and reported.

2.6 CRM-Specific CD4 T cell Profile

Objective: To explore the baseline T cell mediated immunity to CRM_{197} and to evaluate the frequency and quality (T helper, activation, and memory profiles) of CRM_{197} specific T cells induced by MenC-CRM_{197}/Aluminium Hydroxide/LHD153R compared to aluminium hydroxide adjuvanted MenC-CRM_{197} Conjugate Vaccine at Day 8 and Day 29.

The frequency of T cells specific for the CRM_{197} protein will be determined by FACS analysis using intracellular staining with a wide panel of cytokines and surface markers to identify cell populations. Blood samples will be collected at 3 time points: at baseline (Day 1, pre-vaccination) and at Day 8 and Day 29 after vaccination.

The expectation is that there will be an increase in cytokine producing T cells with LHD153, in particular in the IFN-γ producing T cells. Table 3 lists the markers and combinations of interest for this study.

Table 3 Markers of T Cell Read-outs in PBMCs

CMI (exploratory endpoints)	**List of markers and combinations[1]**	
Functional markers (number per million of total CD4+ T-cells)	**Markers:**	CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21
	Combinations:	at least one marker (any immune marker) among CD3+CD4+CD45RA- cells
T helper type 0 (Th0) (number per million of total CD4+ T-cells)	**Markers:**	CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21
	Combinations:	CD4 CRM19740L+G-2+13-17-21-T+/CD4 CD4 CRM19740L+G-2+13-17-21-T-/CD4 CD4 CRM19740L+G-2-13-17-21-T+/CD4 CD4 CRM19740L+G-2-13-17-21-T-/CD4 among CD3+CD4+CD45RA- cells
T helper type 1 (Th1) (number per million of total CD4+ T-cells)	**Markers:**	CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21
	Combinations:	CD4 CRM19740L+G+2+13-17-21-T+/CD4 CD4 CRM19740L+G+2+13-17-21-T-/CD4 CD4 CRM19740L+G+2-13-17-21-T+/CD4 CD4 CRM19740L+G+2-13-17-21-T-/CD4 among CD3+CD4+CD45RA- cells
T helper type 2 (Th2) (number per million of total CD4+ T-cells)	**Markers:**	CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21
	Combinations:	CD4 CRM19740L+G+2+13+17-21-T+/CD4 CD4 CRM19740L+G+2+13+17-21-T-/CD4 CD4 CRM19740L+G+2-13+17-21-T+/CD4 CD4 CRM19740L+G+2-13+17-21-T-/CD4 CD4 CRM19740L+G-2+13+17-21-T+/CD4 CD4 CRM19740L+G-2+13+17-21-T-/CD4 CD4 CRM19740L+G-2-13+17-21-T+/CD4 CD4 CRM19740L+G-2-13+17-21-T-/CD4 among CD3+CD4+CD45RA- cells
	Markers:	CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21

T helper type 17 (Th17) (number per million of total CD4+ T-cells)	**Combinations:**	CD4 CRM19740L+G+2+13+17+21-T+/CD4 CD4 CRM19740L+G+2+13+17+21-T-/CD4 CD4 CRM19740L+G+2+13-17+21-T+/CD4 CD4 CRM19740L+G+2+13-17+21-T-/CD4 CD4 CRM19740L+G+2-13+17+21-T+/CD4 CD4 CRM19740L+G+2-13+17+21-T-/CD4 CD4 CRM19740L+G+2-13-17+21-T+/CD4 CD4 CRM19740L+G+2-13-17+21-T-/CD4 CD4 CRM19740L+G-2+13+17+21-T+/CD4 CD4 CRM19740L+G-2+13+17+21-T-/CD4 CD4 CRM19740L+G-2+13-17+21-T+/CD4 CD4 CRM19740L+G-2+13-17+21-T-/CD4 CD4 CRM19740L+G-2-13+17+21-T+/CD4

CMI (exploratory endpoints)	**List of markers and combinations[1]**	
		CD4 CRM19740L+G-2-13+17+21-T-/CD4 CD4 CRM19740L+G-2-13-17+21-T+/CD4 CD4 CRM19740L+G-2-13-17+21-T-/CD4 among CD3+CD4+CD45RA- cells
	Markers:	CD40L, IL-13, IL-17, IL-2, TNF, IFN-γ, IL-21

T follicular helper cells (Tfh) (number per million of total CD4+ Tcells)	**Combinations:**	CD4 CRM19740L+G+2+13+17+21+T+/CD4 CD4 CRM19740L+G+2+13+17+21+T-/CD4 CD4 CRM19740L+G+2+13+17-21+T+/CD4 CD4 CRM19740L+G+2+13+17-21+T-/CD4 CD4 CRM19740L+G+2+13-17+21+T+/CD4 CD4 CRM19740L+G+2+13-17+21+T-/CD4 CD4 CRM19740L+G+2+13-17-21+T+/CD4 CD4 CRM19740L+G+2+13-17-21+T-/CD4 CD4 CRM19740L+G+2-13+17+21+T+/CD4 CD4 CRM19740L+G+2-13+17+21+T-/CD4 CD4 CRM19740L+G+2-13+17-21+T+/CD4 CD4 CRM19740L+G+2-13+17-21+T-/CD4 CD4 CRM19740L+G+2-13-17+21+T+/CD4 CD4 CRM19740L+G+2-13-17+21+T-/CD4 CD4 CRM19740L+G+2-13-17-21+T+/CD4 CD4 CRM19740L+G+2-13-17-21+T-/CD4 CD4 CRM19740L+G-2+13+17+21+T+/CD4 CD4 CRM19740L+G-2+13+17+21+T-/CD4 CD4 CRM19740L+G-2+13+17-21+T+/CD4 CD4 CRM19740L+G-2+13+17-21+T-/CD4 CD4 CRM19740L+G-2+13-17+21+T+/CD4 CD4 CRM19740L+G-2+13-17+21+T-/CD4 CD4 CRM19740L+G-2+13-17-21+T+/CD4 CD4 CRM19740L+G-2+13-17-21+T-/CD4 CD4 CRM19740L+G-2-13+17+21+T+/CD4 CD4 CRM19740L+G-2-13+17+21+T-/CD4 CD4 CRM19740L+G-2-13+17-21+T+/CD4 CD4 CRM19740L+G-2-13+17-21+T-/CD4 CD4 CRM19740L+G-2-13-17+21+T+/CD4 CD4 CRM19740L+G-2-13-17+21+T-/CD4 CD4 CRM19740L+G-2-13-17-21+T+/CD4 CD4 CRM19740L+G-2-13-17-21+T-/CD4 among CD3+CD4+CD45RA- cells
T follicular helper cells (Tfh)(1) (number per million of total CD4+ Tcells)	This analysis was put on hold and may be performed later.	
CMI (exploratory endpoints)	**List of markers and combinations[1]**	
	Markers:	CD45RA**,** CXCR5, CXCR3, CCR6, ICOS, PD1

T follicular helper cells (Tfh)(2) (number per million of total PBMCs)	**Combinations:**	CXCR3+CCR6-ICOS+ CXCR3+CCR6-PD1+ CXCR3-CCR6+ ICOS+ CXCR3-CCR6+ PD1+ CXCR3-CCR6- ICOS+ CXCR3-CCR6- PD1+ Treated as six individual populations Among CD3+CD4+CD45RA-CXCR5+ cells
Differentiation (frequency in % of antigen-specific CD4+ T-cells)	This analysis was put on hold and may be performed later.	

1 For the different markers and combinations, the "CD3+" is omitted from the laboratory test description in the datasets.

Endpoints:

a. The number and percentage of subjects with CRM197-specific CD4+ T-cells at each blood sampling time point.

T-cell functionality

b. For each functional marker, the number of cells expressing the given marker at each blood sampling time point. The number of cells will be obtained by calculating the sum of the cytokine combinations for each subject first.

c. The number of cells expressing at least one functional marker (among CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21) expressed per million total CD4+ T cells at each blood sampling time point. The number of cells will be obtained by calculating the sum of the cytokine combinations for each subject first.

d. The number and percentage of subjects with a given polyfunctional CD4+ profile.

e. The number of CRM197-specific CD4+ T-cells, expressed per million of total CD4+ T cells, in each Th subset (Th0, Th1, Th2, Th17, Tfh). The number of cells will be obtained by calculating the sum of the cytokine combinations for each subject first.

T follicular helper cells Tfh(2)

f. Number of CD4+CXCR5+ T-cells expressing chemokine receptors (CXCR3, CCR6) and activation markers (ICOS, PD1), expressed per million of PBMCs

Antigen-specific T follicular helper cells (Tfh(1) was put on hold and may be performed later)

g. Number of CRM197-specific CD4+ IL-21+ ICOS+ T-cells expressed per million of CD4+ T cells

h. Number of CRM197-specific CD4+ IL-21+ T-cells expressing activation markers (ICOS, CXCR5), expressed per million of CD4 T cells

T-cell differentiation (This analysis was put on hold and may be performed later)

i. Number of CRM197-specific CD4+ T-cells expressing at least one functional marker (among CD40L, IL-2, TNF, IFN-γ, IL-13, IL-17, IL-21) in each differentiation subset (naïve, TCM, TEM27+, TEM27-, TEMRA), expressed per million of CD4+ T cells. Analysis Method:

a. The percentage of subjects with CRM197-specific CD4+ T-cells and associated twosided 95% Clopper-Pearson CIs will be summarized by vaccine dosage group for each blood sampling time point.

b. The number of cells (per million of total CD4+ T-cells) expressing at least one functional marker will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

c. The change from baseline in number of cells (per million of total CD4+ T-cells) expressing at least one functional marker will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

d. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of cells (per million of total CD4+ T-cells) expressing at least one functional marker and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

e. The number of cells (per million of total CD4+ T-cells) expressing a given marker will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

f. The change from baseline in number of cells (per million of total CD4+ T-cells) expressing a given marker will be calculated per subject and summarized using

medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

g. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of cells (per million of total CD4+ T-cells) expressing a given marker and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

h. The percentage of subjects with a given polyfunctional CD4+ profiles will be tabulated and presented graphically by vaccine dosage group for each blood sampling time point.

i. The number of CRM197-specific CD4+ T-cells in each Th subset (Th0, Th1, Th2, Th17, Tfh) expressed per million of total CD4+ T cells will be tabulated and presented by vaccine dosage group for each blood sampling time point.

j. The change from baseline in number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each Th subset (Th0, Th1, Th2, Th17, Tfh) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

k. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each Th subset (Th0, Th1, Th2, Th17, Tfh) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

l. Number of CD4+CXCR5+ T-cells (per million PBMCs) expressing follicular markers (CXCR3, CCR6) and activation markers (ICOS, PD1) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

m. The change from baseline in number of CD4+ CXCR5+ T-cells (per million PBMCs) expressing follicular markers (CXCR3, CCR6) and activation markers (ICOS, PD1) will be calculated per subject and summarized using medians and corresponding twosided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

n. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CD4+ CXCR5+ T-cells (per million PBMCs) expressing follicular markers (CXCR3, CCR6) and activation markers (ICOS, PD1) and

corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

o. Number of CRM197-specific CD4+ IL-21+ ICOS+ T-cells (per million CD4+ T cells) will be calculated by adding the CXCR5+ and CXCR5- subpopulations for each subject, and summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

p. The change from baseline in number of CRM197-specific CD4+ IL-21+ ICOS+ T cells (per million CD4+ T cells) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

q. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ IL-21+ ICOS+ T-cells (per million CD4+ T cells) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

r. Number of CRM197-specific CD4+ IL-21+ T-cells (per million CD4+ T-cells) expressing activation markers (ICOS, CXCR5) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

s. The change from baseline in number of CRM197-specific CD4+ IL-21+ T-cells (per million CD4+ T cells) expressing activation markers (ICOS, CXCR5) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

t. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ IL-21+ T-cells (per million CD4+ T cells) expressing activation markers (ICOS, CXCR5) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

u. The number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each differentiation subset (naïve, TCM, TEM27+, TEM27-, TEMRA) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

v. The change from baseline in number CRM197-specific CD4+ T-cells (per million

CD4+ T cells) in each differentiation substet (naïve, TCM, TEM27+, TEM27-, TEMRA) will be calculated per subject and summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

w. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of CRM197-specific CD4+ T-cells (per million CD4+ T cells) in each differentiation subset (naïve, TCM, TEM27+, TEM27-, TEMRA) and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point.

x. To test for differences in the proportion of expressing cells among the dose groups, a Kruskal-Wallis test will be performed for each cytokine/surface marker for each time point. If significant, then pairwise testing of the dose groups will be performed using the Hodges Lehmann (HL) approach which provides the median of the pairwise difference of the dose groups along with its 95% CI. The Kruskal-Wallis test will be repeated on the Day 8 and Day 29 values after adjusting for Day 1 baseline (i.e, Day 8 - Day 1 baseline and Day 29 - Day 1 baseline), followed by pairwise testing.

Graphical Displays: To better illustrate the differences between the dosage groups, the number of T cells expressing specific immune markers may be graphically displayed as a box plot or bar chart with the dosage groups differentiated by symbol, color, or grouping.

Criteria for Assessment: The impact of vaccination on frequency of T cell populations will be described by dosage group using the change from baseline in number of cells expressing specific immune markers.

a. The impact of LHD153R on frequency of T cell populations will be described using the differences between the LHD153R groups and the MenC control group.

b. To describe the impact of the dosage of LHD153R on frequency of T cell populations, the pairwise differences among the LHD153R groups will be used.

Possible additional exploratory analyses: The relationship between antibody response (ELISA and SBA; y-axis) and the T-cell percentages for selected cytokines/surface markers may be plotted differentiating the dose groups by symbol, color or grouping.

2.7 MenC Polysaccharide and CRM-specific B-cells

Objective: The objective is to assess the frequency of antigen specific B cells and long lasting memory B cells (MBCs) induced by LHD153R. The expectation is that there will be increases in the plasma and memory B-cells with LHD153R and that the increases will be dosage-dependent.

The frequency of B cells specific for MenC polysaccharide (Ps) and CRM_{197} will be determined by ELISPOT at Day 1 baseline (prior to vaccination), Day 8, Day 29 and Day 181 in order to evaluate the baseline specific B-cell frequency (Day 1 baseline), the peak of plasmablast responses (Day 8), the peak of B cell memory responses (Day 29), and the persistence of memory B cell responses (Day 181).

Endpoints:

a. The frequency of circulating MenC Ps and CRM-specific plasmablasts at Day 8 (expressed as Antibody Secreting Cells (ASC) IgG+/million PBMC and Antibody Secreting Cells (ASC) IgM+/million PBMC)

b. The number and percentage of subjects with detectable frequencies of MenC Ps-MBC and CRM-MBC at Day 1, Day 29, and Day 181.

c. The frequency of circulating MenC Ps-MBC and CRM-MBC (expressed as percentage of antigen-specific MBC/Total IgG and antigen-specific MBC/Total IgM) at Day 1, Day 29, and Day 181.

d. Within subject fold change of circulating MenC PS-MBC and CRM-MBC from baseline Day 1 to Day 29 and to Day 181.

e. Within subject fold change of circulating MenC PS-MBC and CRM-MBC from Day 29 to Day 181.

Analysis Method:

a. The number of circulating IgG+ and IgM+ MenC Ps and CRM-specific plasmablasts at Day 8 (expressed as ASC/million PBMC) will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

b. The percentage of subjects with detectable frequencies of IgG+ and IgM+ MenC PsMBC and CRM-MBC will be summarized using two-sided 95% Clopper-Pearson CIs by vaccine dosage group for samples taken at days 1, 29 and 181.

c. The frequencies of circulating IgG+ and IgM+ MenC Ps-MBC and CRM-MBC will be summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group for samples taken at days 1, 29 and 181. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

d. When baseline day 1 values are non-zero, the fold changes of circulating MBC between Day 29 and baseline Day 1, and Day 181 and baseline Day 1, will be

summarized using medians and corresponding two-sided, 95% CIs around the median by vaccine dosage group. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

Graphical Displays:

a. The number of IgG+ and IgM+ MenC Ps and CRM-specific plasmablasts induced by each dosage of LHD153R at Day 8 will be explored by plotting the median number of IgG+ and IgM+ plasmablasts per million PBMC (y-axis) against LHD153 dose (xaxis) differentiating each dosage group by symbol or color.

b. A graphical display will be generated for the Day 1, Day 29 and Day 181 median frequencies of IgG+ and IgM+ MenC Ps and CRM-specific memory B-cells of different vaccination groups differentiating each dosage group by symbol, color or line type.

Criteria for Assessment:

a. To test for differences in the number of circulating IgG+ and IgM+ MenC Ps and CRM-specific plasmablasts at Day 8, the Kruskal-Wallis test will be performed. If the overall test is significant, then pairwise testing of the dose groups will be performed using the HL approach which provides the median of the pairwise difference of the dose groups along with its 95% CI.

b. To test for the percentage of subjects with detectable frequencies of MenC Ps-MBC and CRM-MBC at days 1, 29 and 181, a test will be performed at each time point. If significant, then pairwise comparisons of the dose groups will be performed with no adjustment for multiplicity.

c. To test for the frequencies of circulating MenC Ps-MBC and CRM-MBC at days 1, 29 and 181, the Kruskal-Wallis test will be performed. If the overall test is significant, then pairwise testing of the dose groups will be performed using the HL approach which provides the median of the pairwise difference of the dose groups along with its 95% CI. The Kruskal-Wallis test will be repeated on the fold changes, followed by pairwise testing.

d. To evaluate differences among the dosage groups in the eCDFs of frequencies of IgG+ and IgM+ MenC Ps and CRM-specific memory B-cells, the KolmogorovSmirnov test will be performed (Brittain, 1984 and 1987). If significant, then pairwise comparisons of the eCDFs will be performed.

Possible additional exploratory analyses: The relationship between antibody response (ELISA and SBA; y-axis) and the B-cell percentages for selected markers may be plotted differentiating the dose groups by symbol, color or grouping. Additionally, the Spearman correlation coefficients will be provided.

2.8 Early Biomarkers of Safety and Innate Immune Response

2.8.1 Microarrays

Objective: The objective is to evaluate the vaccine-induced modulation of transcriptome responses in blood transcriptional modules (BTMs), specifically the interferon and inflammatory BTMs.

The vaccine-induced modulation of transcriptome responses will be evaluated on whole blood samples collected at 5 time points: Day 1 (pre-vaccination and 6h after vaccination), Day 2 (24h after vaccination), Day 4 and Day 8. Base analysis will be performed using sets of coordinately regulated genes, or BTMs), as defined by Obermoser, G. *et al.* (2013).

Previously conducted analyses in a non-human primate model have shown that the inclusion of LDH153R in the formulation produces a significant upregulation of 3 BTMs (M1.2, M3.4 and M5.12) containing interferon stimulated genes at 24 hours after vaccine administration. Furthermore, the addition of LDH153R did not upregulate any of the BTMs containing proinflammatory genes (M3.2, M4.2, M4.6, M4.13, M5.1, M5.7 and M7.1).

Specifically, the aim is to show that the LHD153R adjuvant significantly upregulates the response of the interferon BTMs (M1.2, M3.4 and M5.12) but not the pro-inflammatory BTMs (M3.2, M4.2, M4.6, M4.13, M5.1, M5.7 and M7.1) in at least one LHD153R dosage group compared to the MenC control group at 24 hours post-vaccination.

Endpoints:

Vaccine Induced Modulation of Interferon and Pro-Inflammatory Transcriptional Modules

a. The module-specific geometric mean response for each blood sampling time point. For each of the 10 BTMs (3 interferon, 7 pro-inflammatory), the subject level module response will be determined by computing the average log2 fluorescence intensity of genes belonging to the module at each blood sampling time point.

b. The module-specific geometric mean fold change from baseline Day 1 to each postvaccination sampling time point. For each BTM, the subject-level fold change from pre-vaccination to each post-vaccination time point will be computed (ie, postvaccination value / pre-vaccination value). Module level responses will be computed by averaging the log2 scaled, subject-level fold-changes for each dosage group and blood sampling time point.

Vaccine Induced Transcriptome Responses

c. Gene level fold change from baseline in transcriptome response for each gene at each post-vaccination blood sampling time point. In order to reduce the false discovery rate, the

initial set of genes will be reduced by applying a non-specific filtering to the pooled samples coming from all available dosage groups, including the control group. Only those genes showing a between subject interquartile range, in the log2transformed fold change from baseline, ≥ 0.5 will be retained. Analysis Methods:

a. To evaluate the LHD153R ability to upregulate the expression level of a given BTM at a specified time point the following hypothesis needs to be tested for each BTM:
H_0: $(\mu_{LHD153-12.5} \leq \mu_{MenC})$ and $(\mu_{LHD153-25} \leq \mu_{MenC})$ and $(\mu_{LHD153-50} \leq \mu_{MenC})$
and $(\mu_{LHD153-100} \leq \mu_{MenC})$

H_a: $(\mu_{LHD153-12.5} > \mu_{MenC})$ or $(\mu_{LHD153-25} > \mu_{MenC})$ or $(\mu_{LHD153-50} > \mu_{MenC})$
or $(\mu_{LHD153-100} > \mu_{MenC})$

The module response, fold change from baseline at the 24 hour time point, will be analyzed using analysis of variance (ANOVA) with the module response as the dependent variable and a fixed effect for dosage group. The adjusted (model-based) geometric mean fold changes, adjusted ratios of geometric mean responses between vaccine dosage groups and the corresponding two-sided, 95%, confidence intervals will be calculated based on this model. Should the data violate the normality assumption, then a Kruskal-Wallis test will be performed instead, followed by pairwise testing of the dosage groups in the same manner as previously described.

All 10 BTMs will be evaluated and the p-values adjusted using the BenjaminiHochberg False Discovery Rate (FDR) control procedure. BTMs with an adjusted pvalue ≤ 0.05 will be examined further.

b. The module-specific geometric mean fold changes will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

c. To identify transcriptional signatures which are correlated to serum bactericidal assay (SBA) titers, Spearman's rank correlation coefficients will be determined for each gene using the log2 gene-level fold change from baseline and the log2 transformed SBA titer at each post-vaccination time point. Genes will be ranked from largest magnitude to smallest magnitude of the correlation coefficient (ie, by the absolute

value of the coefficient) and presented in rank order with the upper 10-th percentile identified for each post-vaccination time point.

Graphical Displays: The upregulation, or lack thereof, will be presented graphically for the modules being examined by dosage group.

Criteria for Assessment: This exploratory endpoint will be verified if the overall null hypotheses are rejected for at least 2 of the 3 interferon BTMs (M1.2, M3.4 and M5.12) and rejected for at most 2 of the 7 pro-inflammatory BTMs (M3.2, M4.2, M4.6, M4.13, M5.1, M5.7 and M7.1), with significance level $\alpha \leq 0.05$ (after correction for multiple testing), at the 24 hour post-vaccination time point.

As a hypothesis generating exercise, the same procedure will also be used for the other time points [Day 1 (6 hours), Day 4 and Day 8], in order to evaluate LHD153R effects at time points different from the 24 hours.

For innate transcriptome response predictive of hSBA, genes with a correlation coefficient above the 90-th percentile (as defined earlier) will be considered the most correlated genes, either positively or negatively. Possible additional exploratory analyses:

Additionally, the relationship between significant BTMs and solicited AEs may be evaluated by plotting the fold-change (y-axis) for subjects with a given severity of the solicited adverse event (x-axis) with vaccine group differentiated by symbol, color or grouping.

Functional enrichment analysis for those genes identified as correlated, or inversely correlated, to hSBA titers will be performed by testing all gene ontology terms and testing whether any category terms are over represented using the hypergeometric test.

2.8.2 Cytokines and Chemokines

Objective: To evaluate biomarkers that may be predictive of safety and/ or innate immune activation.

The vaccine-induced production of inflammatory cytokines and chemokines will be evaluated on serum samples using a commercially available multiplex electrochemiluminescence immunoassay for a panel of pro-inflammatory cytokines and chemokines. Cytokines and chemokines will be measured from serum collected at 5 time points: Day 1 (pre-vaccination and 6h after vaccination), 24h after vaccination (Day 2), Day 4 and Day 8.

There is no formal statistical hypothesis associated with this objective. However, based on pre-clinical results in non-human primates, inducible 10-kilodalton (kDa) protein (IP-10) concentrations at early time points may be detected at higher levels compared to baseline values of each subject. Further, different levels of serum chemokines and cytokines are expected in human healthy donors (Biancotto, et al, 2013). The kinetics of soluble mediators will be evaluated from baseline to early time points (up to Day 8) in serum. In each subject, cytokine and chemokine concentrations measured at different time points after vaccination will be compared to their baseline levels.

Table 4 List of Cytokines and Chemokines in Plasma by Multiplex (pg/mL)

Assays (units)	List of soluble mediators or markers of cellular effectors
Chemokines indicating activation of immune response which stimulate cell recruitment	
	Eotaxin, Eotaxin-3 MCP-1; MCP-4 MDC MIP-1α; MIP-1β TARC IP-10 IL-8
Cytokines indicating a general activation of the immune system	
Proinflammatory	GM-CSF IL-1α; IL-2; IL-5; IL-7; IL-12/IL-23p40; IL-15; IL-16 TNF- β VEGF-A **tokines indicating activation of the innate immune system**
c	
	IFN-γ IL-1β; IL-4; IL-6; IL-8; IL-10; IL-12 p70; IL-13; IL-17A TNF-α

MCP-1 = monocyte chemo-attractant protein – 1; MIP-1α = macrophage inflammatory protein – 1α; MDC = macrophage-derived chemokine; TARC = thymus and activation-regulated chemokine; IP-10 = inducible 10kilodalton (kDa) protein; IL-8 = interleukin – 8; IFN-γ = interferon gamma; GM-CSF = granulocyte macrophage colony stimulating factor; TNF-β = tumor necrosis factor – beta; VEGF-A = vascular endothelial growth factor – A.

Endpoint(s):

a. The number and percentage of subjects with evaluable concentrations at or above the lower limit of detection (LLOD), as well as below the LLOD for each cytokine/chemokine for each dosage group and blood sampling time point.

b. Cytokine and chemokine geometric mean concentrations for each dosage group and blood sampling time point.

c. Subject level fold change from baseline in the concentration for each cytokine/chemokine for each post-vaccination blood sampling time point.

Analysis Method:

a. The percentage of subjects above and below LLOD and associated two-sided 95% Clopper-Pearson CIs will be summarized by dosage group for each cytokine/chemokine at each blood sampling time point.

b. Cytokine and chemokine geometric mean concentrations will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

c. Change from baseline in the concentration of each cytokine and chemokine (subjectlevel fold change) will be summarized using unadjusted geometric means and corresponding two-sided, 95% CIs by vaccine dosage group for each post-vaccination blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

Graphical Displays: For each cytokine or chemokine with detectable levels, plot the mean concentration level over time for each group, indicating each dosage group with a symbol, color, or line type.

Additionally, for each cytokine or chemokine with detectable levels, plot the cumulative percentage of subjects with at least an *n*-fold change over baseline (n ranges from the minimum to maximum fold change across all time points) for each time point, indicating each dosage group with a symbol, color or line type.

Criteria for Assessment:

a. Geometric mean fold rises and corresponding CIs will be used to determine which cytokines and chemokines have higher concentrations as compared to baseline concentrations.

b. To evaluate differences in geometric mean ratios (GMRs) among the dosage groups, a Kruskal-Wallis test will be performed for each time point. If significant, then pairwise comparisons of the dosage groups will be performed with no adjustment for multiple comparisons. This is to identify any chemokines or cytokines that may be predictive of safety and/or innate immune activation.

c. To evaluate differences in proportions of subjects with at least a two-fold change from baseline among the dosage groups, a test will be performed for each postvaccination time point. If significant, then pairwise comparisons of the dosage groups will be performed with no adjustment for multiple comparisons.

d. To evaluate differences among the dosage groups in the empirical cumulative distribution functions (eCDFs) of the proportions of subjects with at least an *n*-fold change over baseline, the Kolmogorov-Smirnov test will be performed. If significant, then pairwise comparisons of the eCDFs will be performed using the two-sample Kolmogorov-Smirnov test.

Possible additional exploratory analyses:

If the number of observations with measurable levels permit, the kinetics of the soluble mediator(s) will be evaluated from baseline up to day 8 post-vaccination in serum.

Should LHD153 have detectable levels also, a graphical representation of the correlation between the any cytokine/chemokine with measurable levels and the LHD153 concentration will be generated with dosage group differentiated by symbol, color or line type.

If differences or trends in solicited AEs between vaccine dosage groups are observed, then the relationship between chemokine/cytokine concentrations and solicited AEs at a given time point may be evaluated by plotting the concentrations of the chemokine/cytokine (yaxis) with the severity of the solicited adverse event (x-axis) with vaccine dosage group differentiated by symbol, color or grouping.

Appendices include information about the derivation of the LLODs.

2.8.3 Activation Status of Myeloid and Lymphoid Cells

Objective: The objective is to understand the impact of LHD153R adjuvant on the frequency and activation status of myeloid and lymphoid cells induced by vaccination. Peripheral blood mononuclear cells (PBMCs) will be obtained from blood obtained at baseline (prior to vaccination), 24 hours after vaccination, on Day 4 (72 hours after vaccination) and on Day 8.

Table 5 List of Markers of Cellular Effectors – Innate Cells in PBMCs by Flow Cytometry

Myeloid cells		
	Phenotyping (number of cells per million PBMCs)	
	Classical monocytes (CMo):	Lin- HLADR+ CD14++ CD16-
	Intermediate monocytes (IMo):	Lin- HLADR+ CD14+ CD16+
	Non-classical monocytes (NCMo):	Lin- HLADR+ CD14dim CD16+
	Conventional myeloid DC (cmDC):	Lin- HLADR+ CD14- CD11c+ CD123- CD1c+
		Lin- HLADR+ CD14- CD11c+ CD123- CD1c-
	Plasmacytoid DC (pDC):	Lin- HLADR+ CD14- CD11c- CD123+

	Activation (MFI of activation markers on the different cell subsets)

Classical monocytes (CMo):	CMo/HLADR
	CMo/CD40
	CMo/CD86
	CMo/CD32
	CMo/CD64
Intermediate monocytes (IMo):	IMo/HLADR
	IMo/CD40
	IMo/CD86
	IMo/CD32
	IMo/CD64
Non-classical monocytes (NCMo):	NCMo/HLADR
	NCMo/CD40
	NCMo/CD86
	NCMo/CD32
	NCMo/CD64
Conventional myeloid DC (cmDC):	cmDC CD1c+ /HLADR
	cmDC CD1c- /HLADR
	cmDC CD1c+ /CD40
	cmDC CD1c- /CD40
	cmDC CD1c+ /CD86
	cmDC CD1c- /CD86
	cmDC CD1c+ /CD32
	cmDC CD1c- /CD32
	cmDC CD1c+ /CD64
	cmDC CD1c- /CD64
Plasmacytoid DC (pDC):	pDC /HLADR
	pDC /CD40
	pDC /CD86
	pDC /CD32
	pDC /CD64

Lymphoid cells		
	Phenotyping (number of cells per million PBMCs)[1]	
	γδT:	CD3+ CD19- TCRγδ+
	Natural Killer (NK) cells subtype 1 (NK1):	CD3- CD19- CD16+ CD56dim
	NK cell subtype 2 (NK2):	CD3- CD19- CD16- CD56+
	Activation (MFI of activation markers on the different cell subsets)	
	γδT:	γδT/HLADR+
	NK cells subtype 1:	NK1/HLADR+
	NK cell subtype 2:	NK2/HLADR+

1. Both CD19 and CD20 markers identify the same B-cells population; the only difference between the two markers is that CD20 is downregulated in particular subsets of B-cells under particular conditions while CD19 expression is not modulated. Therefore, we decided to use CD19 as a marker to catch all the B-cells instead of the originally planned CD20.

Endpoint(s): Cellular effectors from the innate/early immune response:

- Innate cell phenotyping at each sampling time:
  (1): Number per million PBMCs of innate cells including myeloid cells (e.g. dendritic cells [DC], monocytes) showing a particular phenotype characterized by a combination of specific surface markers (e.g. HLA-DR, CD14, CD123, CD16), as measured by flow cytometry.
  (2): Number per million PBMCs of innate cells including lymphoid cells (e.g. natural killer [NK], γδT cells) showing a particular phenotype characterized by a combination of specific surface markers (e.g. CD3, CD16, CD56), as measured by flow cytometry.
- Innate cells activation at each sampling time:
  (1): Level of expression (median fluorescence intensity, MFI) of activation markers (e.g., HLA-DR, CD86, CD40, CD32, CD64) on myeloid cells (DC, monocytes) as measured by flow cytometry using PBMC.
  (2): Level of expression (MFI) of activation markers (e.g. HLA-DR) on lymphoid cells (γδ T cells, NK cells) as measured by flow cytometry using PBMC.

Analysis Methods:

a. The number and percentage of subjects with each type of effector cell as listed in Table 5 and associated two-sided 95% Clopper-Pearson CIs will be computed by vaccine dosage group for each blood sampling time point.

b. The number of innate cells expressing specific immune markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately.

Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

c. The level of expression of activation markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

d. The change from baseline in number of innate cells expressing specific immune markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately. Summary statistics will be completed by providing minimum, maximum, first and third quartiles.

e. The change from baseline in level of expression of activation markers will be summarized using medians and corresponding two-sided, 95% CIs by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the mean.

f. Differences between dosage groups (all pairwise differences) in the change from baseline in the number of innate cells expressing specific surface markers and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately.

g. Differences between dosage groups (all pairwise differences) in the change from baseline in the level of expression of activation markers and corresponding two-sided 95% CIs will be summarized by dosage group for each blood sampling time point. Myeloid and lymphoid cells will be summarized separately.

h. To test for differences in the proportion of expressing cells among the dose groups, a Kruskal-Wallis test will be performed for each surface marker for each time point. If significant, then pairwise testing of the dose groups will be performed using the Hodges Lehmann (HL) approach which provides the median of the pairwise difference of the dose groups along with its 95% CI. The Kruskal-Wallis test will be repeated on the Day 1 (24h), Day 4, and Day 8 values after adjusting for Day 1 (baseline) (i.e., Day 8 - Day 1 baseline, Day 4 – Day 1 baseline, and Day 1 24 h - Day 1 baseline), followed by pairwise testing.

Criteria for Assessment:

a. The impact of vaccination on frequency and activation status of myeloid and lymphoid cells will be described by dosage group using the change from baseline in

number of innate cells expressing specific immune markers and the change from baseline in the level of expression of activation markers.

b. The impact of LHD153R on frequency and activation status of myeloid and lymphoid cells will be described using the differences between the LHD153R groups and the MenC control group.

c. To describe the impact of the dosage of LHD153R on frequency and activation status of the myeloid and lymphoid cells, the pairwise differences among the LHD153R groups will be used.

Possible additional exploratory analyses: Graphical displays of the number of innate cells expressing specific immune marker or the level of expression of activation markers may be produced to better illustrate the differences between the dosage groups.

2.9 Conditional Exploratory Data Analysis

The analyses described in this section depend on the outcomes of prior analyses, including the primary and secondary study endpoints as well as the exploratory endpoints described in previous sections. These analyses may be done in a time-frame different from the other analyses proposed in this statistical analysis plan (SAP) and may be reported separately.

2.9.1 MenC polysaccharide and CRM specific B cell repertoire

Objective: The objective is to understand the impact of LHD153R adjuvant on the B cell repertoire. The expectation is that the B cell diversity (i.e., "antibody signature" and clonotypes) will differ between at least one LHD153R dosage group and the MenC control group. Specifically, it is expected that LHD153R will induce more clonal response (a different size distribution of clones) and have a longer average length of the phylogenetic trees within the clones.

The diversity of the antigen specific B-cell repertoire will be analyzed in a selected subset of subjects. The selection of the subset will be based on the most pronounced response to the study vaccines when compared to baseline as determined by the primary and secondary immunogenicity assessment. Subjects with too few cells recovered or with very low frequencies of MenC Polysaccharide-specific B cells (as assessed by ELISpot) will be excluded.

The diversity of the elicited B-cell receptors will be assessed through sequence analysis of cDNA generated from immunoglobulin (Ig) messenger RNA (mRNA). The Ig cDNAs will be analyzed from antigen-specific B-cells obtained at Day 1, Day 29 and/or Day 181 and plasmablasts isolated at Day 8.

The following analyses were planned but will not be performed due to a decision to not perform the required assay procedures.

Endpoints:

a. Size of the clones at each sampling time point

b. Length of the phylogenetic trees within the clones at each sampling time point

Analysis Method:

a. The size of the clones will be summarized using arithmetic means and corresponding two-sided, 95% CIs around the mean by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

b. The length of the phylogenetic trees within the clones will be summarized using arithmetic means and corresponding two-sided, 95% CIs around the mean by vaccine dosage group for each blood sampling time point. Summary statistics will be completed by providing minimum, maximum, first and third quartiles as well as the median.

Graphical Displays:

The distribution of clonal sizes will be graphically displayed by dosage group at each measurement time.

Criteria for Assessment:

The Kruskal-Wallis test will be performed to compare the vaccine groups overall. If the overall test is significant, then the Dunnett multiple comparison procedure will be used to control the overall significance level to compare the LHD153 groups to the Menjugate control group.

Possible additional exploratory analyses:

For clones and phylogenetic trees significantly different between the LHD153R and Men-C control groups, the correlation with SBA levels will be explored. Additionally, the correlation with SBA levels will be displayed graphically by clonal size (x-axis) using symbols and/or color to differentiate vaccine groups.

2.9.2 Functionality of MenC-specific Antibodies

Objective: The objective is to evaluate the functionality of MenC-specific antibodies to fix complement, promote antibody-dependent cell mediated cytoxicity (ADCC), induce phagocytosis and activate FcR+ cells in vitro at Day 1 (baseline), Day 8, Day 29, and Day 181.

2.9.3 Integrated Analysis

The different immunological readouts collected in this trial may be integrated with the primary and secondary readouts collected to identify specific combinations of immune

signals that are associated with the administered adjuvant dosage or that can predict immunogenicity or safety outcomes. This integration may be performed in three steps:

1. Methods from signal detection theory will be applied to single readouts to: a) identify novel patterns and dimensionality-reduction approaches (e.g., trends in readouts not clinically relevant per se but significantly stratified by treatment group, gene expression patterns not already defined as transcriptional modules) and b) search for correlations between single readouts and safety or immunogenicity outcomes using the improved patterns identified.
2. Unsupervised Machine Learning methodologies will be applied to integrate the multiscale data available (possibly dimensionally-reduced as in step 1 and identify combinations of immune signals that a) predict the clinical outcome, and b) are associated with the treatment administered (e.g., combinations of body-temperature trends, transcriptional responses and cytokine/chemokine concentrations predictive of local solicited AEs, some dependent on the adjuvant dosage, some independent).
3. Causal inference models will be explored to identify associations among the data, assumed from scientific knowledge or inferred by the two previous analyses, supported by a causal relationship and influencing directly the final outcome (e.g., contrasting the influence on immunogenicity of pre-vaccination immunity, vaccine administered, early transcriptional responses, B and T cellular frequencies and functional antibody profiles).

3. PEER REVIEW

The type of peer review required for each output is to be identified by the study Biostatistician and Statistical Programmer (SP) in the Table of Contents (TOC, see BCDM14 TEMP 04). Analyses/Outputs requiring statistical peer review correspond usually to the analyses of the primary and secondary objectives, and data conversion programs. Peer review of these analyses should be performed in accordance with the applicable procedures for validation of SAS programs used in clinical data analysis.

The following analyses are identified as analyses to be peer reviewed by a biostatistician independent from the study:

- None

The following programs are identified as programs to be peer reviewed by a second SP:

- The mapping of the phenotypes
- Checking of the distribution free analysis by running a Proc Means and calculating the confidence intervals

4. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

For the complete list of tables, listings and figures (TLFs), please refer to the TOC.

5. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

All TLFs are to include the following header:

GlaxoSmithKline Biologicals, S.A.	Adjuvant: LHD153R
Additional Analysis: Study V132_01EXP	Exploratory Endpoints

In all tables, listings and figures, vaccine groups will be labeled as "MenC", "LHD153R 12.5", "LHD153R 25.0", "LHD153R 50.0" and "LHD153R 100.0".

For the mock-up catalogue to be used during programming, please refer to the document stored in /GSKVX/Files/NVX/analysis/v132/v132_01exp/ within the SAS Drug Development (SDD) server.

Since tables and listings will be produced using SAS® as well as R, the output actually generated may slightly differ from the mock-ups presented in the study specific mock-up catalogue. Graphical figures of study data will be produced using graphical software, such as SAS and R, in a validated, controlled environment.

6. REFERENCES

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7. APPENDICES

Below is the CV% for each of the cytokine and chemokine assays.

Assay	CV%
IFN-γ	12.6
IL-10	10.0
IL-12p70	6.5
IL-13	16.4
IL-1β	24.2
IL-2	16.4
IL-4	15.9
IL-6	6.7
IL-8	3.6
TNF-α	14.7
Eotaxin	8.5

Assay	CV%
MCP-4	9.0
MDC	9.5
MIP-1α	8.7
MIP-1β	12.8
TARC	8.4
GM-CSF	16.1
IL-12/IL-23p40	7.9
IL-15	6.1
IL-16	5.4
IL-17A	13.9
IL-1α	16.0

Eotaxin-3	18.5		IL-5	32.4
IL-8 (HA)	11.5		IL-7	6.6
IP-10	10.9		TNF-β	15.7
MCP-1	11.2		VEGF	5.1

IFN = interferon; IL = interleukin; TNF-α = tumor necrosis factor – alpha; IP-10 = inducible 10-kilodalton (kDa) protein; MCP-1 = monocyte chemo-attractant protein – 1; MDC = macrophage-derived chemokine; MIP-1α = macrophage inflammatory protein – 1α; TARC = thymus and activation-regulated chemokine; GM-CSF = granulocyte macrophage colony stimulating factor; TNF-β = tumor necrosis factor – beta; VEGF = vascular endothelial growth factor.

This section contains additional information related to weighting for summaries of innate cell phenotyping and activation. The expression of specific immune markers and co-stimulatory molecules of interest can be obtained from the weighting in these tables.

Myeloid and Lymphoid Phenotyping and Lymphoid Activation Weights

	HLADR	CD14	CD16	CD11c	CD123	CD1c	CD3	CD56	TCRγδ	Any
Myeloid Phenotyping										
Lin- HLADR+ CD14++ CD16	1	1								1
Lin- HLADR+ CD14+ CD16+	1	1	1							1
Lin- HLADR+ CD14dim CD16+	1		1							1
Lin- HLADR+ CD14- CD11c+ CD123- CD1c+	1			1		1				1
Lin- HLADR+ CD14- CD11c+ CD123- CD1c-	1			1						1
Lin- HLADR+ CD14- CD11c- CD123+	1				1					1
Lymphoid Phenotyping										
CD3+ CD20- $TCR_{\gamma\delta}$+							1		1	1
CD3- CD20- CD16+ CD56dim			1					1		1
CD3- CD20- CD16- CD56+								1		1
Lymphoid Activation										
γδT/HLADR+	1									
NK1/HLADR+	1									
NK2/HLADR+	1									

Myeloid Activation Weights

	HLADR	CD40	CD86	CD32	CD64	CD1c
Myeloid Activation						
CMo/HLADR+	1					
CMo/CD40+		1				
CMo/CD86+			1			
CMo/CD32+				1		
CMo/CD64+					1	
IMo/HLADR+	1					
IMo/CD40+		1				
IMo/CD86+			1			
IMo/CD32+				1		
IMo/CD64+					1	
NCMo/HLADR+	1					
NCMo/CD40+		1				
NCMo/CD86+			1			
NCMo/CD32+				1		
NCMo/CD64+					1	
cmDC CD1c+ /HLADR+	1					1

cmDC CD1c- /HLADR+	1					
cmDC CD1c+ /CD40+		1				1
	HLADR	**CD40**	**CD86**	**CD32**	**CD64**	**CD1c**
cmDC CD1c- /CD40+		1				
cmDC CD1c+ /CD86+			1			1
cmDC CD1c- /CD86+			1			
cmDC CD1c+ /CD32+				1		1
cmDC CD1c- /CD32+				1		
cmDC CD1c+ /CD64+					1	1
cmDC CD1c- /CD64+					1	
pDC /HLADR+	1					
pDC /CD40+		1				
pDC /CD86+			1			
pDC /CD32+				1		
pDC /CD64+					1	

Laboratory Tests (LBTEST) for Cytokine Combinations	
CD4 CRM19740L+G+2+13+17+21+T+/CD4	CD4 SEB40L+G+2+13+17+21+T+/CD4
CD4 CRM19740L+G+2+13+17+21+T-/CD4	CD4 SEB40L+G+2+13+17+21+T-/CD4
CD4 CRM19740L+G+2+13+17+21-T+/CD4	CD4 SEB40L+G+2+13+17+21-T+/CD4
CD4 CRM19740L+G+2+13+17+21-T-/CD4	CD4 SEB40L+G+2+13+17+21-T-/CD4
CD4 CRM19740L+G+2+13+17-21+T+/CD4	CD4 SEB40L+G+2+13+17-21+T+/CD4
CD4 CRM19740L+G+2+13+17-21+T-/CD4	CD4 SEB40L+G+2+13+17-21+T-/CD4
CD4 CRM19740L+G+2+13+17-21-T+/CD4	CD4 SEB40L+G+2+13+17-21-T+/CD4
CD4 CRM19740L+G+2+13+17-21-T-/CD4	CD4 SEB40L+G+2+13+17-21-T-/CD4
CD4 CRM19740L+G+2+13-17+21+T+/CD4	CD4 SEB40L+G+2+13-17+21+T+/CD4
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CD4 CRM19740L+G+2+13-17+21-T+/CD4	CD4 SEB40L+G+2+13-17+21-T+/CD4
CD4 CRM19740L+G+2+13-17+21-T-/CD4	CD4 SEB40L+G+2+13-17+21-T-/CD4
CD4 CRM19740L+G+2+13-17-21+T+/CD4	CD4 SEB40L+G+2+13-17-21+T+/CD4
CD4 CRM19740L+G+2+13-17-21+T-/CD4	CD4 SEB40L+G+2+13-17-21+T-/CD4
CD4 CRM19740L+G+2+13-17-21-T+/CD4	CD4 SEB40L+G+2+13-17-21-T+/CD4
CD4 CRM19740L+G+2+13-17-21-T-/CD4	CD4 SEB40L+G+2+13-17-21-T-/CD4
CD4 CRM19740L+G+2-13+17+21+T+/CD4	CD4 SEB40L+G+2-13+17+21+T+/CD4
CD4 CRM19740L+G+2-13+17+21+T-/CD4	CD4 SEB40L+G+2-13+17+21+T-/CD4
CD4 CRM19740L+G+2-13+17+21-T+/CD4	CD4 SEB40L+G+2-13+17+21-T+/CD4
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CD4 CRM19740L+G+2-13+17-21+T+/CD4	CD4 SEB40L+G+2-13+17-21+T+/CD4
CD4 CRM19740L+G+2-13+17-21+T-/CD4	CD4 SEB40L+G+2-13+17-21+T-/CD4
CD4 CRM19740L+G+2-13+17-21-T+/CD4	CD4 SEB40L+G+2-13+17-21-T+/CD4
CD4 CRM19740L+G+2-13+17-21-T-/CD4	CD4 SEB40L+G+2-13+17-21-T-/CD4
CD4 CRM19740L+G+2-13-17+21+T+/CD4	CD4 SEB40L+G+2-13-17+21+T+/CD4
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CD4 CRM19740L+G+2-13-17-21+T-/CD4	CD4 SEB40L+G+2-13-17-21+T-/CD4
CD4 CRM19740L+G+2-13-17-21-T+/CD4	CD4 SEB40L+G+2-13-17-21-T+/CD4

CD4 CRM19740L+G+2-13-17-21-T-/CD4	CD4 SEB40L+G+2-13-17-21-T-/CD4
CD4 CRM19740L+G-2+13+17+21+T+/CD4	CD4 SEB40L+G-2+13+17+21+T+/CD4
CD4 CRM19740L+G-2+13+17+21+T-/CD4	CD4 SEB40L+G-2+13+17+21+T-/CD4
CD4 CRM19740L+G-2+13+17+21-T+/CD4	CD4 SEB40L+G-2+13+17+21-T+/CD4
Laboratory Tests (LBTEST) for Cytokine Combinations	
CD4 CRM19740L+G-2+13+17+21-T-/CD4	CD4 SEB40L+G-2+13+17+21-T-/CD4
CD4 CRM19740L+G-2+13+17-21+T+/CD4	CD4 SEB40L+G-2+13+17-21+T+/CD4
CD4 CRM19740L+G-2+13+17-21+T-/CD4	CD4 SEB40L+G-2+13+17-21+T-/CD4
CD4 CRM19740L+G-2+13+17-21-T+/CD4	CD4 SEB40L+G-2+13+17-21-T+/CD4
CD4 CRM19740L+G-2+13+17-21-T-/CD4	CD4 SEB40L+G-2+13+17-21-T-/CD4
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CD4 CRM19740L+G-2+13-17+21-T+/CD4	CD4 SEB40L+G-2+13-17+21-T+/CD4
CD4 CRM19740L+G-2+13-17+21-T-/CD4	CD4 SEB40L+G-2+13-17+21-T-/CD4
CD4 CRM19740L+G-2+13-17-21+T+/CD4	CD4 SEB40L+G-2+13-17-21+T+/CD4
CD4 CRM19740L+G-2+13-17-21+T-/CD4	CD4 SEB40L+G-2+13-17-21+T-/CD4
CD4 CRM19740L+G-2+13-17-21-T+/CD4	CD4 SEB40L+G-2+13-17-21-T+/CD4
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CD4 CRM19740L+G-2-13+17-21-T-/CD4	CD4 SEB40L+G-2-13+17-21-T-/CD4
CD4 CRM19740L+G-2-13-17+21+T+/CD4	CD4 SEB40L+G-2-13-17+21+T+/CD4
CD4 CRM19740L+G-2-13-17+21+T-/CD4	CD4 SEB40L+G-2-13-17+21+T-/CD4
CD4 CRM19740L+G-2-13-17+21-T+/CD4	CD4 SEB40L+G-2-13-17+21-T+/CD4
CD4 CRM19740L+G-2-13-17+21-T-/CD4	CD4 SEB40L+G-2-13-17+21-T-/CD4
CD4 CRM19740L+G-2-13-17-21+T+/CD4	CD4 SEB40L+G-2-13-17-21+T+/CD4
CD4 CRM19740L+G-2-13-17-21+T-/CD4	CD4 SEB40L+G-2-13-17-21+T-/CD4
CD4 CRM19740L+G-2-13-17-21-T+/CD4	CD4 SEB40L+G-2-13-17-21-T+/CD4

CD4 CRM19740L+G-2-13-17-21-T-/CD4	CD4 SEB40L+G-2-13-17-21-T-/CD4

The following tables present the genes that are included in the interferon and inflammation modules being considered for this study.

Ge es Included in Module M1.1 - Interferon		
LY6E	OAS1	FLJ20035
IFIT1	MX1	IFITM3
OAS1	BATF2	IFIT3
IFIT1	LAMP3	CXCL10
IFIT3	IFI44L	EPSTI1
OAS3	XAF1	SERPING1
IFIT3	OASL	LOC26010
OAS1	IFI44	OAS2
OASL	OAS2	RSAD2
LOC129607	TRIM6	RTP4
ISG15	HES4	
HERC5	OTOF	

Genes Included in Module M3.2 - Inflammation		
BCL6	SLC37A3	LOC643313
BASP1	LOC642816	FLJ20273
PBEF1	REPS2	MRVI1
KLHL2	F5	CEBPB
SLC2A3	SLA	TSHZ3
SULT1B1	LOC255809	SRPK1
PROK2	ETS2	NCF4
LIN7A	MEGF9	ST3GAL4
ROPN1L	PHTF1	GCA
PYGL	MME	S100A9
SLC11A1	BST1	FAM129A
LOC728417	TLR8	REPS2

LOC641710	GNG10	SEPX1
TGFA	FPRL1	LOC653610
GPR97	SIGLEC5	SLC11A1
KCNJ15	FLJ22662	C16orf57
LOC399744	TLR4	RAB31
TLR6	TLR8	GPR97
ITGAM	MANSC1	CYP4F3
FCGR2A	ALOX5	LTB4R
LOC728417	PFKFB3	STX3
ABHD2	TRIB1	FLOT2
DYSF	FUT7	ZNF438
MLSTD1	SIRPA	MMP25
HCK	Rgr	PHC2
LOC642780	AQP9	CREB5
QPCT	PADI4	IL1RN
CEACAM4	CKAP4	LOC729021
PPP1R3D	TIMP2	FOLR3
CST7	SLC26A8	SERPINA1
LOC641996	EPAS1	CSF3R
LILRA3	SEMA4A	RNF24
PBEF1	TRIM9	C20orf3
STEAP4	LOC399715	LOC642334
LOC728054	RNF149	RFX2

Genes Included in Module M3.2 - Inflammation		
ZNF467	VNN2	ACSL1
FLOT1	DGAT2	OR10G3
ACSL4	GPR160	PLXNC1
DHRS13	SOD2	LOC552891
DUSP1	LOC642267	CRISPLD2
EXOC6	NFIL3	GLT1D1
CD63	LY96	CEBPD
IL1RAP	CDA	SLC22A4

ANKRD33	CCPG1	PGD
HMGB2	GPR97	LOC646434
C14orf94	MKNK1	OSCAR
S100A11	IL17RA	LOC641693
CD55	GNG10	LOC441124
B4GALT5	PDLIM7	

Genes Included in Module M3.4 - Interferon		
IFIH1	ZBP1	CEACAM1
IRF7	WARS	APOL6
PARP14	LAP3	SOCS1
IFIT2	GBP5	LGALS3BP
IFI35	TNFSF10	SCO2
SAMD9L	GBP1	DDX58
STAT1	STAT1	UBE2L6
OAS2	FBXO6	PML
IFIT5	PARP10	TNFAIP6
ATF3	OAS2	INDO
SEPT4	TRIM22	MT2A
HERC6	PARP10	GBP6
IFITM1	GBP3	STAT2
TRIMP1	ZNF684	TIMM10
EIF2AK2	INCA	STAT1
AIM2	GALM	PARP12
MT1A	DHX58	PLSCR1
MOV10	CEACAM1	PARP9
CCL8	UBE2L6	LOC400759
PRIC285	PML	GBP4

Genes Included in Module M4.2 - Inflammation		
LOC728519	IRAK3	WDFY3
ANXA3	CLEC4D	CASP5
TLR5	LMNB1	SIPA1L2
KREMEN1	SAMSN1	S100P
CR1	LOC648984	LIMK2
BMX	LOC391045	S100A12
LRG1	MCTP2	MMP9
OPLAH	VNN2	IL1R2
ALPL	IL1R2	IL18RAP

C19orf59	GRB10	VNN1
LOC642112	CR1	KIAA1881
PGLYRP1	FCAR	PSG3
CA4	IL18R1	KREMEN1
LOC642684	SLPI	MAPK14
MGAM	OSM	C5orf32
SOCS3	NSUN7	SERPINA1
FKBP5	GPR141	SLC2A14

Genes Included in Module M4.6 - Inflammation		
ZFP36	ATF6	CKLF
LOC440093	MGC4093	LOC728069
SLC25A44	DNTTIP1	SBNO2
YIPF1	MSRB2	LSP1
IFITM2	HTATIP2	CHIC2
C6orf166	PIM3	DDAH2
STAT3	NCSTN	PDK3
RNF13	LAMP2	FCGR2A
PHF21A	NFKBIZ	RAB24
PRKCD	CHSY1	GNG5
LOC651143	SELL	C6orf32
MTX1	CTNNA1	RHOT1
C9orf66	STX10	CLIC1
PCNX	CD97	CASP4
SNX27	LRRK2	VAMP3
PLOD1	ATP6V0D1	CYBA
FTH1	CFLAR	IRF2
NT5C2	KIAA1754	CBARA1
GMPR2	STAT5B	TMEM188
APBB1IP	SAT1	MEFV
SNX10	MIDN	USP15
ZCCHC6	SLCO3A1	PSCD4

AXUD1	ENTPD1	LYRM1
LITAF	MTX1	APAF1
MYD88	IFNGR1	MLKL
BRI3	IFNGR2	APH1B
TCIRG1	HEBP2	RALB
ZYX	RIT1	ETV6
MAPK3	C9orf19	PIM3
S100A6	ATG7	NAGK
ERO1L	STK17B	IL10RB
MLKL	P2RY13	RNASEL
KIAA1600	FBXL5	LAT2
GRN	SQRDL	ALOX5AP
THOC5	SNX11	DIP2B
Genes Included in Module M4.6 - Inflammation		
SSFA2	RAB24	MVP
IFNAR1	LYN	GLA
PELO	PFTK1	CHMP2A
C16orf72	JDP2	CSNK1D

Genes Included in Module M4.13 - Inflammation		
LENG4	FAM53C	MTHFS
FRAT1	NINJ1	NLRP12
SIRPB1	TLE3	USP10
DOCK5	SPI1	RAB6IP1
XPO6	CTBS	FRAT1
ACOX1	VNN3	MAG1
GALNAC4S-6ST	CXCL1	SMAP1L
ST6GALNAC2	C1orf24	LOC283547
TREML2	MTMR3	PFKFB4
TSEN34	SKAP2	IL1B
IL8RA	EMR2	C5AR1
ACTN1	NLRP12	NCF4

SSH2	DENND3	IL8RB
SDCBP	SLC19A1	C1RL
LRP10	SLC6A6	CSF2RA
FOS	ZDHHC18	TNFRSF10C
TMEM71	PELI1	PTEN
HLX	CD58	TNFRSF1A
P2RY13	DDEF1	UBTD1
C3orf34	ELF2	RRAGD
TLR6	LPPR2	PDLIM7
PANX2	MXD1	GAB2
TBC1D14	FPR1	IL13RA1
NUMB	FLJ10357	SIRPD
PACSIN2	C7orf53	IFRD1
TNFRSF10B	SVIL	LAMP2
FRAT2	MOSPD2	RNF141

Genes Included in Module M5.1 - Inflammation		
GNAI3	UBE2J1	RAB5A
SLK	PXN	CASP9
HIATL1	RPS6KA1	ATP6V0B
SNX13	HHEX	ROD1
MAP3K8	FLJ10986	CLIP1
LBR	EDEM2	CCND3
SPPL2A	GADD45G	ARHGAP19
FEM1C	OSTM1	GSTO1
KIAA0040	LOC645058	LRRFIP2
CHUK	C1orf25	GRB2
SAP30L	TMEM2	NARF
SFT2D1	TOLLIP	MS4A6A
TOR1AIP1	CTDP1	ZNF281
CAST	INSIG2	GSK3B
ATP6V1D	ZFP106	TMLHE

MAP1LC3B	EHD1	FBXO30
ATG3	PPP2R3C	FOSL2
C1GALT1C1	PTAFR	MAPK1
BAT5	PTPN1	PSMB3
LAPTM5	C20orf24	ARFGAP3
ANXA5	PPP1R10	ACAA1
CAPZA2	SLC15A3	LOC647195
LOC653972	RBMS1	TMEM149
FAM49B	PRCP	NANS
LTA4H	RAB7A	MAPKAPK2
TBXAS1	ME2	FYB
IGSF6	RENBP	C2orf25
SNX16	PHF20L1	PTTG1IP
GBE1	C9orf89	DUSP18
DNAJB6	NDEL1	CRADD
ATP6V0E1	WSB1	SDF2
FOXN2	PGM2	KIAA1434
FKBP15	CHMP2B	GNAI2
PGK1	NEU1	CNN2
LRRFIP2	GRN	RASSF3

Genes Included in Module M5.1 - Inflammation		
E2F3	CFP	PARP4
FBXO38	SRGN	TBXAS1
ARID3A	NOLA3	TPM3
PCMT1	BNIP2	HOXA9
ARPC3	KLHL8	ARPC5
PRKAA1	CTNNB1	CD53
C1orf119	OSTF1	FLII
ILK	DPH3	ZNF319
RAP2C	SCYL2	CHMP2A
KIAA0241	EFHD2	OTUD1
CMTM3	TKT	ACTB

VIM	PSENEN	ATP6AP1
PHF20L1	URP2	GLT25D1
GRB2	NIN	CMTM6
SERPINB8	PLA2G4A	PHKA2
CSNK1D	HK2	MSL3L1
ANKS1A	KCTD21	CD44
LOXL3	CCR1	MFAP3
USP3	LPGAT1	RABAC1
ZNF787	AGPAT2	UBQLN2
ELMOD2	DTX2	UBE2W
SLC30A1	GNA13	LACTB
CAB39	C14orf4	DSE
PTPRC	ZMPSTE24	ALDOA
AZI2	RAB10	GALNT4
TRIOBP	OS9	CSF2RA
SLC12A6	FNDC3A	TMEM50A
MIER1	PRKAR1A	PIK3CB
TM9SF2	BTBD10	FKBP1A
TMEM185B	TMUB2	NIN
ZSWIM6	TMEM180	RANBP9
RBPJ	LOC642489	KLHL6
GMFG	RHOG	ATP6V1C1
NDRG1	ACSS2	TNFSF13B
MAPK1	DHRS7B	ATP6V1B2

Genes Included in Module M5.1 - Inflammation		
TXN	ZDHHC3	NRD1
SELT	RTN4	NDUFB3
HCLS1	MBOAT5	GNA15
TUBA1A	MON1B	DIRC2
RAC2	YIPF4	RB1CC1
USP9X	FKBP1A	LOC648605
MAP2K1IP1	AGPAT2	RAB2A

GNS	ARIH1	TMOD3
PRR13	RAB1A	BIN2
TBK1	KIDINS220	NFE2L2
PPP2R5A	TYROBP	CYB5R4
TMEM97	HEXB	ANTXR2

Genes Included in Module M5.7 - Inflammation		
MAP2K4	TMEM43	HBP1
CHMP1B	PGCP	ZDHHC7
HSD17B11	CARD8	LMBRD1
STXBP5	SERINC1	MAP3K2
IDS	HLA-E	ERGIC1
H3F3B	CTSS	MANBA
KIAA0232	STAT6	CASC4
FAM49A	RGL2	HPSE
TNRC5	RNASET2	MYO5A
ATP6V1A	SPATA2L	KIAA0247
MBP	C14orf138	SUPT4H1
HSPA1L	INPP5A	FCGRT
CD46	RNF130	INPP5A
PGM1	TOPORS	RAF1
PBX2	FAM79A	RAB27A
KLHL21	LONRF1	VAV3
STXBP3	TGFBR2	CORO1C
MARCH7	EGLN1	CPD
ELF1	KBTBD7	CRK
C9orf72	DDX3X	ZBTB34
HSDL2	IDS	GOLGA7
NSMAF	LOC644935	LOC339745
SLC15A4	ATXN1	PYCARD
CD93	ITM2B	IMPA2
TMF1	TMCO3	MAP4K4
MBOAT1	PTPRE	CXCL16
HMGCR	TRIM8	S100A4
VPS24	DHRS7	NUP50
PIK3CD	BICD2	CUGBP2
APPL2	AMICA1	KIAA0513
C7orf25	CDK5R1	TMCC3

PRMT5	SULT1A1	OSBPL8
KIAA0701	LEPROT	EXTL3
FNIP1	MFSD1	PPP3CA
NCOA1	NUP214	FCGR2B

Genes Included in Module M5.7 - Inflammation		
RGS18	ADAM19	CENTB2
UBR2	IGF2R	CLEC4A
CYBRD1	PHF2	CBL
PISD	TBL1X	PPT1
ZNF238	UBE4B	ARHGAP9
NCOA1	SLC44A2	DHRS12
ZNF217	ZNF746	PRDM8
IQGAP1	RRM2B	SPAG9
TXNDC13	EVA1	JARID1B
RFWD2	BID	ICAM3
PLXDC2	CAMK2G	RBPJ

Genes Included in Module M5.12 - Interferon		
RBCK1	GBP2	TRIM5
TRAFD1	TRIM5	NT5C3
TRIM21	RHBDF2	SASP
LOC401433	TMEM140	ISGF3G
COP1	ADAR	REC8
CHMP5	BTN3A1	KIAA1618
TAP2	PARP10	ISG20
SP110	LGALS9	DYNLT1
GADD45B	NBN	LHFPL2
IFI16	ECGF1	TRIM56
TAP1	SAMD9	SP140
ZNFX1	SRBD1	TRIM25
PHF11	NCOA7	TRIM38
ACTA2	DRAP1	ETV7
C1QA	UNC93B1	PSMB9
SP140	SP100	CPT1B
ABCA1	NTNG2	BST2
TCN2	DHRS9	CASP1
ZC3HAV1	TDRD7	NMI
HSH2D	LBA1	
LOC554203	MDK	

Genes Included in Module M7.1 - Inflammation		
MYADM	ACPP	ARHGAP26
ALDH3B1	RIPK3	RIN3
TMEM8	CHKA	CTSA
SUMF1	GSN	DCTN2
TNIP1	DENND1A	PPP4C
RASGEF1A	CDC42EP4	RAB5C
RGS19	DBNL	SERTAD3
SEMA4B	ARF5	MSRA

TADA3L	APOB48R	ZNF213
KCTD2	ZDHHC17	PTPN6
METRNL	RAB1B	ATP13A3
GAPDH	RHOU	MAP3K5
TALDO1	ZDHHC12	PPP1R15A
C9orf72	SH3PXD2B	MOSPD3
TLN1	ULK1	LRPAP1
CAPN1	PLEKHM1	LOC440525
TMEM127	WDR13	GLRX
G6PD	ARHGAP30	UBE1
GPSM3	BLOC1S1	TMLHE
C22orf9	CPNE1	IL2RG
CYB5R1	METRNL	TANK
XRN2	HYAL2	PREX1
CAPZB	KIAA1602	IIP45
TWF2	IRAK4	RARA
GRK6	LOC644964	TIMP1
LOC653888	EIF2C4	LTBR
TK2	MED12	SH2B2
PKM2	AGXT2L2	CDKN2C
STEAP3	GMIP	DEDD
PLD1	RAB4B	JMJD2B
TMEM119	PLEC1	TXNDC3
CYB5R3	HRH2	TGFBR1
OTUD1	ATXN7L3	GBGT1
CHP	DNM2	RAB38
TESK2	SLC16A5	TNPO3
Genes Included in Module M7.1 - Inflammation		
LSP1	FAM70B	RTN2
CDKN2D	H2AFY	LOC652675
KPNA4	AMPH	MYH9
CAP1	DPYD	WAS
ULK1	RNF135	MFN2

C20orf177	CAT	ACTR1A
BCORL1	COQ2	MBD6
ADCK4	CD300LF	RUNX1
METRNL	ECOP	TAZ
FKSG30	RAB3D	FAM20C
PJA2	TIMP2	SSH1
PPP1R12A	NCF2	CUTL1
FAM45A	PICALM	RHBDD2
MLX	ANXA1	MLF2
NFKBIB	PLP2	RASSF2
SLC9A8	LOC648605	CHD7
CORO2A	SYK	GLTP
KIAA1539	TMBIM1	CDC123
SIRPB2	MYL6	TSC22D3
AGXT2L2	PTEN	AP3S2
SCOTIN	SH3BP5L	TMEM142B
CALML4	PAM	C9orf167
PLEKHQ1	MAP1S	IMPDH1
CCDC128	MSN	CPNE3
LOC651524	CARS	MTMR6
C17orf62	ARHGEF11	
EDG6	PNRC1	

LOD Cytokine and Chemokine

	V132_01EXP_Proinflammatory_07_20160 9-22-1550	V132_01EXP_Proinflammatory_10_20160 9-29-1600	V132_01EXP_Proinflammatory_13_20161 0-04-1610
IFNG	2,895419212	1,513315388	1,450320966
INTLK1 3	1,30690239	1,952667366	14,85807496
INTLK1 2	0,254195266	0,36117814	0,288739346
TNFA	0,243281184	0,214676754	0,535962642
INTLK8	0,135646326	0,183181994	0,22125872
INTLK6	0,127853462	0,118660098	0,150990066
INTLK2	0,118460032	0,124574492	0,252435556
INTLK1 0	0,087541554	0,15925643	0,195526434
INTLK4	0,079040974	0,089722332	0,11317629
INTLK1 B	0,043173272	0,458105394	0,337679062

	V132_01EXP_Proinflammatory_16_201610 -14-1550	V132_01EXP_Proinflammatory_18_201611 -10-1600	V132_01EXP_Proinflammatory_21_201611 -11-1640
IFNG	2,0702718	1,298684436	1,929802491
INTLK1 3	2,027811576	0,864135352	1,185874905
INTLK1 2	0,347168348	0,245174788	0,151280694
TNFA	0,315276598	0,177849452	0,116227752

INTLK8	0,226276644	0,119211462	0,103223743
INTLK6	0,16909986	0,11362425	0,121248611
INTLK2	0,178198596	0,08519466	0,184969687
INTLK10	0,181460976	0,119166262	0,042767087
INTLK4	0,136202534	0,072774482	0,07110623
INTLK1B	0,29854159	0,191460608	0,075941905

	V132_01EXP_Proinflammatory_25_201611-21-1615
IFNG	1,514153374
INTLK13	1,29990294
INTLK12	0,438865129
TNFA	0,23953273
INTLK8	0,196552631
INTLK6	0,18351503
INTLK2	0,125636051
INTLK10	0,153365632
INTLK4	0,117117322
INTLK1B	0,04796712

	V132_01EXP_Cytokine_08_2016-09-221600	V132_01EXP_Cytokine_11_2016-09-291610	V132_01EXP_Cytokine_14_2016-10-041620
GMCSF	0,200462791	0,212806922	0,242754037

INTLK12B	0,6514685	0,69701348	0,791635655
INTLK15	0,219962467	0,253257164	0,286673471
INTLK16	0,692670427	0,28984188	0,474223777
INTLK17A	0,78070622	1,123217838	0,805407231
INTLK1A	1,874293216	0,262125622	0,39014113
INTLK5	0,384072335	0,30091852	2,229062884
INTLK7	0,227866847	0,39052141	0,339918955
TNFB	0,087927193	0,129672744	0,083663836
VEGF	0,549986747	0,941592778	0,757804297
	V132_01EXP_Cytokine_17_2016-10-141555	**V132_01EXP_Cytokine_19_2016-11-101610**	**V132_01EXP_Cytokine_22_2016-11-111645**
GMCSF	0,165048304	0,171963035	0,388514935
INTLK12B	0,555392187	0,594448527	0,912792456
INTLK15	0,174460332	0,180713721	0,355229718
INTLK16	0,57325466	0,933402392	1,460617953
INTLK17A	0,745538802	0,6340689	1,757826436
INTLK1A	0,435147792	0,226546511	0,277694908
INTLK5	0,467582563	0,234036721	0,916199162
INTLK7	0,208964892	0,238831703	0,38690284
TNFB	0,101087941	0,07603156	0,111999713
VEGF	1,722596188	1,031304047	1,842545561

GMCSF	**V132_01EXP_Cytokine_26_2016-11-211620**
	0,245210757
INTLK12B	1,113886855
INTLK15	0,304432135
INTLK16	2,049245526
INTLK17A	0,970202673
INTLK1A	0,288699809
INTLK5	0,527046103
INTLK7	0,404607233
TNFB	0,103840483
VEGF	3,300997125

	V132_01EXP_Chemokine_09_2016-0922-1610	**V132_01EXP_Chemokine_12_2016-0929-1620**	**V132_01EXP_Chemokine_15_2016-10-041630**
CCL17	0,517748156	1,42914944	0,407874989
CXCL10	0,378183883	0,440872446	0,374121412
EOTAXIN1	6,370053773	21,64187815	5,141005392
EOTAXIN3	7,036675961	17,03110728	17,90717121
INTLK8HA	417,9079311	517,2894168	262,2190136
MCP1	0,110920842	0,284548945	0,125310561
MCP4	12,93933451	30,78808737	10,57300576
MDC	5,263520986	10,66792548	4,649689735
MIP1A	2,853955639	6,92118964	3,058317824
MIP1B	0,285401075	0,506552964	0,265393383

	V132_01EXP_Chemokine_20_2016-1110-1615	V132_01EXP_Chemokine_23_2016-1111-1650	V132_01EXP_Chemokine_24_2016-11-141530
CCL17	0,517411393	0,368521092	1,007298755
CXCL10	0,71651136	1,123839441	0,539450198
EOTAXIN1	10,17485573	22,30252656	19,54119467
EOTAXIN3	29,58820943	22,85611836	6,810226751
INTLK8HA	595,4336596	745,2416767	305,1506734
MCP1	0,356170818	0,392437728	0,298700968
MCP4	16,54125324	31,431346	7,082234764
MDC	10,65601257	14,85685791	6,782009964
MIP1A	4,826074466	14,36594563	3,36973396
MIP1B	0,650349964	1,473839444	0,585877613

	V132_01EXP_Chemokine_27_2016-1121-1625
CCL17	1,232538947
CXCL10	0,334432036
EOTAXIN1	13,56572825
EOTAXIN3	7,175654765
INTLK8HA	569,0666342
MCP1	0,220825131
MCP4	14,42632296
MDC	8,056521872
MIP1A	14,59308764

MIP1B	1,079787401

Subject Run by Run Chemiokines and Cytokines

V132_01EXP_Chemokine_09_2016-09-22-1610

V132_01EXP-000:15PRE -213-5248977631@3032@V132_01EXP-0010085@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -214-5248977731@3032@V132_01EXP-0010086@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -215-5248977833@3032@V132_01EXP-0010081@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -216-5248977933@3032@V132_01EXP-0010093@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -217-5248978033@3032@V132_01EXP-0010094@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -218-5248978133@3032@V132_01EXP-0010080@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -219-5248978233@3032@V132_01EXP-0010087@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -220-5248978333@3032@V132_01EXP-0010089@1@DAY1,PREDOSE
V132_01EXP-006:00POST -213-5248989631@3032@V132_01EXP-0010085@1@DAY1,6HOUR
V132_01EXP-006:00POST -214-5248989731@3032@V132_01EXP-0010086@1@DAY1,6HOUR
V132_01EXP-006:00POST -215-5248989833@3032@V132_01EXP-0010081@1@DAY1,6HOUR
V132_01EXP-006:00POST -216-5248989933@3032@V132_01EXP-0010093@1@DAY1,6HOUR
V132_01EXP-006:00POST -217-5248990033@3032@V132_01EXP-0010094@1@DAY1,6HOUR
V132_01EXP-006:00POST -218-5248990133@3032@V132_01EXP-0010080@1@DAY1,6HOUR
V132_01EXP-006:00POST -219-5248990233@3032@V132_01EXP-0010087@1@DAY1,6HOUR
V132_01EXP-006:00POST -220-5248990333@3032@V132_01EXP-0010089@1@DAY1,6H OUR
V132_01EXP-024:00POST -213-5248997631@3032@V132_01EXP-0010085@1@DAY1,24HOUR
V132_01EXP-024:00POST -214-5248997731@3032@V132_01EXP-0010086@1@DAY1,24HOUR
V132_01EXP-024:00POST -215-5248997833@3032@V132_01EXP-0010081@1@DAY1,24HOUR
V132_01EXP-024:00POST -216-5248997933@3032@V132_01EXP-0010093@1@DAY1,24HOUR
V132_01EXP-024:00POST -217-5248998033@3032@V132_01EXP-0010094@1@DAY1,24HOUR
V132_01EXP-024:00POST -218-5248998133@3032@V132_01EXP-0010080@1@DAY1,24HOUR
V132_01EXP-024:00PO ST-219-5248998233@3032@V132_01EXP-0010087@1@DAY1,24HOUR
V132_01EXP-024:00POST -220-5248998333@3032@V132_01EXP-0010089@1@DAY1,24HOUR
V132_01EXP-072:00POST -213-5249005631@3032@V132_01EXP-0010085@2@DAY4
V132_01EXP-072:00POST -214-5249005731@3032@V132_01EXP-0010086@2@DAY4
V132_01EXP-072:00POST -215-5249005833@3032@V132_01EXP-0010081@2@DAY4
V132_01EXP-072:00POST -216-5249005933@3032@V132_01EXP-0010093@2@DAY4
V132_01EXP-072:00POST -217-5249006033@3032@V132_01EXP-0010094@2@DAY4
V132_01EXP-072:00POST -218-5249006133@3032@V132_01EXP-0010080@2@DAY4
072:00POST -219-5249006233@3032@V132_01EXP-0010087@2@DAY4
072:00POST -220-5249006333@3032@V132_01EXP-0010089@2@DAY4

V132_01EXP-
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168:00POST -213-5249013631@3032@V132_01EXP-0010085@3@DAY8
168:00POST -214-5249013731@3032@V132_01EXP-0010086@3@DAY8
168:00POST -215-5249013833@3032@V132_01EXP-0010081@3@DAY8
168:00POST -216-5249013933@3032@V132_01EXP-0010093@3@DAY8
168:00POST -217-5249014033@3032@V132_01EXP-0010094@3@DAY8
168:00POST -218-5249014133@3032@V132_01EXP-0010080@3@DAY8
168:00POST -219-5249014233@3032@V132_01EXP-0010087@3@DAY8
168:00POST -220-5249014333@3032@V132_01EXP-0010089@3@DAY8

V132_01EXP_Chemokine_12_2016-09-29-1620

V132_01EXP-000:15PRE -301-5251924031@3032@V132_01EXP-0010088@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -302-5251924131@3032@V132_01EXP-0010111@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -303-5251924231@3032@V132_01EXP-0010090@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -304-5251924331@3032@V132_01EXP-0010099@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -305-5251924431@3032@V132_01EXP-0010100@1@DAY1,PREDOSE
V132_01EXP-006:00POST -301-5251936031@3032@V132_01EXP-0010088@1@DAY1,6HOUR
V132_01EXP-006:00POST -302-5251936131@3032@V132_01EXP-0010111@1@DAY1,6HOUR
V132_01EXP-006:00POST -303-5251936231@3032@V132_01EXP-0010090@1@DAY1,6HOUR
V132_01EXP-006:00POST -304-5251936331@3032@V132_01EXP-0010099@1@DAY1,6HOUR
V132_01EXP-006:00POST -305-5251936431@3032@V132_01EXP-0010100@1@DAY1,6HOUR
V132_01EXP-024:00POST -301-5251944031@3032@V132_01EXP-0010088@1@DAY1,24HOUR
V132_01EXP-024:00POST -302-5251944131@3032@V132_01EXP-0010111@1@DAY1,24HOUR
V132_01EXP-024:00POST -303-5251944231@3032@V132_01EXP-0010090@1@DAY1,24HOUR
V132_01EXP-024:00POST -304-5251944331@3032@V132_01EXP-0010099@1@DAY1,24HOUR
V132_01EXP-024:00POST -305-5251944431@3032@V132_01EXP-0010100@1@DAY1,24HOUR
V132_01EXP-072:00POST -301-5251952031@3032@V132_01EXP-0010088@2@DAY4
V132_01EXP-072:00POST -302-5251952131@3032@V132_01EXP-0010111@2@DAY4
V132_01EXP-072:00POST -303-5251952231@3032@V132_01EXP-0010090@2@DAY4
V132_01EXP-072:00POST -304-5251952331@3032@V132_01EXP-0010099@2@DAY4
V132_01EXP-072:00POST -305-5251952431@3032@V132_01EXP-0010100@2@DAY4
V132_01EXP-168:00 POST-301-5251960031@3032@V132_01EXP-0010088@3@DAY8
V132_01EXP-168:00POST -302-5251960131@3032@V132_01EXP-0010111@3@DAY8
V132_01EXP-168:00POST -303-5251960231@3032@V132_01EXP-0010090@3@DAY8
V132_01EXP-168:00POST -304-5251960331@3032@V132_01EXP-0010099@3@DAY8
V132_01EXP-168:00POST -305-5251960431@3032@V132_01EXP-0010100@3@DAY8

V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP_Chemokine_15_2016-10-04-1630
V132_01EXP-000:15PRE -306-5251924531@3032@V132_01EXP-0010125@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -307-5251924631@3032@V132_01EXP-0010130@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -308-5251924731@3032@V132_01EXP-0010133@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -309-5251924831@3032@V132_01EXP-0010121@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -310-5251924931@3032@V132_01EXP-0010135@1@DAY1,PREDOSE
V132_01EXP-000:15 PRE -311-5251925031@3032@V132_01EXP-0010136@1@DAY 1, PREDOSE
000:15PRE -312-5251925131@3032@V132_01EXP-0010122@1@DAY1,PREDOSE
000:15PRE -313-5251925231@3032@V132_01EXP-0010138@1@DAY1,PREDOSE
000:15PRE -314-5251925331@3032@V132_01EXP-0010140@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -315-5251925431@3032@V132_01EXP-0010139@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -316-5251925531@3032@V132_01EXP-0010143@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -317-5251925631@3032@V132_01EXP-0010147@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -319-5251925831@3032@V132_01EXP-0010131@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -320-5251925931@3032@V132_01EXP-0010141@1@DAY1,PREDOSE
V132_01EXP-006:00POST -306-5251936531@3032@V132_01EXP-0010125@1@DAY1,6HOUR
V132_01EXP-006:00POST -307-5251936631@3032@V132_01EXP-0010130@1@DAY1,6HOUR
V132_01EXP-006:00POST -308-5251936731@3032@V132_01EXP-0010133@1@DAY1,6HOUR
V132_01EXP-006:00POST -309-5251936831@3032@V132_01EXP-0010121@1@DAY1,6HOUR
V132_01EXP-006:00POST -310-5251936931@3032@V132_01EXP-0010135@1@DAY1,6HOUR
V132_01EXP-006:00POST -311-5251937031@3032@V132_01EXP-0010136@1@DAY1,6HOUR
V132_01EXP-006:00POST -312-5251937131@3032@V132_01EXP-0010122@1@DAY1,6H OUR
V132_01EXP-006:00POST -313-5251937231@3032@V132_01EXP-0010138@1@DAY1,6HOUR
V132_01EXP-006:00POST -314-5251937331@3032@V132_01EXP-0010140@1@DAY1,6HOUR
V132_01EXP-006:00POST -315-5251937431@3032@V132_01EXP-0010139@1@DAY1,6HOUR
V132_01EXP-006:00POST -316-5251937531@3032@V132_01EXP-0010143@1@DAY1,6HOUR
V132_01EXP-006:00POST -317-5251937631@3032@V132_01EXP-0010147@1@DAY1,6HOUR
V132_01EXP-006:00POST -319-5251937831@3032@V132_01EXP-0010131@1@DAY1,6HOUR
V132_01EXP-006:00POST -320-5251937931@3032@V132_01EXP-0010141@1@DAY1,6HOUR
V132_01EXP-024:00POST -306-5251944531@3032@V132_01EXP-0010125@1@DAY1,24HOUR
V132_01EXP-024:00POST -307-5251944631@3032@V132_01EXP-0010130@1@DAY1,24HOUR
V132_01EXP-024:00POST -308-5251944731@3032@V132_01EXP-0010133@1@DAY1,24HOUR
V132_01EXP-
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V132_01EXP-024:00POST -309-5251944831@3032@V132_01EXP-0010121@1@DAY1,24HOUR
V132_01EXP-024:00POST -310-5251944931@3032@V132_01EXP-0010135@1@DAY1,24HOUR
V132_01EXP-024:00POST -311-5251945031@3032@V132_01EXP-0010136@1@DAY1,24HOUR
V132_01EXP-024:00POST -312-5251945131@3032@V132_01EXP-0010122@1@DAY1,24HOUR
V132_01EXP-024:00POST -313-5251945231@3032@V132_01EXP-0010138@1@DAY1,24HOUR
V132_01EXP-024:00POST -314-5251945331@3032@V132_01EXP-0010140@1@DAY1,24HOUR
V132_01EXP-024:00POST -315-5251945431@3032@V132_01EXP-0010139@1@DAY1,24HOUR
V132_01EXP-024:00POST -316-5251945531@3032@V132_01EXP-0010143@1@DAY1,24HOUR
024:00POST -317-5251945631@3032@V132_01EXP-0010147@1@DAY1,24HOUR
024:00POS T-319-5251945831@3032@V132_01EXP-0010131@1@DAY1,24HOUR
024:00POST -320-5251945931@3032@V132_01EXP-0010141@1@DAY1,24HOUR
072:00POST -306-5251952531@3032@V132_01EXP-0010125@2@DAY4
072:00POST -307-5251952631@3032@V132_01EXP-0010130@2@DAY4
072:00 POST-308-5251952731@3032@V132_01EXP-0010133@2@DAY4
072:00POST -309-5251952831@3032@V132_01EXP-0010121@2@DAY4

V132_01EXP-
V132_01EXP-
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072:00POST -310-5251952931@3032@V132_01EXP-0010135@2@DAY4
072:00POST -311-5251953031@3032@V132_01EXP-0010136@2@DAY4
072:00POST -312-5251953131@3032@V132_01EXP-0010122@2@DAY4
V132_01EXP-072:00POST -313-5251953231@3032@V132_01EXP-0010138@2@DAY4
V132_01EXP-072:00POST -314-5251953331@3032@V132_01EXP-0010140@2@DAY4
V132_01EXP-072:00POST -315-5251953431@3032@V132_01EXP-0010139@2@DAY4
V132_01EXP-072:00POST -316-5251953531@3032@V132_01EXP-0010143@2@DAY4
V132_01EXP-072:00POST -317-5251953631@3032@V132_01EXP-0010147@2@DAY4
V132_01EXP-072:00POST -319-5251953831@3032@V132_01EXP-0010131@2@DAY4
V132_01EXP-072:00POST -320-5251953931@3032@V132_01EXP-0010141@2@DAY4
V132_01EXP-168:00POST -306-5251960531@3032@V132_01EXP-0010125@3@DAY8
V132_01EXP-168:00POST -307-5251960631@3032@V132_01EXP-0010130@3@DAY8
V132_01EXP-168:00POST -308-5251960731@3032@V132_01EXP-0010133@3@DAY8
V132_01EXP-168:00POST -309-5251960831@3032@V132_01EXP-0010121@3@DAY8
V132_01EXP-168:00POST -310-5251960931@3032@V132_01EXP-0010135@3@DAY8
V132_01EXP-168:00POST -311-5251961031@3032@V132_01EXP-0010136@3@DAY8
V132_01EXP-168:00POST -312-5251961131@3032@V132_01EXP-0010122@3@DAY8
V132_01EXP-168:00POST -313-5251961231@3032@V132_01EXP-0010138@3@DAY8
V132_01EXP-168:00POST -314-5251961331@3032@V132_01EXP-0010140@3@DAY8
V132_01EXP-168:00POST -315-5251961431@3032@V132_01EXP-0010139@3@DAY8
V132_01EXP-168:00POST -316-5251961531@3032@V132_01EXP-0010143@3@DAY8
V132_01EXP-168:00POST -317-5251961631@3032@V132_01EXP-0010147@3@DAY8
V132_01EXP-168:00POST -319-5251961831@3032@V132_01EXP-0010131@3@DAY8
V132_01EXP-168:00POST -320-5251961931@3032@V132_01EXP-0010141@3@DAY8

V132_01EXP_Chemokine_20_2016-11-10-1615

V132_01EXP-000:15PRE -101-5248494533@3032@V132_01EXP-0010001@1@DAY1,PREDOSE
V132_01EXP-000:15P RE-102-5248494633@3032@V132_01EXP-0010006@1@DAY1,PREDOSE

V132_01EXP-
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V132_01EXP-000:15PRE -103-5248494733@3032@V132_01EXP-0010014@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -104-5248494833@3032@V132_01EXP-0010013@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -105-5248494933@3032@V132_01EXP-0010016@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -106-5248495033@3032@V132_01EXP-0010024@1@DAY1,PREDOSE
000:15PRE -107-5248495133@3032@V132_01EXP-0010025@1@DAY1,PREDOSE
000:15PRE -111-5248495533@3032@V132_01EXP-0010026@1@DAY1,PREDOSE
000:15PRE -112-5248495633@3032@V132_01EXP-0010028@1@DAY1,PREDOSE
000:15PRE -113-5248495733@3032@V132_01EXP-0010034@1@DAY1,PREDOSE
000:15PRE -114-5248495833@3032@V132_01EXP-0010051@1@DAY1,PREDOSE
000:15PRE -115-5248495933@3032@V132_01EXP-0010033@1@DAY1,PREDOSE
000:15PRE -116-5248496033@3032@V132_01EXP-0010038@1@DAY1,PREDOSE
000:15PRE -117-5248496133@3032@V132_01EXP-0010044@1@DAY1,PREDOSE
006:00POST -101-5248518533@3032@V132_01EXP-0010001@1@DAY1,6HOUR
006:00POS T-102-5248518633@3032@V132_01EXP-0010006@1@DAY1,6HOUR
V132_01EXP-006:00POST -103-5248518733@3032@V132_01EXP-0010014@1@DAY1,6HOUR
V132_01EXP-006:00POST -104-5248518833@3032@V132_01EXP-0010013@1@DAY1,6HOUR
V132_01EXP-006:00POST -105-5248518933@3032@V132_01EXP-0010016@1@DAY1,6HOUR
V132_01EXP-006:00POST -106-5248519033@3032@V132_01EXP-0010024@1@DAY1,6HOUR
V132_01EXP-006:00POST -107-5248519133@3032@V132_01EXP-0010025@1@DAY1,6HOUR
V132_01EXP-006:00POST -111-5248519533@3032@V132_01EXP-0010026@1@DAY1,6HOUR
V132_01EXP-006:00POST -112-5248519633@3032@V132_01EXP-0010028@1@DAY1,6HOUR
V132_01EXP-006:00POST -113-5248519733@3032@V132_01EXP-0010034@1@DAY1,6HOUR
V132_01EXP-006:00POST -114-5248519833@3032@V132_01EXP-0010051@1@DAY1, 6HOUR
V132_01EXP-006:00POST -115-5248519933@3032@V132_01EXP-0010033@1@DAY1,6HOUR
V132_01EXP-006:00POST -116-5248520033@3032@V132_01EXP-0010038@1@DAY1,6HOUR
V132_01EXP-006:00POST -117-5248520133@3032@V132_01EXP-0010044@1@DAY1,6HOUR
V132_01EXP-024:00POST -101-5248534533@3032@V132_01EXP-0010001@1@DAY1,24HOUR
V132_01EXP-024:00POST -102-5248534633@3032@V132_01EXP-0010006@1@DAY1,24HOUR
V132_01EXP-024:00POST -103-5248534733@3032@V132_01EXP-0010014@1@DAY1,24HOUR

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V132_01EXP-024:00P OST-104-5248534833@3032@V132_01EXP-0010013@1@DAY1,24HOUR
V132_01EXP-024:00POST -105-5248534933@3032@V132_01EXP-0010016@1@DAY1,24HOUR
V132_01EXP-024:00POST -106-5248535033@3032@V132_01EXP-0010024@1@DAY1,24HOUR
V132_01EXP-024:00POST -107-5248535133@3032@V132_01EXP-0010025@1@DAY1,24HOUR
V132_01EXP-024:00POST -111-5248535533@3032@V132_01EXP-0010026@1@DAY1,24HOUR
V132_01EXP-024:00POST -112-5248535633@3032@V132_01EXP-0010028@1@DAY1,24HOUR
V132_01EXP-024:00POST -113-5248535733@3032@V132_01EXP-0010034@1@DAY1,24HOUR
V132_01EXP-024:00POST -114-5248535833@3032@V132_01EXP-0010051@1@DAY1,24HOUR
V132_01EXP-024:00POST -115-5248535933@3032@V132_01EXP-0010033@1@DAY1,24HOUR
V132_01EXP-024:00POST -116-5248536033@3032@V132_01EXP-0010038@1@DAY1,24HOUR
V132_01EXP-024:00POST -117-5248536133@3032@V132_01EXP-0010044@1@DAY1,24HOUR
V132_01EXP-072:00POST -101-5248550533@3032@V132_01EXP-0010001@2@DAY4
V132_01EXP-072:00POST -102-5248550633@3032@V132_01EXP-0010006@2@DAY4
V132_01EXP-072:00POST -103-5248550733@3032@V132_01EXP-0010014@2@DAY4
V132_01EXP-072:00POST -104-5248550833@3032@V132_01EXP-0010013@2@DAY4
072:00POST -105-5248550933@3032@V132_01EXP-0010016@2@DAY4
072:00POST -106-5248551033@3032@V132_01EXP-0010024@2@DAY4
072:00POST -107-5248551133@3032@V132_01EXP-0010025@2@DAY4
072:00POST -111-5248551533@3032@V132_01EXP-0010026@2@DAY4
072:00POST -112-5248551633@3032@V132_01EXP-0010028@2@DAY4
072:00POST -113-5248551733@3032@V132_01EXP-0010034@2@DAY4
072:00PO ST-114-5248551833@3032@V132_01EXP-0010051@2@DAY4
072:00POST -115-5248551933@3032@V132_01EXP-0010033@2@DAY4072:00
POST-116-5248552033@3032@V132_01EXP-0010038@2@DAY4
072:00POST -117-5248552133@3032@V132_01EXP-0010044@2@DAY4
V132_01EXP-168:00POST -101-5248566533@3032@V132_01EXP-0010001@3@DAY8
V132_01EXP-168:00POST -102-5248566633@3032@V132_01EXP-0010006@3@DAY8
V132_01EXP-168:00POST -103-5248566733@3032@V132_01EXP-0010014@3@DAY8
V132_01EXP-168:00POST -104-5248566833@3032@V132_01EXP-0010013@3@DAY8

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V132_01EXP-
V132_01EXP-168:00POST -105-5248566933@3032@V132_01EXP-0010016@3@DAY8
V132_01EXP-168:00POST -106-5248567033@3032@V132_01EXP-0010024@3@DAY8
V132_01EXP-168:00POST -107-5248567133@3032@V132_01EXP-0010025@3@DAY8
V132_01EXP-168:00POST -111-5248567533@3032@V132_01EXP-0010026@3@DAY8
V132_01EXP-168:00POST -112-5248567633@3032@V132_01EXP-0010028@3@DAY8
V132_01EXP-168:00POST -113-5248567733@3032@V132_01EXP-0010034@3@DAY8
V132_01EXP-168:00POST -114-5248567833@3032@V132_01EXP-0010051@3@DAY8
V132_01EXP-168:00POST -115-5248567933@3032@V132_01EXP-0010033@3@DAY8
V132_01EXP-168:00POST -116-5248568033@3032@V132_01EXP-0010038@3@DAY8
V132_01EXP-168:00POST -117-5248568133@3032@V132_01EXP-0010044@3@DAY8

V132_01EXP_Chemokine_23_2016-11-11-1650

V132_01EXP-000:15PRE -118-5248496233@3032@V132_01EXP-0010031@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -119-5248496333@3032@V132_01EXP-0010041@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -120-5248496433@3032@V132_01EXP-0010042@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -201-5248976434@3032@V132_01EXP-0010036@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -202-5248976534@3032@V132_01EXP-0010027@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -203-5248976634@3032@V132_01EXP-0010067@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -204-5248976734@3032@V132_01EXP-0010048@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -206-5248976934@3032@V132_01EXP-0010071@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -207-5248977034@3032@V132_01EXP-0010072@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -208-5248977132@3032@V132_01EXP-0010074@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -209-5248977232@3032@V132_01EXP-0010073@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -210-5248977332@3032@V132_01EXP-0010075@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -211-5248977432@3032@V132_01EXP-0010076@1@DAY1,PREDOSE
000:15PRE -212-5248977532@3032@V132_01EXP-0010083@1@DAY1,PREDOSE
006:00POST -118-5248520233@3032@V132_01EXP-0010031@1@DAY1,6HOUR

V132_01EXP-
V132_01EXP-
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V132_01EXP-
V132_01EXP-
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V132_01EXP-
V132_01EXP-
V132_01EXP-
006:00POST -119-5248520333@3032@V132_01EXP-0010041@1@DAY1,6HOUR
006:00POST -120-5248520433@3032@V132_01EXP-0010042@1@DAY1,6HOUR
006:00POST -201-5248988434@3032@V132_01EXP-0010036@1@DAY1,6HOUR
006:00POST -202-5248988534@3032@V132_01EXP-0010027@1@DAY1,6HOUR
006:00POST -203-5248988634@3032@V132_01EXP-0010067@1@DAY1,6HOUR
006:00POST -204-5248988734@3032@V132_01EXP-0010048@1@DAY1,6HOUR
006:00POST -206-5248988934@3032@V132_01EXP-0010071@1@DAY1,6HOUR
006:00POST -207-5248989034@3032@V132_01EXP-0010072@1@DAY1,6HOUR
V132_01EXP-006:00POST -208-5248989132@3032@V132_01EXP-0010074@1@DAY1,6HOUR
V132_01EXP-006:00POST -209-5248989232@3032@V132_01EXP-0010073@1@DAY1,6HOUR
V132_01EXP-006:00POST -210-5248989332@3032@V132_01EXP-0010075@1@DAY1,6HOUR
V132_01EXP-006:00POST -211-5248989432@3032@V132_01EXP-0010076@1@DAY1,6HOUR
V132_01EXP-006:00POST -212-5248989532@3032@V132_01EXP-0010083@1@DAY1,6HOUR
V132_01EXP-024:00POST -118-5248536233@3032@V132_01EXP-0010031@1@DAY1,24HOUR
V132_01EXP-024:00POST -119-5248536333@3032@V132_01EXP-0010041@1@DAY1,24HOUR
V132_01EXP-024:00POST -120-5248536433@3032@V132_01EXP-0010042@1@DAY1,24HOUR
V132_01EXP-024:00POST -201-5248996434@3032@V132_01EXP-0010036@1@DAY1,24HOUR
V132_01EXP-024:00POST -202-5248996534@3032@V132_01EXP-0010027@1@DAY1,24HOUR
V132_01EXP-024:00POST -203-5248996634@3032@V132_01EXP-0010067@1@DAY1,24HOUR
V132_01EXP-024:00POST -204-5248996734@3032@V132_01EXP-0010048@1@DAY1,24HOUR
V132_01EXP-024:00POST -206-5248996934@3032@V132_01EXP-0010071@1@DAY1,24HOUR
V132_01EXP-024:00POST -207-5248997034@3032@V132_01EXP-0010072@1@DAY1,24HOUR
V132_01EXP-024:00POST -208-5248997132@3032@V132_01EXP-0010074@1@DAY1,24HOUR
V132_01EXP-024:00POST -209-5248997232@3032@V132_01EXP-0010073@1@DAY1,24HOUR
V132_01EXP-024:00POST -210-5248997332@3032@V132_01EXP-0010075@1@DAY1,24HOUR
V132_01EXP-024:00POST -211-5248997432@3032@V132_01EXP-0010076@1@DAY1,24HOUR
V132_01EXP-024:00POST -212-5248997532@3032@V132_01EXP-0010083@1@DAY1,24HOUR
V132_01EXP-072:00POST -118-5248552233@3032@V132_01EXP-0010031@2@DAY4
V132_01EXP-072:00POST -119-5248552333@3032@V132_01EXP-0010041@2@DAY4

V132_01EXP-
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V132_01EXP-072:00POST -120-5248552433@3032@V132_01EXP-0010042@2@DAY4
V132_01EXP-072:00POST -201-5249004434@3032@V132_01EXP-0010036@2@DAY4
V132_01EXP-072:00PO ST-202-5249004534@3032@V132_01EXP-0010027@2@DAY4
V132_01EXP-072:00POST -203-5249004634@3032@V132_01EXP-0010067@2@DAY4
V132_01EXP-072:00POST -204-5249004734@3032@V132_01EXP-0010048@2@DAY4
V132_01EXP-072:00POST -206-5249004934@3032@V132_01EXP-0010071@2@DAY4
V132_01EXP-072:00POST -207-5249005034@3032@V132_01EXP-0010072@2@DAY4
V132_01EXP-072:00POST -208-5249005132@3032@V132_01EXP-0010074@2@DAY4
V132_01EXP-072:00POST -209-5249005232@3032@V132_01EXP-0010073@2@DAY4
072:00POST -210-5249005332@3032@V132_01EXP-0010075@2@DAY4
072:00POST -211-5249005432@3032@V132_01EXP-0010076@2@DAY4
072:00POST -212-5249005532@3032@V132_01EXP-0010083@2@DAY4
168:00POST -118-5248568233@3032@V132_01EXP-0010031@3@DAY8
168:00POST -119-5248568333@3032@V132_01EXP-0010041@3@DAY8
168:00POST -120-5248568433@3032@V132_01EXP-0010042@3@DAY8
168:00POST -201-5249012434@3032@V132_01EXP-0010036@3@DAY8

V132_01EXP-
V132_01EXP-
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V132_01EXP-168:00POST -202-5249012534@3032@V132_01EXP-0010027@3@DAY8
V132_01EXP-168:00POST -203-5249012634@3032@V132_01EXP-0010067@3@DAY8
V132_01EXP-168:00POST -204-5249012734@3032@V132_01EXP-0010048@3@DAY8
V132_01EXP-168:00POST -206-5249012934@3032@V132_01EXP-0010071@3@DAY8
V132_01EXP-168:00POST -207-5249013034@3032@V132_01EXP-0010072@3@DAY8
V132_01EXP-168:00POST -208-5249013132@3032@V132_01EXP-0010074@3@DAY8
V132_01EXP-168:00POST -209-5249013232@3032@V132_01EXP-0010073@3@DAY8
V132_01EXP-168:00POST -210-5249013332@3032@V132_01EXP-0010075@3@DAY8
V132_01EXP-168:00POST -211-5249013432@3032@V132_01EXP-0010076@3@DAY8
V132_01EXP-168:00POST -212-5249013532@3032@V132_01EXP-0010083@3@DAY8

V132_01EXP_Chemokine_24_2016-11-14-1530

V132_01EXP-000:15PRE -401-5253675032@3032@V132_01EXP-0010134@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -402-5253675132@3032@V132_01EXP-0010153@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -403-5253675232@3032@V132_01EXP-0010150@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -404-5253675332@3032@V132_01EXP-0010152@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -405-5253675432@3032@V132_01EXP-0010162@1@DAY1, PREDOSE
V132_01EXP-000:15PRE -406-5253675532@3032@V132_01EXP-0010168@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -407-5253675632@3032@V132_01EXP-0010171@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -408-5253675732@3032@V132_01EXP-0010172@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -409-5253675832@3032@V132_01EXP-0010175@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -410-5253675932@3032@V132_01EXP-0010178@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -411-5253676032@3032@V132_01EXP-0010165@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -412-5253676132@3032@V132_01EXP-0010170@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -413-5253676232@3032@V132_01EXP-0010180@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -414-5253676332@3032@V132_01EXP-0010188@1@DAY1,PREDOSE
V132_01EXP-006:00POST -401-5253687032@3032@V132_01EXP-0010134@1@DAY1,6HOUR
V132_01EXP-006:00POST -402-5253687132@3032@V132_01EXP-0010153@1@DAY1,6HOUR
V132_01EXP-006:00POST -403-5253687232@3032@V132_01EXP-0010150@1@DAY1,6HOUR
V132_01EXP-006:00POST -404-5253687332@3032@V132_01EXP-0010152@1@DAY1,6HOUR
V132_01EXP-006:00POST -405-5253687432@3032@V132_01EXP-0010162@1@DAY1,6HOUR

V132_01EXP-
V132_01EXP-
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V132_01EXP-
V132_01EXP-
V132_01EXP-

V132_01EXP-006:00POST -406-5253687532@3032@V132_01EXP-0010168@1@DAY1,6HOUR
006:00POST -407-5253687632@3032@V132_01EXP-0010171@1@DAY1,6HO UR
006:00POST -408-5253687732@3032@V132_01EXP-0010172@1@DAY1,6HOUR
006:00POST -409-5253687832@3032@V132_01EXP-0010175@1@DAY1,6HOUR
006:00POST -410-5253687932@3032@V132_01EXP-0010178@1@DAY1,6HOUR
006:00POST -411-5253688032@3032@V132_01EXP-0010165@1@DAY1,6HOUR
006:00POST -412-5253688132@3032@V132_01EXP-0010170@1@DAY1,6HOUR
006:00POST -413-5253688232@3032@V132_01EXP-0010180@1@DAY1,6HOUR
006:00POST -414-5253688332@3032@V132_01EXP-0010188@1@DAY1,6HOUR
V132_01EXP-024:00POST -401-5253695032@3032@V132_01EXP-0010134@1@DAY1,24HOUR
V132_01EXP-024:00POST -402-5253695132@3032@V132_01EXP-0010153@1@DAY1,24HOUR
V132_01EXP-024:00POST -403-5253695232@3032@V132_01EXP-0010150@1@DAY1,24HOUR
V132_01EXP-024:00POST -404-5253695332@3032@V132_01EXP-0010152@1@DAY1,24HOUR
V132_01EXP-024:00POST -405-5253695432@3032@V132_01EXP-0010162@1@DAY1,24HOUR
V132_01EXP-024:00POST -406-5253695532@3032@V132_01EXP-0010168@1@DAY1,24HOUR
V132_01EXP-024:00POST -407-5253695632@3032@V132_01EXP-0010171@1@DAY1,24HOUR
V132_01EXP-024:00POST -408-5253695732@3032@V132_01EXP-0010172@1@DAY1,24HOUR
V132_01EXP-024:00POST -409-5253695832@3032@V132_01EXP-0010175@1@DAY1,24HOUR
V132_01EXP-024:00POST -410-5253695932@3032@V132_01EXP-0010178@1@DAY1,24HOUR
V132_01EXP-024:00POST -411-5253696032@3032@V132_01EXP-0010165@1@DAY1,24HOUR
V132_01EXP-024:00POST -412-5253696132@3032@V132_01EXP-0010170@1@DAY1,24HOUR
V132_01EXP-024:00POST -413-5253696232@3032@V132_01EXP-0010180@1@DAY1,24HOUR
V132_01EXP-024:00POST -414-5253696332@3032@V132_01EXP-0010188@1@DAY1,24HOUR
V132_01EXP-072:00POST -401-5253703032@3032@V132_01EXP-0010134@2@DAY4
V132_01EXP-072:00POST -402-5253703132@3032@V132_01EXP-0010153@2@DAY4
V132_01EXP-072:00POST -403-5253703232@3032@V132_01EXP-0010150@2@DAY4
V132_01EXP-072:00POST -404-5253703332@3032@V132_01EXP-0010152@2@DAY4
V132_01EXP-072:00POST -405-5253703432@3032@V132_01EXP-0010162@2@DAY4
V132_01EXP-072:00POST -406-5253703532@3032@V132_01EXP-0010168@2@DAY4
V132_01EXP-072:00POST -407-5253703632@3032@V132_01EXP-0010171@2@DAY4
V132_01EXP-072:00POST -408-5253703732@3032@V132_01EXP-0010172@2@DAY4
V132_01EXP-072:00POST -409-5253703832@3032@V132_01EXP-0010175@2@DAY4
V132_01EXP-072:00POST -410-5253703932@3032@V132_01EXP-0010178@2@DAY4
V132_01EXP-072:00POST -411-5253704032@3032@V132_01EXP-0010165@2@DAY4
V132_01EXP-072:00POST -412-5253704132@3032@V132_01EXP-0010170@2@DAY4
V132_01EXP-072:00POST -413-5253704232@3032@V132_01EXP-0010180@2@DAY4
V132_01EXP-072:00POST -414-5253704332@3032@V132_01EXP-0010188@2@DAY4

V132_01EXP-
V132_01EXP-168:00POST -401-5253711032@3032@V132_01EXP-0010134@3@DAY8
V132_01EXP-168:00POST -402-5253711132@3032@V132_01EXP-0010153@3@DAY8
V132_01EXP-168:00POST -403-5253711232@3032@V132_01EXP-0010150@3@DAY8
V132_01EXP-168:00POST -404-5253711332@3032@V132_01EXP-0010152@3@DAY8
168:00POST -405-5253711432@3032@V132_01EXP-0010162@3@DAY8
168:00POST -406-5253711532@3032@V132_01EXP-0010168@3@DAY8
168:00POST -407-5253711632@3032@V132_01EXP-0010171@3@DAY8
168:00POST -408-5253711732@3032@V132_01EXP-0010172@3@DAY8
168:00POST -409-5253711832@3032@V132_01EXP-0010175@3@DAY8
168:00POST -410-5253711932@3032@V132_01EXP-0010178@3@DAY8
168:00POST -411-5253712032@3032@V132_01EXP-0010165@3@DAY8
V132_01EXP-168:00POST -412-5253712132@3032@V132_01EXP-0010170@3@DAY8
V132_01EXP-168:00POST -413-5253712232@3032@V132_01EXP-0010180@3@DAY8
V132_01EXP-168:00POST -414-5253712332@3032@V132_01EXP-0010188@3@DAY8

V132_01EXP_Chemokine_27_2016-11-21-1625
V132_01EXP-000:15PRE -415-5253676431@3032@V132_01EXP-0010190@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -416-5253676531@3032@V132_01EXP-0010176@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -417-5253676631@3032@V132_01EXP-0010179@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -418-5253676731@3032@V132_01EXP-0010184@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -419-5253676831@3032@V132_01EXP-0010182@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -420-5253676931@3032@V132_01EXP-0010191@1@DAY1, PREDOSE
V132_01EXP-006:00POST -415-5253688431@3032@V132_01EXP-0010190@1@DAY1,6HOUR
V132_01EXP-006:00POST -416-5253688531@3032@V132_01EXP-0010176@1@DAY1,6HOUR
V132_01EXP-006:00POST -417-5253688631@3032@V132_01EXP-0010179@1@DAY1,6HOUR
V132_01EXP-006:00POST -418-5253688731@3032@V132_01EXP-0010184@1@DAY1,6HOUR
V132_01EXP-006:00POST -419-5253688831@3032@V132_01EXP-0010182@1@DAY1,6HOUR
V132_01EXP-006:00POST -420-5253688931@3032@V132_01EXP-0010191@1@DAY1,6HOUR
V132_01EXP-024:00POST -415-5253696431@3032@V132_01EXP-0010190@1@DAY1,24HOUR
V132_01EXP-024:00POST -416-5253696531@3032@V132_01EXP-0010176@1@DAY1,24HOUR
V132_01EXP-024:00POST -417-5253696631@3032@V132_01EXP-0010179@1@DAY1,24HOUR
V132_01EXP-024:00POST -418-5253696731@3032@V132_01EXP-0010184@1@DAY1,24HOUR
V132_01EXP-024:00POST -419-5253696831@3032@V132_01EXP-0010182@1@DAY1,24HOUR

V132_01EXP-
V132_01EXP-
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V132_01EXP-024:00POST -420-5253696931@3032@V132_01EXP-0010191@1@DAY1,24HOUR
V132_01EXP-072:00POST -415-5253704431@3032@V132_01EXP-0010190@2@DAY4
V132_01EXP-072:00POST -416-5253704531@3032@V132_01EXP-0010176@2@DAY4
V132_01EXP-072:00POST -417-5253704631@3032@V132_01EXP-0010179@2@DAY4
V132_01EXP-072:00POST -418-5253704731@3032@V132_01EXP-0010184@2@DAY4
V132_01EXP-072:00POST -419-5253704831@3032@V132_01EXP-0010182@2@DAY4
V132_01EXP-072:00POST -420-5253704931@3032@V132_01EXP-0010191@2@DAY4
V132_01EXP-168:00POST -415-5253712431@3032@V132_01EXP-0010190@3@DAY8
V132_01EXP-168:00POST -416-5253712531@3032@V132_01EXP-0010176@3@DAY8
V132_01EXP-168:00POST -417-5253712631@3032@V132_01EXP-0010179@3@DAY8
V132_01EXP-168:00POST -418-5253712731@3032@V132_01EXP-0010184@3@DAY8
V132_01EXP-168:00POST -419-5253712831@3032@V132_01EXP-0010182@3@DAY8
V132_01EXP-168:00 POST-420-5253712931@3032@V132_01EXP-0010191@3@DAY8

V132_01EXP_Cytokine_08_2016-09-22-1600

V132_01EXP-000:15PRE -213-5248977631@3032@V132_01EXP-0010085@1@DAY1,PREDOSE

V132_01EXP-

000:15 PRE -214-5248977731@3032@V132_01EXP-0010086@1@DAY 1, PREDOSE
V132_01EXP-000:15PRE -215-5248977833@3032@V132_01EXP-0010081@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -216-5248977933@3032@V132_01EXP-0010093@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -217-5248978033@3032@V132_01EXP-0010094@1@DAY1,PRE DOSE
V132_01EXP-000:15PRE -218-5248978133@3032@V132_01EXP-0010080@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -219-5248978233@3032@V132_01EXP-0010087@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -220-5248978333@3032@V132_01EXP-0010089@1@DAY1,PREDOSE
V132_01EXP-006:00POST -213-5248989631@3032@V132_01EXP-0010085@1@DAY1,6HOUR
V132_01EXP-006:00POST -214-5248989731@3032@V132_01EXP-0010086@1@DAY1,6HOUR
V132_01EXP-006:00POST -215-5248989833@3032@V132_01EXP-0010081@1@DAY1,6HOUR
V132_01EXP-006:00POST -216-5248989933@3032@V132_01EXP-0010093@1@DAY1,6HOUR
V132_01EXP-006:00POST -217-5248990033@3032@V132_01EXP-0010094@1@DAY1,6HOUR
V132_01EXP-006:00POST -218-5248990133@3032@V132_01EXP-0010080@1@DAY1,6HOUR
V132_01EXP-006:00POST -219-5248990233@3032@V132_01EXP-0010087@1@DAY1,6HOUR
V132_01EXP-006:00POST -220-5248990333@3032@V132_01EXP-0010089@1@DAY1,6HOUR
V132_01EXP-024:00POST -213-5248997631@3032@V132_01EXP-0010085@1@DAY1,24HOUR
V132_01EXP-024:00POST -214-5248997731@3032@V132_01EXP-0010086@1@DAY1,24HOUR
V132_01EXP-024:00POST -215-5248997833@3032@V132_01EXP-0010081@1@DAY1,24HOUR
V132_01EXP-024:00POST -216-5248997933@3032@V132_01EXP-0010093@1@DAY1,24HOUR
V132_01EXP-024:00POST -217-5248998033@3032@V132_01EXP-0010094@1@DAY1,24HOUR
V132_01EXP-024:00POST -218-5248998133@3032@V132_01EXP-0010080@1@DAY1,24HOUR
V132_01EXP-024:00POST -219-5248998233@3032@V132_01EXP-0010087@1@DAY1,24HOUR
V132_01EXP-024:00POST -220-5248998333@3032@V132_01EXP-0010089@1@DAY 1,24HOUR
V132_01EXP-072:00POST -213-5249005631@3032@V132_01EXP-0010085@2@DAY4
V132_01EXP-072:00POST -214-5249005731@3032@V132_01EXP-0010086@2@DAY4
V132_01EXP-072:00POST -215-5249005833@3032@V132_01EXP-0010081@2@DAY4
V132_01EXP-072:00POST -216-5249005933@3032@V132_01EXP-0010093@2@DAY4
V132_01EXP-072:00POST -217-5249006033@3032@V132_01EXP-0010094@2@DAY4
V132_01EXP-072:00POST -218-5249006133@3032@V132_01EXP-0010080@2@DAY4
V132_01EXP-072:00POST -219-5249006233@3032@V132_01EXP-0010087@2@DAY4

V132_01EXP-
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V132_01EXP-072:00POST -220-5249006333@3032@V132_01EXP-0010089@2@DAY4
V132_01EXP-168:00POST -213-5249013631@3032@V132_01EXP-0010085@3@DAY8
V132_01EXP-168:00POST -214-5249013731@3032@V132_01EXP-0010086@3@DAY8
V132_01EXP-168:00POST -215-5249013833@3032@V132_01EXP-0010081@3@DAY8
V132_01EXP-168:00POST -216-5249013933@3032@V132_01EXP-0010093@3@DAY8
168:00POST -217-5249014033@3032@V132_01EXP-0010094@3@DAY8
168:00POST -218-5249014133@3032@V132_01EXP-0010080@3@DAY8
168:00POST -219-5249014233@3032@V132_01EXP-0010087@3@DAY8
168:00 POST -220-5249014333@3032@V132_01EXP-0010089@3@DAY 8
V132_01EXP_Cytokine_11_2016-09-29-1610
V132_01EXP-000:15PRE -301-5251924031@3032@V132_01EXP-0010088@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -302-5251924131@3032@V132_01EXP-0010111@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -303-5251924231@3032@V132_01EXP-0010090@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -304-5251924331@3032@V132_01EXP-0010099@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -305-5251924431@3032@V132_01EXP-0010100@1@DAY1,PREDOSE
V132_01EXP-006:00POST -301-5251936031@3032@V132_01EXP-0010088@1@DAY1,6HOUR
V132_01EXP-006:00POST -302-5251936131@3032@V132_01EXP-0010111@1@DAY1,6HOUR
V132_01EXP-006:00POST -303-5251936231@3032@V132_01EXP-0010090@1@DAY1,6HOUR
V132_01EXP-006:00POST -304-5251936331@3032@V132_01EXP-0010099@1@DAY1,6HOUR
V132_01EXP-006:00POST -305-5251936431@3032@V132_01EXP-0010100@1@DAY1,6HOUR
V132_01EXP-024:00POST -301-5251944031@3032@V132_01EXP-0010088@1@DAY1,24HOUR
V132_01EXP-024:00POST -302-5251944131@3032@V132_01EXP-0010111@1@DAY1,24HOUR
V132_01EXP-024:00POST -303-5251944231@3032@V132_01EXP-0010090@1@DAY1,24HOUR
V132_01EXP-024:00POST -304-5251944331@3032@V132_01EXP-0010099@1@DAY1,24HOUR
V132_01EXP-024:00POST -305-5251944431@3032@V132_01EXP-0010100@1@DAY1,24HOUR
V132_01EXP-072:00POST -301-5251952031@3032@V132_01EXP-0010088@2@DAY4
V132_01EXP-072:00POST -302-5251952131@3032@V132_01EXP-0010111@2@DAY4
V132_01EXP-072:00POST -303-5251952231@3032@V132_01EXP-0010090@2@DAY4
V132_01EXP-072:00POST -304-5251952331@3032@V132_01EXP-0010099@2@DAY4
V132_01EXP-072:00POST -305-5251952431@3032@V132_01EXP-0010100@2@DAY4
V132_01EXP-168:00POST -301-5251960031@3032@V132_01EXP-0010088@3@DAY8
V132_01EXP-168:00POST -302-5251960131@3032@V132_01EXP-0010111@3@DAY8
V132_01EXP-168:00POST -303-5251960231@3032@V132_01EXP-0010090@3@DAY8
V132_01EXP-
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V132_01EXP-168:00POST -304-5251960331@3032@V132_01EXP-0010099@3@DAY8
V132_01EXP-168:00POST -305-5251960431@3032@V132_01EXP-0010100@3@DAY8

V132_01EXP_Cytokine_14_2016-10-04-1620

V132_01EXP-000:15PRE -306-5251924531@3032@V132_01EXP-0010125@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -307-5251924631@3032@V132_01EXP-0010130@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -308-5251924731@3032@V132_01EXP-0010133@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -309-5251924831@3032@V132_01EXP-0010121@1@DAY1,PREDOSE
000:15PRE -310-5251924931@3032@V132_01EXP-0010135@1@DAY1,PREDOSE
000:15PRE -311-5251925031@3032@V132_01EXP-0010136@1@DAY1,PREDOSE
000:15PRE -312-5251925131@3032@V132_01EXP-0010122@1@DAY1,PREDOSE
000:15PRE -313-5251925231@3032@V132_01EXP-0010138@1@DAY1,PREDOSE
000:15PRE -314-5251925331@3032@V132_01EXP-0010140@1@DAY1,PREDOSE
000:15PRE -315-5251925431@3032@V132_01EXP-0010139@1@DAY1,PREDOSE
000:15PRE -316-5251925531@3032@V132_01EXP-0010143@1@DAY1,PREDOSE
000:15 PRE -317-5251925631@3032@V132_01EXP-0010147@1@DAY 1, PREDOSE
V132_01EXP-000:15PRE -319-5251925831@3032@V132_01EXP-0010131@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -320-5251925931@3032@V132_01EXP-0010141@1@DAY1,PREDOSE
V132_01EXP-006:00POST -306-5251936531@3032@V132_01EXP-0010125@1@DAY1,6HOUR
V132_01EXP-006:00POST -307-5251936631@3032@V132_01EXP-0010130@1@DAY1,6HOUR
V132_01EXP-006:00POST -308-5251936731@3032@V132_01EXP-0010133@1@DAY1,6HOUR
V132_01EXP-006:00POST -309-5251936831@3032@V132_01EXP-0010121@1@DAY1,6HOUR
V132_01EXP-006:00POST -310-5251936931@3032@V132_01EXP-0010135@1@DAY1,6HOUR
V132_01EXP-006:00POST -311-5251937031@3032@V132_01EXP-0010136@1@DAY1,6HOUR
V132_01EXP-006:00POST -312-5251937131@3032@V132_01EXP-0010122@1@DAY1,6HOUR
V132_01EXP-006:00POST -313-5251937231@3032@V132_01EXP-0010138@1@DAY1,6HOUR
V132_01EXP-006:00POST -314-5251937331@3032@V132_01EXP-0010140@1@DAY1,6HOUR
V132_01EXP-006:00POST -315-5251937431@3032@V132_01EXP-0010139@1@DAY1,6HOUR
V132_01EXP-006:00POST -316-5251937531@3032@V132_01EXP-0010143@1@DAY1,6HOUR

V132_01EXP-
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V132_01EXP-006:00POST -317-5251937631@3032@V132_01EXP-0010147@1@DAY1,6HOUR
V132_01EXP-006:00POST -319-5251937831@3032@V132_01EXP-0010131@1@DAY1,6HOUR
V132_01EXP-006:00POST -320-5251937931@3032@V132_01EXP-0010141@1@DAY1,6HOUR
V132_01EXP-024:00POST -306-5251944531@3032@V132_01EXP-0010125@1@DAY1,24HOUR
V132_01EXP-024:00POST -307-5251944631@3032@V132_01EXP-0010130@1@DAY1,24HOUR
V132_01EXP-024:00POST -308-5251944731@3032@V132_01EXP-0010133@1@DAY1,24HOUR
V132_01EXP-024:00POST -309-5251944831@3032@V132_01EXP-0010121@1@DAY 1,24HOUR
V132_01EXP-024:00POST -310-5251944931@3032@V132_01EXP-0010135@1@DAY1,24HOUR
V132_01EXP-024:00POST -311-5251945031@3032@V132_01EXP-0010136@1@DAY1,24HOUR
V132_01EXP-024:00POST -312-5251945131@3032@V132_01EXP-0010122@1@DAY1,24HOUR
V132_01EXP-024:00POST -313-5251945231@3032@V132_01EXP-0010138@1@DAY1,24HOUR
V132_01EXP-024:00POST -314-5251945331@3032@V132_01EXP-0010140@1@DAY1,24HOUR
V132_01EXP-024:00POST -315-5251945431@3032@V132_01EXP-0010139@1@DAY1,24HOUR
V132_01EXP-024:00POST -316-5251945531@3032@V132_01EXP-0010143@1@DAY1,24HOUR
V132_01EXP-024:00POST -317-5251945631@3032@V132_01EXP-0010147@1@DAY1,24HOUR
V132_01EXP-024:00POST -319-5251945831@3032@V132_01EXP-0010131@1@DAY1,24HOUR
V132_01EXP-024:00POST -320-5251945931@3032@V132_01EXP-0010141@1@DAY1,24HOUR
V132_01EXP-072:00POST -306-5251952531@3032@V132_01EXP-0010125@2@DAY4
V132_01EXP-072:00POST -307-5251952631@3032@V132_01EXP-0010130@2@DAY4
V132_01EXP-072:00POST -308-5251952731@3032@V132_01EXP-0010133@2@DAY4
072:00POST -309-5251952831@3032@V132_01EXP-0010121@2@DAY4
072:00POST -310-5251952931@3032@V132_01EXP-0010135@2@DAY4
072:00POST -311-5251953031@3032@V132_01EXP-0010136@2@DAY4
072:00POST -312-5251953131@3032@V132_01EXP-0010122@2@DAY4
072:00POST -313-5251953231@3032@V132_01EXP-0010138@2@DAY4
072:00POST -314-5251953331@3032@V132_01EXP-0010140@2@DAY4

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072:00POST -315-5251953431@3032@V132_01EXP-0010139@2@DAY4
072:00POST -316-5251953531@3032@V132_01EXP-0010143@2@DAY4
072:00POST -317-5251953631@3032@V132_01EXP-0010147@2@DAY4
V132_01EXP-072:00POST -319-5251953831@3032@V132_01EXP-0010131@2@DAY4
V132_01EXP-072:00POST -320-5251953931@3032@V132_01EXP-0010141@2@DAY4
V132_01EXP-168:00POST -306-5251960531@3032@V132_01EXP-0010125@3@DAY8
V132_01EXP-168:00POST -307-5251960631@3032@V132_01EXP-0010130@3@DAY8
V132_01EXP-168:00POST -308-5251960731@3032@V132_01EXP-0010133@3@DAY8
V132_01EXP-168:00POST -309-5251960831@3032@V132_01EXP-0010121@3@DAY8
V132_01EXP-168:00POST -310-5251960931@3032@V132_01EXP-0010135@3@DAY8
V132_01EXP-168:00POST -311-5251961031@3032@V132_01EXP-0010136@3@DAY8
V132_01EXP-168:00POST -312-5251961131@3032@V132_01EXP-0010122@3@DAY8
V132_01EXP-168:00POST -313-5251961231@3032@V132_01EXP-0010138@3@DAY8
V132_01EXP-168:00POST -314-5251961331@3032@V132_01EXP-0010140@3@DAY8
V132_01EXP-168:00POST -315-5251961431@3032@V132_01EXP-0010139@3@DAY8
V132_01EXP-168:00P OST-316-5251961531@3032@V132_01EXP-0010143@3@DAY8
V132_01EXP-168:00POST -317-5251961631@3032@V132_01EXP-0010147@3@DAY8
V132_01EXP-168:00POST -319-5251961831@3032@V132_01EXP-0010131@3@DAY8
V132_01EXP-168:00POST -320-5251961931@3032@V132_01EXP-0010141@3@DAY8

V132_01EXP_Cytokine_17_2016-10-14-1555

V132_01EXP-000:15PRE -401-5253675031@3032@V132_01EXP-0010134@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -402-5253675131@3032@V132_01EXP-0010153@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -403-5253675231@3032@V132_01EXP-0010150@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -404-5253675331@3032@V132_01EXP-0010152@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -405-5253675431@3032@V132_01EXP-0010162@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -406-5253675531@3032@V132_01EXP-0010168@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -407-5253675631@3032@V132_01EXP-0010171@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -408-5253675731@3032@V132_01EXP-0010172@1@DAY1,PREDOSE
V132_01EXP-
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V132_01EXP-000:15PRE -409-5253675831@3032@V132_01EXP-0010175@1@DAY1,PRE DOSE
V132_01EXP-000:15PRE -410-5253675931@3032@V132_01EXP-0010178@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -411-5253676031@3032@V132_01EXP-0010165@1@DAY1,PREDOSE
000:15PRE -412-5253676131@3032@V132_01EXP-0010170@1@DAY1,PREDOSE
000:15PRE -413-5253676231@3032@V132_01EXP-0010180@1@DAY1,PREDOSE
000:15PRE -414-5253676331@3032@V132_01EXP-0010188@1@DAY1,PREDOSE
006:00POST -401-5253687031@3032@V132_01EXP-0010134@1@DAY1,6HOUR
006:00POST -402-5253687131@3032@V132_01EXP-0010153@1@DAY1,6HO UR
006:00POST -403-5253687231@3032@V132_01EXP-0010150@1@DAY1,6HOUR
006:00POST -404-5253687331@3032@V132_01EXP-0010152@1@DAY1,6HOUR
006:00POST -405-5253687431@3032@V132_01EXP-0010162@1@DAY1,6HOUR
006:00POST -406-5253687531@3032@V132_01EXP-0010168@1@DAY1,6HOUR
006:00POST -407-5253687631@3032@V132_01EXP-0010171@1@DAY1,6HOUR
V132_01EXP-006:00POST -408-5253687731@3032@V132_01EXP-0010172@1@DAY1,6HOUR
V132_01EXP-006:00POST -409-5253687831@3032@V132_01EXP-0010175@1@DAY1,6HOUR
V132_01EXP-006:00POST -410-5253687931@3032@V132_01EXP-0010178@1@DAY1,6HOUR
V132_01EXP-006:00POST -411-5253688031@3032@V132_01EXP-0010165@1@DAY1,6HOUR
V132_01EXP-006:00POST -412-5253688131@3032@V132_01EXP-0010170@1@DAY1,6HOUR
V132_01EXP-006:00POST -413-5253688231@3032@V132_01EXP-0010180@1@DAY1,6HOUR
V132_01EXP-006:00POST -414-5253688331@3032@V132_01EXP-0010188@1@DAY1,6HOUR
V132_01EXP-024:00POST -401-5253695031@3032@V132_01EXP-0010134@1@DAY1,24HOUR
V132_01EXP-024:00POST -402-5253695131@3032@V132_01EXP-0010153@1@DAY1,24HOUR
V132_01EXP-024:00POST -403-5253695231@3032@V132_01EXP-0010150@1@DAY1,24HOUR
V132_01EXP-024:00POST -404-5253695331@3032@V132_01EXP-0010152@1@DAY1,24HOUR
V132_01EXP-024:00POST -405-5253695431@3032@V132_01EXP-0010162@1@DAY1,24HOUR
V132_01EXP-024:00POST -406-5253695531@3032@V132_01EXP-0010168@1@DAY1,24HOUR
V132_01EXP-024:00POST -407-5253695631@3032@V132_01EXP-0010171@1@DAY1,24HOUR
V132_01EXP-024:00POST -408-5253695731@3032@V132_01EXP-0010172@1@DAY1,24HOUR
V132_01EXP-024:00POST -409-5253695831@3032@V132_01EXP-0010175@1@DAY1,24HOUR

V132_01EXP-
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V132_01EXP-024:00POST -410-5253695931@3032@V132_01EXP-0010178@1@DAY1,24HOUR
V132_01EXP-024:00POST -411-5253696031@3032@V132_01EXP-0010165@1@DAY 1,24HOUR
V132_01EXP-024:00POST -412-5253696131@3032@V132_01EXP-0010170@1@DAY1,24HOUR
V132_01EXP-024:00POST -413-5253696231@3032@V132_01EXP-0010180@1@DAY1,24HOUR
V132_01EXP-024:00POST -414-5253696331@3032@V132_01EXP-0010188@1@DAY1,24HOUR
V132_01EXP-072:00POST -401-5253703031@3032@V132_01EXP-0010134@2@DAY4
V132_01EXP-072:00POST -402-5253703131@3032@V132_01EXP-0010153@2@DAY4
V132_01EXP-072:00POST -403-5253703231@3032@V132_01EXP-0010150@2@DAY4
V132_01EXP-072:00POST -404-5253703331@3032@V132_01EXP-0010152@2@DAY4
V132_01EXP-072:00POST -405-5253703431@3032@V132_01EXP-0010162@2@DAY4
V132_01EXP-072:00POST -406-5253703531@3032@V132_01EXP-0010168@2@DAY4
V132_01EXP-072:00POST -407-5253703631@3032@V132_01EXP-0010171@2@DAY4
V132_01EXP-072:00POST -408-5253703731@3032@V132_01EXP-0010172@2@DAY4
V132_01EXP-072:00POST -409-5253703831@3032@V132_01EXP-0010175@2@DAY4
072:00POST -410-5253703931@3032@V132_01EXP-0010178@2@DAY4
072:00POST -411-5253704031@3032@V132_01EXP-0010165@2@DAY4
072:00POST -412-5253704131@3032@V132_01EXP-0010170@2@DAY4
072:00POST -413-5253704231@3032@V132_01EXP-0010180@2@DAY4
072:00POST -414-5253704331@3032@V132_01EXP-0010188@2@DAY4
168:00POST -401-5253711031@3032@V132_01EXP-0010134@3@DAY8
168:00POST -402-5253711131@3032@V132_01EXP-0010153@3@DAY8
168:00POST -403-5253711231@3032@V132_01EXP-0010150@3@DAY8
168:00POST -404-5253711331@3032@V132_01EXP-0010152@3@DAY8
168:00POST -405-5253711431@3032@V132_01EXP-0010162@3@DAY8
V132_01EXP-168:00POST -406-5253711531@3032@V132_01EXP-0010168@3@DAY8
V132_01EXP-168:00POST -407-5253711631@3032@V132_01EXP-0010171@3@DAY8
V132_01EXP-168:00POST -408-5253711731@3032@V132_01EXP-0010172@3@DAY8
V132_01EXP-168:00POST -409-5253711831@3032@V132_01EXP-0010175@3@DAY 8
V132_01EXP-168:00POST -410-5253711931@3032@V132_01EXP-0010178@3@DAY8

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V132_01EXP-168:00POST -411-5253712031@3032@V132_01EXP-0010165@3@DAY8
V132_01EXP-168:00POST -412-5253712131@3032@V132_01EXP-0010170@3@DAY8
V132_01EXP-168:00POST -413-5253712231@3032@V132_01EXP-0010180@3@DAY8
V132_01EXP-168:00POST -414-5253712331@3032@V132_01EXP-0010188@3@DAY8

V132_01EXP_Cytokine_19_2016-11-10-1610

V132_01EXP-000:15PRE -101-5248494533@3032@V132_01EXP-0010001@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -102-5248494633@3032@V132_01EXP-0010006@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -103-5248494733@3032@V132_01EXP-0010014@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -104-5248494833@3032@V132_01EXP-0010013@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -105-5248494933@3032@V132_01EXP-0010016@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -106-5248495033@3032@V132_01EXP-0010024@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -107-5248495133@3032@V132_01EXP-0010025@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -111-5248495533@3032@V132_01EXP-0010026@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -112-5248495633@3032@V132_01EXP-0010028@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -113-5248495733@3032@V132_01EXP-0010034@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -114-5248495833@3032@V132_01EXP-0010051@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -115-5248495933@3032@V132_01EXP-0010033@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -116-5248496033@3032@V132_01EXP-0010038@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -117-5248496133@3032@V132_01EXP-0010044@1@DAY1,PREDOSE
V132_01EXP-006:00POST -101-5248518533@3032@V132_01EXP-0010001@1@DAY1,6HOUR
V132_01EXP-006:00POST -102-5248518633@3032@V132_01EXP-0010006@1@DAY1,6HOUR
V132_01EXP-006:00POST -103-5248518733@3032@V132_01EXP-0010014@1@DAY1,6HOUR
V132_01EXP-006:00POST -104-5248518833@3032@V132_01EXP-0010013@1@DAY1,6HOUR
006:00POST -105-5248518933@3032@V132_01EXP-0010016@1@DAY1,6HOUR
006:00POST -106-5248519033@3032@V132_01EXP-0010024@1@DAY1,6HOUR
006:00POST -107-5248519133@3032@V132_01EXP-0010025@1@DAY1,6HOUR
006:00POST -111-5248519533@3032@V132_01EXP-0010026@1@DAY1,6HOUR
006:00POST -112-5248519633@3032@V132_01EXP-0010028@1@DAY1,6HOUR
V132_01EXP-
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006:00POST -113-5248519733@3032@V132_01EXP-0010034@1@DAY1,6HOUR
006:00POST -114-5248519833@3032@V132_01EXP-0010051@1@DAY1,6HOUR
006:00POST -115-5248519933@3032@V132_01EXP-0010033@1@DAY1,6HOUR
006:00POST -116-5248520033@3032@V132_01EXP-0010038@1@DAY1,6HOUR
006:00POST -117-5248520133@3032@V132_01EXP-0010044@1@DAY1,6HOUR
V132_01EXP-024:00PO ST-101-5248534533@3032@V132_01EXP-0010001@1@DAY1,24HOUR
V132_01EXP-024:00POST -102-5248534633@3032@V132_01EXP-0010006@1@DAY1,24HOUR
V132_01EXP-024:00POST -103-5248534733@3032@V132_01EXP-0010014@1@DAY1,24HOUR
V132_01EXP-024:00POST -104-5248534833@3032@V132_01EXP-0010013@1@DAY1,24HOUR
V132_01EXP-024:00POST -105-5248534933@3032@V132_01EXP-0010016@1@DAY1,24HOUR
V132_01EXP-024:00POST -106-5248535033@3032@V132_01EXP-0010024@1@DAY1,24HOUR
V132_01EXP-024:00POST -107-5248535133@3032@V132_01EXP-0010025@1@DAY1,24HOUR
V132_01EXP-024:00POST -111-5248535533@3032@V132_01EXP-0010026@1@DAY1,24HOUR
V132_01EXP-024:00POST -112-5248535633@3032@V132_01EXP-0010028@1@DAY1,24HOUR
V132_01EXP-024:00POST -113-5248535733@3032@V132_01EXP-0010034@1@DAY1,24HOUR
V132_01EXP-024:00POST -114-5248535833@3032@V132_01EXP-0010051@1@DAY1,24HOUR
V132_01EXP-024:00POST -115-5248535933@3032@V132_01EXP-0010033@1@DAY1,24HOUR
V132_01EXP-024:00POST -116-5248536033@3032@V132_01EXP-0010038@1@DAY1,24HOUR
V132_01EXP-024:00POST -117-5248536133@3032@V132_01EXP-0010044@1@DAY1,24HOUR
V132_01EXP-072:00POST -101-5248550533@3032@V132_01EXP-0010001@2@DAY4
V132_01EXP-072:00POST -102-5248550633@3032@V132_01EXP-0010006@2@DAY4
V132_01EXP-072:00POST -103-5248550733@3032@V132_01EXP-0010014@2@DAY4
V132_01EXP-072:00POST -104-5248550833@3032@V132_01EXP-0010013@2@DAY4
V132_01EXP-072:00POST -105-5248550933@3032@V132_01EXP-0010016@2@DAY4
V132_01EXP-072:00POST -106-5248551033@3032@V132_01EXP-0010024@2@DAY4
V132_01EXP-072:00POST -107-5248551133@3032@V132_01EXP-0010025@2@DAY4
V132_01EXP-072:00POST -111-5248551533@3032@V132_01EXP-0010026@2@DAY4
V132_01EXP-072:00POST -112-5248551633@3032@V132_01EXP-0010028@2@DAY 4
V132_01EXP-072:00POST -113-5248551733@3032@V132_01EXP-0010034@2@DAY4

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V132_01EXP-072:00POST -114-5248551833@3032@V132_01EXP-0010051@2@DAY4
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V132_01EXP-072:00POST -116-5248552033@3032@V132_01EXP-0010038@2@DAY4
V132_01EXP-072:00POST -117-5248552133@3032@V132_01EXP-0010044@2@DAY4
V132_01EXP-168:00POST -101-5248566533@3032@V132_01EXP-0010001@3@DAY8
V132_01EXP-168:00POST -102-5248566633@3032@V132_01EXP-0010006@3@DAY8
168:00POST -103-5248566733@3032@V132_01EXP-0010014@3@DAY8
168:00POST -104-5248566833@3032@V132_01EXP-0010013@3@DAY8
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168:00POST -107-5248567133@3032@V132_01EXP-0010025@3@DAY8
168:00POST -111-5248567533@3032@V132_01EXP-0010026@3@DAY8
168:00POST -112-5248567633@3032@V132_01EXP-0010028@3@DAY8
168:00POST -113-5248567733@3032@V132_01EXP-0010034@3@DAY8
168:00POST -114-5248567833@3032@V132_01EXP-0010051@3@DAY8
168:00POST -115-5248567933@3032@V132_01EXP-0010033@3@DAY8
V132_01EXP-168:00POST -116-5248568033@3032@V132_01EXP-0010038@3@DAY8
V132_01EXP-168:00POST -117-5248568133@3032@V132_01EXP-0010044@3@DAY8

V132_01EXP_Cytokine_22_2016-11-11-1645

V132_01EXP-000:15PRE -118-5248496233@3032@V132_01EXP-0010031@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -119-5248496333@3032@V132_01EXP-0010041@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -120-5248496433@3032@V132_01EXP-0010042@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -201-5248976434@3032@V132_01EXP-0010036@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -202-5248976534@3032@V132_01EXP-0010027@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -203-5248976634@3032@V132_01EXP-0010067@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -204-5248976734@3032@V132_01EXP-0010048@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -206-5248976934@3032@V132_01EXP-0010071@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -207-5248977034@3032@V132_01EXP-0010072@1@DAY1,PREDOSE
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V132_01EXP-000:15PRE -208-5248977132@3032@V132_01EXP-0010074@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -209-5248977232@3032@V132_01EXP-0010073@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -210-5248977332@3032@V132_01EXP-0010075@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -211-5248977432@3032@V132_01EXP-0010076@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -212-5248977532@3032@V132_01EXP-0010083@1@DAY1,PREDOSE
V132_01EXP-006:00POST -118-5248520233@3032@V132_01EXP-0010031@1@DAY1,6HOUR
V132_01EXP-006:00POST -119-5248520333@3032@V132_01EXP-0010041@1@DAY1,6HOUR
V132_01EXP-006:00POST -120-5248520433@3032@V132_01EXP-0010042@1@DAY1,6HOUR
V132_01EXP-006:00POST -201-5248988434@3032@V132_01EXP-0010036@1@DAY1,6HOUR
V132_01EXP-006:00POST -202-5248988534@3032@V132_01EXP-0010027@1@DAY1,6HOUR
V132_01EXP-006:00POST -203-5248988634@3032@V132_01EXP-0010067@1@DAY1,6HOUR
V132_01EXP-006:00POST -204-5248988734@3032@V132_01EXP-0010048@1@DAY1,6HOUR
V132_01EXP-006:00POST -206-5248988934@3032@V132_01EXP-0010071@1@DAY1,6HOUR
V132_01EXP-006:00POST -207-5248989034@3032@V132_01EXP-0010072@1@DAY1,6HOUR
V132_01EXP-006:00POST -208-5248989132@3032@V132_01EXP-0010074@1@DAY1,6HOUR
V132_01EXP-006:00POST -209-5248989232@3032@V132_01EXP-0010073@1@DAY1, 6HOUR
006:00POST -210-5248989332@3032@V132_01EXP-0010075@1@DAY1,6HOUR
006:00POST -211-5248989432@3032@V132_01EXP-0010076@1@DAY1,6HOUR
006:00POST -212-5248989532@3032@V132_01EXP-0010083@1@DAY1,6HOUR
024:00POST -118-5248536233@3032@V132_01EXP-0010031@1@DAY1,24HOUR
024:00POST -119-5248536333@3032@V132_01EXP-0010041@1@DAY1,24HOUR
024:00POST -120-5248536433@3032@V132_01EXP-0010042@1@DAY1,24HOUR
024:00POST -201-5248996434@3032@V132_01EXP-0010036@1@DAY1,24HOUR

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024:00POST -202-5248996534@3032@V132_01EXP-0010027@1@DAY1,24HOUR
024:00POST -203-5248996634@3032@V132_01EXP-0010067@1@DAY1,24HOUR
024:00POST -204-5248996734@3032@V132_01EXP-0010048@1@DAY1,24HOUR
V132_01EXP-024:00POST -206-5248996934@3032@V132_01EXP-0010071@1@DAY1,24HOUR
V132_01EXP-024:00POST -207-5248997034@3032@V132_01EXP-0010072@1@DAY1,24HOUR
V132_01EXP-024:00POST -208-5248997132@3032@V132_01EXP-0010074@1@DAY1,24HOUR
V132_01EXP-024:00POST -209-5248997232@3032@V132_01EXP-0010073@1@DAY1,24HOUR
V132_01EXP-024:00POST -210-5248997332@3032@V132_01EXP-0010075@1@DAY1,24HOUR
V132_01EXP-024:00POST -211-5248997432@3032@V132_01EXP-0010076@1@DAY1,24HOUR
V132_01EXP-024:00POST -212-5248997532@3032@V132_01EXP-0010083@1@DAY1,24HOUR
V132_01EXP-072:00POST -118-5248552233@3032@V132_01EXP-0010031@2@DAY4
V132_01EXP-072:00POST -119-5248552333@3032@V132_01EXP-0010041@2@DAY4
V132_01EXP-072:00POST -120-5248552433@3032@V132_01EXP-0010042@2@DAY4
V132_01EXP-072:00POST -201-5249004434@3032@V132_01EXP-0010036@2@DAY4
V132_01EXP-072:00POST -202-5249004534@3032@V132_01EXP-0010027@2@DAY4
V132_01EXP-072:00POST -203-5249004634@3032@V132_01EXP-0010067@2@DAY4
V132_01EXP-072:00POST -204-5249004734@3032@V132_01EXP-0010048@2@DAY4
V132_01EXP-072:00POST -206-5249004934@3032@V132_01EXP-0010071@2@DAY4
V132_01EXP-072:00POST -207-5249005034@3032@V132_01EXP-0010072@2@DAY4
V132_01EXP-072:00POST -208-5249005132@3032@V132_01EXP-0010074@2@DAY4
V132_01EXP-072:00POST -209-5249005232@3032@V132_01EXP-0010073@2@DAY4
V132_01EXP-072:00POST -210-5249005332@3032@V132_01EXP-0010075@2@DAY4
V132_01EXP-072:00POST -211-5249005432@3032@V132_01EXP-0010076@2@DAY4
V132_01EXP-072:00POST -212-5249005532@3032@V132_01EXP-0010083@2@DAY4
V132_01EXP-168:00POST -118-5248568233@3032@V132_01EXP-0010031@3@DAY8
V132_01EXP-168:00POST -119-5248568333@3032@V132_01EXP-0010041@3@DAY8
V132_01EXP-168:00POST -120-5248568433@3032@V132_01EXP-0010042@3@DAY8
V132_01EXP-168:00POST -201-5249012434@3032@V132_01EXP-0010036@3@DAY8
V132_01EXP-168:00POST -202-5249012534@3032@V132_01EXP-0010027@3@DAY8
V132_01EXP-168:00POST -203-5249012634@3032@V132_01EXP-0010067@3@DAY8
V132_01EXP-168:00POST -204-5249012734@3032@V132_01EXP-0010048@3@DAY8
V132_01EXP-168:00POST -206-5249012934@3032@V132_01EXP-0010071@3@DAY8
V132_01EXP-168:00POST -207-5249013034@3032@V132_01EXP-0010072@3@DAY8

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168:00POST -208-5249013132@3032@V132_01EXP-0010074@3@DAY8168:00
POST-209-5249013232@3032@V132_01EXP-0010073@3@DAY8168:00POST -
210-5249013332@3032@V132_01EXP-0010075@3@DAY8
168:00POST -211-5249013432@3032@V132_01EXP-0010076@3@DAY8
168:00 POST -212-5249013532@3032@V132_01EXP-0010083@3@DAY 8
V132_01EXP_Cytokine_26_2016-11-21-1620
V132_01EXP-000:15PRE -415-5253676431@3032@V132_01EXP-0010190@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -416-5253676531@3032@V132_01EXP-0010176@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -417-5253676631@3032@V132_01EXP-0010179@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -418-5253676731@3032@V132_01EXP-0010184@1@DAY1,PREDOSE
V132_01EXP-000:15 PRE-419-5253676831@3032@V132_01EXP-0010182@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -420-5253676931@3032@V132_01EXP-0010191@1@DAY1,PREDOSE
V132_01EXP-006:00POST -415-5253688431@3032@V132_01EXP-0010190@1@DAY1,6HOUR
V132_01EXP-006:00POST -416-5253688531@3032@V132_01EXP-0010176@1@DAY1,6HOUR
V132_01EXP-006:00POST -417-5253688631@3032@V132_01EXP-0010179@1@DAY1,6HOUR
V132_01EXP-006:00POST -418-5253688731@3032@V132_01EXP-0010184@1@DAY1,6HOUR
V132_01EXP-006:00POST -419-5253688831@3032@V132_01EXP-0010182@1@DAY1,6HOUR
V132_01EXP-006:00POST -420-5253688931@3032@V132_01EXP-0010191@1@DAY1,6HOUR
V132_01EXP-024:00POST -415-5253696431@3032@V132_01EXP-0010190@1@DAY1,24HOUR
V132_01EXP-024:00POST -416-5253696531@3032@V132_01EXP-0010176@1@DAY1,24HOUR
V132_01EXP-024:00POST -417-5253696631@3032@V132_01EXP-0010179@1@DAY1,24HOUR
V132_01EXP-024:00POST -418-5253696731@3032@V132_01EXP-0010184@1@DAY1,24HOUR
V132_01EXP-024:00POST -419-5253696831@3032@V132_01EXP-0010182@1@DAY 1,24HOUR
V132_01EXP-024:00POST -420-5253696931@3032@V132_01EXP-0010191@1@DAY1,24HOUR
V132_01EXP-072:00POST -415-5253704431@3032@V132_01EXP-0010190@2@DAY4
V132_01EXP-072:00POST -416-5253704531@3032@V132_01EXP-0010176@2@DAY4
V132_01EXP-072:00 POST-417-5253704631@3032@V132_01EXP-0010179@2@DAY4
V132_01EXP-072:00POST -418-5253704731@3032@V132_01EXP-0010184@2@DAY4
V132_01EXP-072:00POST -419-5253704831@3032@V132_01EXP-0010182@2@DAY4
V132_01EXP-072:00POST -420-5253704931@3032@V132_01EXP-0010191@2@DAY4
V132_01EXP-168:00POST -415-5253712431@3032@V132_01EXP-0010190@3@DAY8
V132_01EXP-168:00POST -416-5253712531@3032@V132_01EXP-0010176@3@DAY8
V132_01EXP-168:00POST -417-5253712631@3032@V132_01EXP-0010179@3@DAY8
V132_01EXP-168:00POST -418-5253712731@3032@V132_01EXP-0010184@3@DAY8
V132_01EXP-168:00POST -419-5253712831@3032@V132_01EXP-0010182@3@DAY8
V132_01EXP-168:00POST -420-5253712931@3032@V132_01EXP-0010191@3@DAY8

V132_01EXP_Proinflammatory_07_2016-09-22-1550

000:15PRE -213-5248977631@3032@V132_01EXP-0010085@1@DAY1,PREDOSE
000:15PRE -214-5248977731@3032@V132_01EXP-0010086@1@DAY1,PREDOSE
000:15PRE -215-5248977833@3032@V132_01EXP-0010081@1@DAY1,PREDOSE
000:15PRE -216-5248977933@3032@V132_01EXP-0010093@1@DAY1,PREDOSE
000:15PRE -217-5248978033@3032@V132_01EXP-0010094@1@DAY1,PREDOSE
000:15PRE -218-5248978133@3032@V132_01EXP-0010080@1@DAY1,PREDOSE
000:15PRE -219-5248978233@3032@V132_01EXP-0010087@1@DAY1,PREDOSE
000:15PRE -220-5248978333@3032@V132_01EXP-0010089@1@DAY1,PREDOSE
006:00POST -213-5248989631@3032@V132_01EXP-0010085@1@DAY1,6HOUR
V132_01EXP-006:00POST -214-5248989731@3032@V132_01EXP-0010086@1@DAY1,6HOUR
V132_01EXP-006:00POST -215-5248989833@3032@V132_01EXP-0010081@1@DAY1,6HOUR
V132_01EXP-006:00POST -216-5248989933@3032@V132_01EXP-0010093@1@DAY1,6HOUR
V132_01EXP-006:00POST -217-5248990033@3032@V132_01EXP-0010094@1@DAY1,6HOUR
V132_01EXP-006:00POST -218-5248990133@3032@V132_01EXP-0010080@1@DAY1,6HOUR
V132_01EXP-006:00POST -219-5248990233@3032@V132_01EXP-0010087@1@DAY1,6HOUR
V132_01EXP-006:00POST -220-5248990333@3032@V132_01EXP-0010089@1@DAY1,6HOUR
V132_01EXP-024:00POST -213-5248997631@3032@V132_01EXP-0010085@1@DAY1,24HOUR
V132_01EXP-024:00POST -214-5248997731@3032@V132_01EXP-0010086@1@DAY1,24HOUR
V132_01EXP-024:00POST -215-5248997833@3032@V132_01EXP-0010081@1@DAY1,24HOUR
V132_01EXP-024:00POST -216-5248997933@3032@V132_01EXP-0010093@1@DAY1,24HOUR
V132_01EXP-024:00P OST-217-5248998033@3032@V132_01EXP-0010094@1@DAY1,24HOUR
V132_01EXP-024:00POST -218-5248998133@3032@V132_01EXP-0010080@1@DAY1,24HOUR
V132_01EXP-024:00POST -219-5248998233@3032@V132_01EXP-0010087@1@DAY1,24HOUR
V132_01EXP-024:00POST -220-5248998333@3032@V132_01EXP-0010089@1@DAY1,24HOUR
V132_01EXP-072:00POST -213-5249005631@3032@V132_01EXP-0010085@2@DAY4
V132_01EXP-072:00POST -214-5249005731@3032@V132_01EXP-0010086@2@DAY4
V132_01EXP-072:00POST -215-5249005833@3032@V132_01EXP-0010081@2@DAY4
V132_01EXP-072:00POST -216-5249005933@3032@V132_01EXP-0010093@2@DAY4
V132_01EXP-072:00POST -217-5249006033@3032@V132_01EXP-0010094@2@DAY4
V132_01EXP-072:00POST -218-5249006133@3032@V132_01EXP-0010080@2@DAY4

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V132_01EXP-072:00POST -219-5249006233@3032@V132_01EXP-0010087@2@DAY4
V132_01EXP-072:00POST -220-5249006333@3032@V132_01EXP-0010089@2@DAY4
V132_01EXP-168:00POST -213-5249013631@3032@V132_01EXP-0010085@3@DAY8
V132_01EXP-168:00POST -214-5249013731@3032@V132_01EXP-0010086@3@DAY8
V132_01EXP-168:00POST -215-5249013833@3032@V132_01EXP-0010081@3@DAY8
V132_01EXP-168:00POST -216-5249013933@3032@V132_01EXP-0010093@3@DAY8
V132_01EXP-168:00POST -217-5249014033@3032@V132_01EXP-0010094@3@DAY8
V132_01EXP-168:00POST -218-5249014133@3032@V132_01EXP-0010080@3@DAY8
V132_01EXP-168:00POST -219-5249014233@3032@V132_01EXP-0010087@3@DAY8
V132_01EXP-168:00POST -220-5249014333@3032@V132_01EXP-0010089@3@DAY8

V132_01EXP_Proinflammatory_10_2016-09-29-1600
V132_01EXP-000:15PRE -301-5251924031@3032@V132_01EXP-0010088@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -302-5251924131@3032@V132_01EXP-0010111@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -303-5251924231@3032@V132_01EXP-0010090@1@DAY1,PREDOSE

V132_01EXP-
V132_01EXP-
V132_01EXP-
000:15 PRE -304-5251924331@3032@V132_01EXP-0010099@1@DAY 1, PREDOSE
000:15PRE -305-5251924431@3032@V132_01EXP-0010100@1@DAY1,PREDOSE
006:00POST -301-5251936031@3032@V132_01EXP-0010088@1@DAY1,6HOUR
V132_01EXP-006:00POST -302-5251936131@3032@V132_01EXP-0010111@1@DAY1,6HOUR
V132_01EXP-006:00POST -303-5251936231@3032@V132_01EXP-0010090@1@DAY1,6HOUR
V132_01EXP-006:00POST -304-5251936331@3032@V132_01EXP-0010099@1@DAY1,6HOUR
V132_01EXP-006:00POST -305-5251936431@3032@V132_01EXP-0010100@1@DAY1,6HOUR
V132_01EXP-024:00POST -301-5251944031@3032@V132_01EXP-0010088@1@DAY1,24HOUR
V132_01EXP-024:00POST -302-5251944131@3032@V132_01EXP-0010111@1@DAY1,24HOUR
V132_01EXP-024:00POST -303-5251944231@3032@V132_01EXP-0010090@1@DAY1,24HOUR
V132_01EXP-024:00POST -304-5251944331@3032@V132_01EXP-0010099@1@DAY1,24HOUR
V132_01EXP-024:00POST -305-5251944431@3032@V132_01EXP-0010100@1@DAY1,24HOUR
V132_01EXP-072:00POST -301-5251952031@3032@V132_01EXP-0010088@2@DAY4
V132_01EXP-072:00POST -302-5251952131@3032@V132_01EXP-0010111@2@DAY4
V132_01EXP-072:00POST -303-5251952231@3032@V132_01EXP-0010090@2@DAY4
V132_01EXP-072:00POST -304-5251952331@3032@V132_01EXP-0010099@2@DAY4
V132_01EXP-072:00POST -305-5251952431@3032@V132_01EXP-0010100@2@DAY4
V132_01EXP-168:00POST -301-5251960031@3032@V132_01EXP-0010088@3@DAY8
V132_01EXP-168:00POST -302-5251960131@3032@V132_01EXP-0010111@3@DAY8
V132_01EXP-168:00POST -303-5251960231@3032@V132_01EXP-0010090@3@DAY8
V132_01EXP-168:00POST -304-5251960331@3032@V132_01EXP-0010099@3@DAY8
V132_01EXP-168:00POST -305-5251960431@3032@V132_01EXP-0010100@3@DAY8

V132_01EXP_Proinflammatory_13_2016-10-04-1610

V132_01EXP-000:15PRE -306-5251924531@3032@V132_01EXP-0010125@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -307-5251924631@3032@V132_01EXP-0010130@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -308-5251924731@3032@V132_01EXP-0010133@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -309-5251924831@3032@V132_01EXP-0010121@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -310-5251924931@3032@V132_01EXP-0010135@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -311-5251925031@3032@V132_01EXP-0010136@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -312-5251925131@3032@V132_01EXP-0010122@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -313-5251925231@3032@V132_01EXP-0010138@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -314-5251925331@3032@V132_01EXP-0010140@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -315-5251925431@3032@V132_01EXP-0010139@1@DAY1,PREDOSE
V132_01EXP-
V132_01EXP-

V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-000:15PRE -316-5251925531@3032@V132_01EXP-0010143@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -317-5251925631@3032@V132_01EXP-0010147@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -319-5251925831@3032@V132_01EXP-0010131@1@DAY1,PREDOSE
000:15PRE -320-5251925931@3032@V132_01EXP-0010141@1@DAY1,PREDOSE
006:00POST -306-5251936531@3032@V132_01EXP-0010125@1@DAY1,6HOUR
006:00POST -307-5251936631@3032@V132_01EXP-0010130@1@DAY1,6HOUR
006:00POST -308-5251936731@3032@V132_01EXP-0010133@1@DAY1,6HOUR
006:00POST -309-5251936831@3032@V132_01EXP-0010121@1@DAY1,6HOUR
V132_01EXP-006:00POST -310-5251936931@3032@V132_01EXP-0010135@1@DAY1,6HOUR
V132_01EXP-006:00POST -311-5251937031@3032@V132_01EXP-0010136@1@DAY1,6HOUR
V132_01EXP-006:00POST -312-5251937131@3032@V132_01EXP-0010122@1@DAY1,6HOUR
V132_01EXP-006:00POST -313-5251937231@3032@V132_01EXP-0010138@1@DAY1,6HOUR
V132_01EXP-006:00POST -314-5251937331@3032@V132_01EXP-0010140@1@DAY1,6HOUR
V132_01EXP-006:00POST -315-5251937431@3032@V132_01EXP-0010139@1@DAY1,6HOUR
V132_01EXP-006:00 POST-316-5251937531@3032@V132_01EXP-0010143@1@DAY1,6HOUR
V132_01EXP-006:00POST -317-5251937631@3032@V132_01EXP-0010147@1@DAY1,6HOUR
V132_01EXP-006:00POST -319-5251937831@3032@V132_01EXP-0010131@1@DAY1,6HOUR
V132_01EXP-006:00POST -320-5251937931@3032@V132_01EXP-0010141@1@DAY1,6HOUR
V132_01EXP-024:00POST -306-5251944531@3032@V132_01EXP-0010125@1@DAY1,24HOUR
V132_01EXP-024:00POST -307-5251944631@3032@V132_01EXP-0010130@1@DAY1,24HOUR
V132_01EXP-024:00POST -308-5251944731@3032@V132_01EXP-0010133@1@DAY1,24HOUR
V132_01EXP-024:00POST -309-5251944831@3032@V132_01EXP-0010121@1@DAY1,24HOUR
V132_01EXP-024:00POST -310-5251944931@3032@V132_01EXP-0010135@1@DAY1,24HOUR
V132_01EXP-024:00POST -311-5251945031@3032@V132_01EXP-0010136@1@DAY1,24HOUR
V132_01EXP-024:00POST -312-5251945131@3032@V132_01EXP-0010122@1@DAY1,24HOUR
V132_01EXP-024:00POST -313-5251945231@3032@V132_01EXP-0010138@1@DAY1,24HOUR
V132_01EXP-024:00POST -314-5251945331@3032@V132_01EXP-0010140@1@DAY 1,24HOUR
V132_01EXP-024:00POST -315-5251945431@3032@V132_01EXP-0010139@1@DAY1,24HOUR
V132_01EXP-024:00POST -316-5251945531@3032@V132_01EXP-0010143@1@DAY1,24HOUR

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V132_01EXP-024:00POST -317-5251945631@3032@V132_01EXP-0010147@1@DAY1,24HOUR
V132_01EXP-024:00POST -319-5251945831@3032@V132_01EXP-0010131@1@DAY1,24HOUR
V132_01EXP-024:00POST -320-5251945931@3032@V132_01EXP-0010141@1@DAY1,24HOUR
V132_01EXP-072:00POST -306-5251952531@3032@V132_01EXP-0010125@2@DAY4
V132_01EXP-072:00POS T-307-5251952631@3032@V132_01EXP-0010130@2@DAY4
V132_01EXP-072:00POST -308-5251952731@3032@V132_01EXP-0010133@2@DAY4
V132_01EXP-072:00POST -309-5251952831@3032@V132_01EXP-0010121@2@DAY4
V132_01EXP-072:00POST -310-5251952931@3032@V132_01EXP-0010135@2@DAY4
V132_01EXP-072:00POST -311-5251953031@3032@V132_01EXP-0010136@2@DAY4
072:00POST -312-5251953131@3032@V132_01EXP-0010122@2@DAY4
072:00POST -313-5251953231@3032@V132_01EXP-0010138@2@DAY4
072:00POST -314-5251953331@3032@V132_01EXP-0010140@2@DAY4
072:00POST -315-5251953431@3032@V132_01EXP-0010139@2@DAY4
072:00POST -316-5251953531@3032@V132_01EXP-0010143@2@DAY4
072:00POST -317-5251953631@3032@V132_01EXP-0010147@2@DAY4072:00
POST-319-5251953831@3032@V132_01EXP-0010131@2@DAY4072:00POST -
320-5251953931@3032@V132_01EXP-0010141@2@DAY4
168:00POST -306-5251960531@3032@V132_01EXP-0010125@3@DAY8
168:00 POST -307-5251960631@3032@V132_01EXP-0010130@3@DAY 8
V132_01EXP-168:00POST -308-5251960731@3032@V132_01EXP-0010133@3@DAY8
V132_01EXP-168:00POST -309-5251960831@3032@V132_01EXP-0010121@3@DAY8
V132_01EXP-168:00POST -310-5251960931@3032@V132_01EXP-0010135@3@DAY8
V132_01EXP-168:00POST -311-5251961031@3032@V132_01EXP-0010136@3@DAY8
V132_01EXP-168:00POST -312-5251961131@3032@V132_01EXP-0010122@3@DAY8
V132_01EXP-168:00POST -313-5251961231@3032@V132_01EXP-0010138@3@DAY8
V132_01EXP-168:00POST -314-5251961331@3032@V132_01EXP-0010140@3@DAY8
V132_01EXP-168:00POST -315-5251961431@3032@V132_01EXP-0010139@3@DAY8
V132_01EXP-168:00P OST-316-5251961531@3032@V132_01EXP-0010143@3@DAY8
V132_01EXP-168:00POST -317-5251961631@3032@V132_01EXP-0010147@3@DAY8
V132_01EXP-168:00POST -319-5251961831@3032@V132_01EXP-0010131@3@DAY8
V132_01EXP-
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V132_01EXP-
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V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-168:00POST -320-5251961931@3032@V132_01EXP-0010141@3@DAY8

V132_01EXP_Proinflammatory_16_2016-10-14-1550

V132_01EXP-000:15PRE -401-5253675031@3032@V132_01EXP-0010134@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -402-5253675131@3032@V132_01EXP-0010153@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -403-5253675231@3032@V132_01EXP-0010150@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -404-5253675331@3032@V132_01EXP-0010152@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -405-5253675431@3032@V132_01EXP-0010162@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -406-5253675531@3032@V132_01EXP-0010168@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -407-5253675631@3032@V132_01EXP-0010171@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -408-5253675731@3032@V132_01EXP-0010172@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -409-5253675831@3032@V132_01EXP-0010175@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -410-5253675931@3032@V132_01EXP-0010178@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -411-5253676031@3032@V132_01EXP-0010165@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -412-5253676131@3032@V132_01EXP-0010170@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -413-5253676231@3032@V132_01EXP-0010180@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -414-5253676331@3032@V132_01EXP-0010188@1@DAY1,PREDOSE
V132_01EXP-006:00POST -401-5253687031@3032@V132_01EXP-0010134@1@DAY1,6HOUR
006:00POST -402-5253687131@3032@V132_01EXP-0010153@1@DAY1,6HOUR
006:00POST -403-5253687231@3032@V132_01EXP-0010150@1@DAY1,6HOUR
006:00POST -404-5253687331@3032@V132_01EXP-0010152@1@DAY1,6HOUR
006:00POST -405-5253687431@3032@V132_01EXP-0010162@1@DAY1,6HOUR
006:00POST -406-5253687531@3032@V132_01EXP-0010168@1@DAY1,6HOUR
006:00POST -407-5253687631@3032@V132_01EXP-0010171@1@DAY1,6HOUR
006:00POST -408-5253687731@3032@V132_01EXP-0010172@1@DAY1,6HOUR

V132_01EXP-
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V132_01EXP-
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006:00POST -409-5253687831@3032@V132_01EXP-0010175@1@DAY1,6HOUR
006:00 POST -410-5253687931@3032@V132_01EXP-0010178@1@DAY 1, 6 HOUR
V132_01EXP-006:00POST -411-5253688031@3032@V132_01EXP-0010165@1@DAY1,6HOUR
V132_01EXP-006:00POST -412-5253688131@3032@V132_01EXP-0010170@1@DAY1,6HOUR
V132_01EXP-006:00POST -413-5253688231@3032@V132_01EXP-0010180@1@DAY1,6HO UR
V132_01EXP-006:00POST -414-5253688331@3032@V132_01EXP-0010188@1@DAY1,6HOUR
V132_01EXP-024:00POST -401-5253695031@3032@V132_01EXP-0010134@1@DAY1,24HOUR
V132_01EXP-024:00POST -402-5253695131@3032@V132_01EXP-0010153@1@DAY1,24HOUR
V132_01EXP-024:00POST -403-5253695231@3032@V132_01EXP-0010150@1@DAY1,24HOUR
V132_01EXP-024:00POST -404-5253695331@3032@V132_01EXP-0010152@1@DAY1,24HOUR
V132_01EXP-024:00POST -405-5253695431@3032@V132_01EXP-0010162@1@DAY1,24HOUR
V132_01EXP-024:00POST -406-5253695531@3032@V132_01EXP-0010168@1@DAY1,24HOUR
V132_01EXP-024:00POST -407-5253695631@3032@V132_01EXP-0010171@1@DAY1,24HOUR
V132_01EXP-024:00POST -408-5253695731@3032@V132_01EXP-0010172@1@DAY1,24HOUR
V132_01EXP-024:00POST -409-5253695831@3032@V132_01EXP-0010175@1@DAY1,24HOUR
V132_01EXP-024:00POST -410-5253695931@3032@V132_01EXP-0010178@1@DAY1,24HOUR
V132_01EXP-024:00POST -411-5253696031@3032@V132_01EXP-0010165@1@DAY1,24HOUR
V132_01EXP-024:00POST -412-5253696131@3032@V132_01EXP-0010170@1@DAY1,24HOUR
V132_01EXP-024:00POST -413-5253696231@3032@V132_01EXP-0010180@1@DAY1,24HOUR
V132_01EXP-024:00POST -414-5253696331@3032@V132_01EXP-0010188@1@DAY1,24HOUR
V132_01EXP-072:00POST -401-5253703031@3032@V132_01EXP-0010134@2@DAY4
V132_01EXP-072:00POST -402-5253703131@3032@V132_01EXP-0010153@2@DAY4
V132_01EXP-072:00POST -403-5253703231@3032@V132_01EXP-0010150@2@DAY4
V132_01EXP-072:00POST -404-5253703331@3032@V132_01EXP-0010152@2@DAY4
V132_01EXP-072:00PO ST-405-5253703431@3032@V132_01EXP-0010162@2@DAY4
V132_01EXP-072:00POST -406-5253703531@3032@V132_01EXP-0010168@2@DAY4
V132_01EXP-072:00POST -407-5253703631@3032@V132_01EXP-0010171@2@DAY4
V132_01EXP-072:00POST -408-5253703731@3032@V132_01EXP-0010172@2@DAY4
V132_01EXP-072:00POST -409-5253703831@3032@V132_01EXP-0010175@2@DAY4
V132_01EXP-072:00POST -410-5253703931@3032@V132_01EXP-0010178@2@DAY4
V132_01EXP-072:00POST -411-5253704031@3032@V132_01EXP-0010165@2@DAY4
V132_01EXP-
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V132_01EXP-072:00POST -412-5253704131@3032@V132_01EXP-0010170@2@DAY4
V132_01EXP-072:00POST -413-5253704231@3032@V132_01EXP-0010180@2@DAY4
072:00POST -414-5253704331@3032@V132_01EXP-0010188@2@DAY4
168:00POST -401-5253711031@3032@V132_01EXP-0010134@3@DAY8
168:00POST -402-5253711131@3032@V132_01EXP-0010153@3@DAY8
168:00POST -403-5253711231@3032@V132_01EXP-0010150@3@DAY8
168:00POST -404-5253711331@3032@V132_01EXP-0010152@3@DAY8
168:00POST -405-5253711431@3032@V132_01EXP-0010162@3@DAY8
168:00POST -406-5253711531@3032@V132_01EXP-0010168@3@DAY8
168:00POST -407-5253711631@3032@V132_01EXP-0010171@3@DAY8
168:00 POST -408-5253711731@3032@V132_01EXP-0010172@3@DAY 8
V132_01EXP-168:00POST -409-5253711831@3032@V132_01EXP-0010175@3@DAY8
V132_01EXP-168:00PO ST-410-5253711931@3032@V132_01EXP-0010178@3@DAY8
V132_01EXP-168:00POST -411-5253712031@3032@V132_01EXP-0010165@3@DAY8
V132_01EXP-168:00POST -412-5253712131@3032@V132_01EXP-0010170@3@DAY8
V132_01EXP-168:00POST -413-5253712231@3032@V132_01EXP-0010180@3@DAY8
V132_01EXP-168:00POST -414-5253712331@3032@V132_01EXP-0010188@3@DAY8

V132_01EXP_Proinflammatory_18_2016-11-10-1600

V132_01EXP-000:15PRE -101-5248494533@3032@V132_01EXP-0010001@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -102-5248494633@3032@V132_01EXP-0010006@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -103-5248494733@3032@V132_01EXP-0010014@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -104-5248494833@3032@V132_01EXP-0010013@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -105-5248494933@3032@V132_01EXP-0010016@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -106-5248495033@3032@V132_01EXP-0010024@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -107-5248495133@3032@V132_01EXP-0010025@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -111-5248495533@3032@V132_01EXP-0010026@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -112-5248495633@3032@V132_01EXP-0010028@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -113-5248495733@3032@V132_01EXP-0010034@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -114-5248495833@3032@V132_01EXP-0010051@1@DAY1, PREDOSE
V132_01EXP-
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V132_01EXP-000:15PRE -115-5248495933@3032@V132_01EXP-0010033@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -116-5248496033@3032@V132_01EXP-0010038@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -117-5248496133@3032@V132_01EXP-0010044@1@DAY1,PREDOSE
V132_01EXP-006:00POST -101-5248518533@3032@V132_01EXP-0010001@1@DAY1,6HOUR
V132_01EXP-006:00POST -102-5248518633@3032@V132_01EXP-0010006@1@DAY1,6HOUR
V132_01EXP-006:00POST -103-5248518733@3032@V132_01EXP-0010014@1@DAY1,6HOUR
V132_01EXP-006:00POS T-104-5248518833@3032@V132_01EXP-0010013@1@DAY1,6HOUR
V132_01EXP-006:00POST -105-5248518933@3032@V132_01EXP-0010016@1@DAY1,6HOUR
V132_01EXP-006:00POST -106-5248519033@3032@V132_01EXP-0010024@1@DAY1,6HOUR
V132_01EXP-006:00POST -107-5248519133@3032@V132_01EXP-0010025@1@DAY1,6HOUR
V132_01EXP-006:00POST -111-5248519533@3032@V132_01EXP-0010026@1@DAY1,6HOUR
006:00POST -112-5248519633@3032@V132_01EXP-0010028@1@DAY1,6HOUR
006:00POST -113-5248519733@3032@V132_01EXP-0010034@1@DAY1,6HOU R
006:00POST -114-5248519833@3032@V132_01EXP-0010051@1@DAY1,6HOUR
006:00POST -115-5248519933@3032@V132_01EXP-0010033@1@DAY1,6HOUR
006:00POST -116-5248520033@3032@V132_01EXP-0010038@1@DAY1,6HOUR
006:00POST -117-5248520133@3032@V132_01EXP-0010044@1@DAY1,6HOUR
024:00POST -101-5248534533@3032@V132_01EXP-0010001@1@DAY1,24HOUR
024:00POST -102-5248534633@3032@V132_01EXP-0010006@1@DAY1,24HOUR
024:00POST -103-5248534733@3032@V132_01EXP-0010014@1@DAY1,24HOUR
V132_01EXP-024:00POST -104-5248534833@3032@V132_01EXP-0010013@1@DAY1,24HOUR
V132_01EXP-024:00POST -105-5248534933@3032@V132_01EXP-0010016@1@DAY1,24HOUR
V132_01EXP-024:00POST -106-5248535033@3032@V132_01EXP-0010024@1@DAY1,24HOUR
V132_01EXP-024:00POST -107-5248535133@3032@V132_01EXP-0010025@1@DAY1,24HOUR
V132_01EXP-024:00POST -111-5248535533@3032@V132_01EXP-0010026@1@DAY1,24HOUR
V132_01EXP-024:00POST -112-5248535633@3032@V132_01EXP-0010028@1@DAY1,24HOUR
V132_01EXP-024:00POST -113-5248535733@3032@V132_01EXP-0010034@1@DAY1,24HOUR
V132_01EXP-024:00POST -114-5248535833@3032@V132_01EXP-0010051@1@DAY1,24HOUR
V132_01EXP-024:00POST -115-5248535933@3032@V132_01EXP-0010033@1@DAY1,24HOUR
V132_01EXP-024:00POST -116-5248536033@3032@V132_01EXP-0010038@1@DAY1,24HOUR
V132_01EXP-024:00POST -117-5248536133@3032@V132_01EXP-0010044@1@DAY1,24HOUR
V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-

V132_01EXP-
V132_01EXP-
V132_01EXP-072:00POST -101-5248550533@3032@V132_01EXP-0010001@2@DAY4
V132_01EXP-072:00POST -102-5248550633@3032@V132_01EXP-0010006@2@DAY4
V132_01EXP-072:00POST -103-5248550733@3032@V132_01EXP-0010014@2@DAY4
V132_01EXP-072:00POST -104-5248550833@3032@V132_01EXP-0010013@2@DAY4
V132_01EXP-072:00POST -105-5248550933@3032@V132_01EXP-0010016@2@DAY4
V132_01EXP-072:00POST -106-5248551033@3032@V132_01EXP-0010024@2@DAY4
V132_01EXP-072:00POST -107-5248551133@3032@V132_01EXP-0010025@2@DAY4
V132_01EXP-072:00POST -111-5248551533@3032@V132_01EXP-0010026@2@DAY4
V132_01EXP-072:00POST -112-5248551633@3032@V132_01EXP-0010028@2@DAY4
V132_01EXP-072:00POST -113-5248551733@3032@V132_01EXP-0010034@2@DAY4
V132_01EXP-072:00POST -114-5248551833@3032@V132_01EXP-0010051@2@DAY4
V132_01EXP-072:00POST -115-5248551933@3032@V132_01EXP-0010033@2@DAY4
V132_01EXP-072:00POST -116-5248552033@3032@V132_01EXP-0010038@2@DAY4
V132_01EXP-072:00POST -117-5248552133@3032@V132_01EXP-0010044@2@DAY4
V132_01EXP-168:00POST -101-5248566533@3032@V132_01EXP-0010001@3@DAY8
V132_01EXP-168:00POST -102-5248566633@3032@V132_01EXP-0010006@3@DAY 8
V132_01EXP-168:00POST -103-5248566733@3032@V132_01EXP-0010014@3@DAY8
V132_01EXP-168:00POST -104-5248566833@3032@V132_01EXP-0010013@3@DAY8
V132_01EXP-168:00POST -105-5248566933@3032@V132_01EXP-0010016@3@DAY8
V132_01EXP-168:00POST -106-5248567033@3032@V132_01EXP-0010024@3@DAY8
168:00POST -107-5248567133@3032@V132_01EXP-0010025@3@DAY8
168:00POST -111-5248567533@3032@V132_01EXP-0010026@3@DAY8
168:00POST -112-5248567633@3032@V132_01EXP-0010028@3@DAY8
168:00POST -113-5248567733@3032@V132_01EXP-0010034@3@DAY8
168:00POST -114-5248567833@3032@V132_01EXP-0010051@3@DAY8
168:00POST -115-5248567933@3032@V132_01EXP-0010033@3@DAY8
168:00POST -116-5248568033@3032@V132_01EXP-0010038@3@DAY8

V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-
V132_01EXP-

V132_01EXP-
168:00POST -117-5248568133@3032@V132_01EXP-0010044@3@DAY8

V132_01EXP_Proinflammatory_21_2016-11-11-1640

V132_01EXP-000:15PRE -118-5248496233@3032@V132_01EXP-0010031@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -119-5248496333@3032@V132_01EXP-0010041@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -120-5248496433@3032@V132_01EXP-0010042@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -201-5248976434@3032@V132_01EXP-0010036@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -202-5248976534@3032@V132_01EXP-0010027@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -203-5248976634@3032@V132_01EXP-0010067@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -204-5248976734@3032@V132_01EXP-0010048@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -206-5248976934@3032@V132_01EXP-0010071@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -207-5248977034@3032@V132_01EXP-0010072@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -208-5248977132@3032@V132_01EXP-0010074@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -209-5248977232@3032@V132_01EXP-0010073@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -210-5248977332@3032@V132_01EXP-0010075@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -211-5248977432@3032@V132_01EXP-0010076@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -212-5248977532@3032@V132_01EXP-0010083@1@DAY1,PREDOSE
V132_01EXP-006:00POST -118-5248520233@3032@V132_01EXP-0010031@1@DAY1,6HOUR
V132_01EXP-006:00POST -119-5248520333@3032@V132_01EXP-0010041@1@DAY1,6 HOUR
V132_01EXP-006:00POST -120-5248520433@3032@V132_01EXP-0010042@1@DAY1,6HOUR
V132_01EXP-006:00POST -201-5248988434@3032@V132_01EXP-0010036@1@DAY1,6HOUR
V132_01EXP-006:00POST -202-5248988534@3032@V132_01EXP-0010027@1@DAY1,6HOUR
V132_01EXP-006:00POST -203-5248988634@3032@V132_01EXP-0010067@1@DAY1,6HOUR
V132_01EXP-006:00POST -204-5248988734@3032@V132_01EXP-0010048@1@DAY1,6HOUR
V132_01EXP-006:00POST -206-5248988934@3032@V132_01EXP-0010071@1@DAY1,6HOUR
V132_01EXP-006:00POST -207-5248989034@3032@V132_01EXP-0010072@1@DAY1,6HOUR
V132_01EXP-006:00POST -208-5248989132@3032@V132_01EXP-0010074@1@DAY1,6HOUR
V132_01EXP-006:00POST -209-5248989232@3032@V132_01EXP-0010073@1@DAY1,6HOUR
V132_01EXP-006:00POST -210-5248989332@3032@V132_01EXP-0010075@1@DAY1,6HOUR
V132_01EXP-006:00POST -211-5248989432@3032@V132_01EXP-0010076@1@DAY1,6HOUR
V132_01EXP-006:00POST -212-5248989532@3032@V132_01EXP-0010083@1@DAY1,6HOUR
V132_01EXP-024:00POST -118-5248536233@3032@V132_01EXP-0010031@1@DAY1,24HOUR
V132_01EXP-024:00POST -119-5248536333@3032@V132_01EXP-0010041@1@DAY1,24HOUR
V132_01EXP-024:00POST -120-5248536433@3032@V132_01EXP-0010042@1@DAY1,24HOUR
V132_01EXP-024:00POST -201-5248996434@3032@V132_01EXP-0010036@1@DAY1, 24HOUR
V132_01EXP-024:00POST -202-5248996534@3032@V132_01EXP-0010027@1@DAY1,24HOUR
024:00POST -203-5248996634@3032@V132_01EXP-0010067@1@DAY1,24HOUR

V132_01EXP-
V132_01EXP-
V132_01EXP-

V132_01EXP-
024:00POST -204-5248996734@3032@V132_01EXP-0010048@1@DAY1,24HOUR
024:00POST -206-5248996934@3032@V132_01EXP-0010071@1@DAY1,24HOUR
024:00POST -207-5248997034@3032@V132_01EXP-0010072@1@DAY1,24HOUR
V132_01EXP-024:00POST -208-5248997132@3032@V132_01EXP-0010074@1@DAY1,24HOUR
V132_01EXP-024:00POST -209-5248997232@3032@V132_01EXP-0010073@1@DAY1,24HOUR
V132_01EXP-024:00POST -210-5248997332@3032@V132_01EXP-0010075@1@DAY1,24HOUR
V132_01EXP-024:00POST -211-5248997432@3032@V132_01EXP-0010076@1@DAY1,24HOUR
V132_01EXP-024:00POST -212-5248997532@3032@V132_01EXP-0010083@1@DAY1,24HOUR
V132_01EXP-072:00POST -118-5248552233@3032@V132_01EXP-0010031@2@DAY4
V132_01EXP-072:00POST -119-5248552333@3032@V132_01EXP-0010041@2@DAY4
V132_01EXP-072:00POST -120-5248552433@3032@V132_01EXP-0010042@2@DAY4
V132_01EXP-072:00POST -201-5249004434@3032@V132_01EXP-0010036@2@DAY4
V132_01EXP-072:00POST -202-5249004534@3032@V132_01EXP-0010027@2@DAY4
V132_01EXP-072:00POST -203-5249004634@3032@V132_01EXP-0010067@2@DAY4
V132_01EXP-072:00POST -204-5249004734@3032@V132_01EXP-0010048@2@DAY4
V132_01EXP-072:00POST -206-5249004934@3032@V132_01EXP-0010071@2@DAY4
V132_01EXP-072:00POST -207-5249005034@3032@V132_01EXP-0010072@2@DAY4
V132_01EXP-072:00POST -208-5249005132@3032@V132_01EXP-0010074@2@DAY4
V132_01EXP-072:00POST -209-5249005232@3032@V132_01EXP-0010073@2@DAY4
V132_01EXP-072:00POST -210-5249005332@3032@V132_01EXP-0010075@2@DAY4
V132_01EXP-072:00POST -211-5249005432@3032@V132_01EXP-0010076@2@DAY4
V132_01EXP-072:00POST -212-5249005532@3032@V132_01EXP-0010083@2@DAY4
V132_01EXP-168:00POST -118-5248568233@3032@V132_01EXP-0010031@3@DAY8
V132_01EXP-168:00POST -119-5248568333@3032@V132_01EXP-0010041@3@DAY8
V132_01EXP-168:00POST -120-5248568433@3032@V132_01EXP-0010042@3@DAY8
V132_01EXP-168:00POST -201-5249012434@3032@V132_01EXP-0010036@3@DAY8
V132_01EXP-168:00POST -202-5249012534@3032@V132_01EXP-0010027@3@DAY8
V132_01EXP-168:00POST -203-5249012634@3032@V132_01EXP-0010067@3@DAY8
V132_01EXP-168:00POST -204-5249012734@3032@V132_01EXP-0010048@3@DAY 8
V132_01EXP-168:00POST -206-5249012934@3032@V132_01EXP-0010071@3@DAY8
V132_01EXP-168:00POST -207-5249013034@3032@V132_01EXP-0010072@3@DAY8
V132_01EXP-168:00POST -208-5249013132@3032@V132_01EXP-0010074@3@DAY8
V132_01EXP-168:00POST -209-5249013232@3032@V132_01EXP-0010073@3@DAY8
V132_01EXP-168:00POST -210-5249013332@3032@V132_01EXP-0010075@3@DAY8
V132_01EXP-168:00POST -211-5249013432@3032@V132_01EXP-0010076@3@DAY8
V132_01EXP-168:00POST -212-5249013532@3032@V132_01EXP-0010083@3@DAY8

V132_01EXP-
V132_01EXP_Proinflammatory_25_2016-11-21-1615
V132_01EXP-000:15PRE -415-5253676431@3032@V132_01EXP-0010190@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -416-5253676531@3032@V132_01EXP-0010176@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -417-5253676631@3032@V132_01EXP-0010179@1@DAY1,PREDOSE
000:15PRE -418-5253676731@3032@V132_01EXP-0010184@1@DAY1,PREDOSEV132_01EXP -
000:15PRE -419-5253676831@3032@V132_01EXP-0010182@1@DAY1,PREDOSE
V132_01EXP-000:15PRE -420-5253676931@3032@V132_01EXP-0010191@1@DAY1,PREDOSE
V132_01EXP-006:00POST -415-5253688431@3032@V132_01EXP-0010190@1@DAY1,6HOUR
V132_01EXP-006:00POST -416-5253688531@3032@V132_01EXP-0010176@1@DAY1,6HOUR
V132_01EXP-006:00POST -417-5253688631@3032@V132_01EXP-0010179@1@DAY1,6HOUR
V132_01EXP-006:00POST -418-5253688731@3032@V132_01EXP-0010184@1@DAY1,6HOUR
V132_01EXP-006:00POST -419-5253688831@3032@V132_01EXP-0010182@1@DAY1,6HOUR
V132_01EXP-006:00POST -420-5253688931@3032@V132_01EXP-0010191@1@DAY1,6HOUR
V132_01EXP-024:00POST -415-5253696431@3032@V132_01EXP-0010190@1@DAY1,24HOUR
V132_01EXP-024:00POST -416-5253696531@3032@V132_01EXP-0010176@1@DAY1,24HOUR
V132_01EXP-024:00POST -417-5253696631@3032@V132_01EXP-0010179@1@DAY1,24HOUR
V132_01EXP-024:00POST -418-5253696731@3032@V132_01EXP-0010184@1@DAY1,24HOUR
V132_01EXP-024:00POST -419-5253696831@3032@V132_01EXP-0010182@1@DAY1,24HOUR
V132_01EXP-024:00POST -420-5253696931@3032@V132_01EXP-0010191@1@DAY1,24HOUR
V132_01EXP-072:00POST -415-5253704431@3032@V132_01EXP-0010190@2@DAY4
V132_01EXP-072:00POST -416-5253704531@3032@V132_01EXP-0010176@2@DAY4
V132_01EXP-072:00POST -417-5253704631@3032@V132_01EXP-0010179@2@DAY4
V132_01EXP-072:00POST -418-5253704731@3032@V132_01EXP-0010184@2@DAY4
V132_01EXP-072:00POST -419-5253704831@3032@V132_01EXP-0010182@2@DAY4
V132_01EXP-072:00POST -420-5253704931@3032@V132_01EXP-0010191@2@DAY4
V132_01EXP-168:00POST -415-5253712431@3032@V132_01EXP-0010190@3@DAY8
V132_01EXP-168:00POST -416-5253712531@3032@V132_01EXP-0010176@3@DAY8
V132_01EXP-168:00POST -417-5253712631@3032@V132_01EXP-0010179@3@DAY8
V132_01EXP-168:00POST -418-5253712731@3032@V132_01EXP-0010184@3@DAY8
V132_01EXP-168:00POST -419-5253712831@3032@V132_01EXP-0010182@3@DAY8
V132_01EXP-168:00PO ST-420-5253712931@3032@V132_01EXP-0010191@3@DAY8