Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'institut 89,
1330 Rixensart, Belgium

Primary Study vaccine(s)/product(s) and number(s)	GlaxoSmithKline (GSK) Biological investigational respiratory syncytial virus (RSV) maternal vaccine (GSK3888550A)
Other Study vaccine(s)/product(s)	Placebo
eTrack study number and Abbreviated Title	208068 (RSV MAT-001)
Investigational New Drug (IND) number	18434
EudraCT number	2018-001340-62
Date of protocol	Final Version 2: 13 August 2018
Title	A study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' investigational unadjuvanted RSV maternal vaccine compared to placebo when administered to healthy non-pregnant women.
Detailed Title	A Phase 1/2 randomised observer-blind placebo controlled study to evaluate the safety, reactogenicity and immunogenicity of different dose levels of GSK Biologicals' investigational unadjuvanted RSV maternal vaccine (GSK3888550A) compared to placebo when administered to healthy non-pregnant women aged 18-45 years.
Co-ordinating author(s)	• PPD, Science Writer
Contributing authors	• PPD, Study Delivery Lead • PPD, Study Delivery Lead • PPD, Clinical Research and Development Lead (CRDL) • PPD, Lead Statistician • PPD Study Statistician • PPD, Oversight Data Manager • PPD, Clinical Readout Team Lead • PPD, Clinical Readout Team Lead

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GSK Biologicals' Protocol DS v 15.0

Protocol Sponsor Signatory Approval

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Sponsor signatory	Ouzama Henry, Clinical and Epidemiological Project Lead (CEPL), US RDC
Signature	
Date	

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Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' study vaccine(s)/product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine(s)/product(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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Investigator name	_____
Signature	_____
Date	_____
Leiter der klinischen Prüfung name, function and title	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals,
Rue de l'institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event:

Refer to the local study contact information document.

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.4.2.

5. GSK Biologicals' Central Safety Physician On-Call Contact information for Emergency Unblinding

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.8

SYNOPSIS

Detailed Title

A Phase 1/2 randomised observer-blind placebo controlled study to evaluate the safety, reactogenicity and immunogenicity of different dose levels of GSK Biologicals' investigational unadjuvanted RSV maternal vaccine (GSK3888550A) compared to placebo when administered to healthy non-pregnant women aged 18-45 years.

Indication

Active immunization of pregnant women during the third trimester of pregnancy to prevent respiratory syncytial virus (RSV) associated lower respiratory tract infection (LRTI) in infants by transfer of maternal antibodies.

Rationale for the study and study design

- Rationale for the study:

The purpose of this study is to evaluate the safety, reactogenicity and immunogenicity of three dose levels (30 µg, 60 µg and 120 µg) of the investigational RSV maternal vaccine antigen compared to placebo administered as a single intramuscular injection.

- Rationale for the study design:

To assess the impact of the investigational RSV maternal vaccine in terms of safety, reactogenicity and immune response, four treatment groups will be evaluated.

Healthy, non-pregnant women aged 18 - 45 years will be enrolled, a population of the same gender and age of the vaccine's target population

- Rationale for the use of placebo:

The placebo group is included as a control for both the safety/reactogenicity and the immunogenicity assessments.

Objective(s)

Primary

- To evaluate the safety and reactogenicity of three dose levels (30, 60, 120 µg) of the RSV maternal investigational vaccine administered as a single intramuscular injection, as compared to placebo up to 1 month post vaccination (Day 31).

Secondary

- To evaluate the safety of three dose levels (30, 60, 120 µg) of the RSV maternal investigational vaccine compared to placebo up to 6 months post vaccination (Day 181).

- To evaluate the humoral immune response to three dose levels (30, 60, 120 μg) of the RSV maternal investigational vaccine compared to placebo up to 3 months post vaccination (Day 91).

Tertiary

- To further evaluate the humoral immune response to the RSV maternal vaccine.

Study design

- Experimental design: Phase I/II, observer-blind, randomised, controlled, multi-centre, multi-country with four parallel groups.
- Duration of the study:
  - Epoch 001: Screening Visit (Day -7 to Day 1)
  - Epoch 002: Active Vaccination phase starting at Visit 1 (Day 1) and concluding at, and including, Visit 3 (Day 31)
  - Epoch 003: Long-term follow-up starting after Visit 3 (Day 31) and concluding at Contact 1 (Day 181)
- Primary completion Date (PCD): Visit 3 (Day 31) or last visit of Epoch 002
- End of Study (EoS): Last testing results released of human biological samples collected at Visit 5 (Day 91) or Last Subject Last Visit (LSLV, i.e. last Contact 1), whichever comes last
- Study groups:

Synopsis Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min - Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
RSV MAT 30	~125	18 - 45 years	x	x	x
RSV MAT 60	~125	18 - 45 years	x	x	x
RSV MAT 120	~125	18 - 45 years	x	x	x
Placebo	~125	18 - 45 years	x	x	x

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups			
		RSV MAT 30	RSV MAT 60	RSV MAT 120	Placebo
RSVPreF3 30	RSVPreF3 low dose	●			
RSVPreF3 60	RSVPreF3 mid dose		●		
RSVPreF3 120	RSVPreF3 high dose			●	
Control	NaCl				●

- Control: placebo control
- Vaccination schedule: Single intramuscular injection at Visit 1 (Day 1)
- Treatment allocation: Subjects will be randomised using a centralized randomisation system on internet (SBIR) at Visit 1 (Day 1). The randomisation algorithm will use a minimization procedure accounting for age (18 - 32 years or 33 - 45 years) and centre
- Blinding:

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	N/A
Epoch 002	observer-blind
Epoch 003	single-blind *

* The study will be conducted in an observer-blind fashion through Day 91. After this day, the study will continue in a single-blind fashion. For more details about blinding see Section[s] 1.5.6, 5.3, 10.11.1.

- Sampling schedule:
  - **Blood samples for haematology/biochemistry**: will be collected (~5.5 mL) from all subjects at Screening, Visit 2 (Day 8), Visit 3 (Day 31) and any Unscheduled Visit(s).
  - **Blood samples for humoral immunogenicity:** will be collected (~30 mL) from all subjects at Screening, Visit 2 (Day 8), Visit 3 (Day 31), Visit 4 (Day 61) and Visit 5 (Day 91).
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)
- Safety monitoring:

As this will be the first time that the RSV maternal vaccine will be administered in humans, the study will enrol subjects in two steps (Step 1 will enroll 60 subjects in the United States [US] only and Step 2 will enroll 440 subjects across multiple countries). Subjects will be randomised to all dose levels from the start. Both blinded and unblinded safety monitoring will be performed, as described below.

The Safety Review Team (SRT) will review blinded data on a regular basis throughout the study, and an internal Safety Review Committee (iSRC) will review unblinded data at specific study timepoints. (Refer to section[s] 8.10.1 and 8.10.2 for more details on the safety monitoring for this study).

During Step 1, until the first 30 subjects have been vaccinated, vaccination will be limited to 10 subjects/ per day across all sites. These subjects will be vaccinated sequentially and at least 60 minutes apart.

Subsequent vaccinations will continue without limitation to the number of subjects vaccinated per day or time lag between vaccination of consecutive subjects.

Screening and enrolment of Step 2 subjects will only be initiated if the iSRC review of Day 31 data results in a recommendation to proceed with Step 2.

Number of subjects Approximately 500 healthy women will be enrolled (~125/group).

Endpoint(s) **Primary**

- Occurrence of any adverse events (AEs) from vaccination during a 30-day follow-up period, for all subjects in all groups:
  - Occurrence of each solicited local and general symptom during a 7-day follow-up period.
  - Occurrence of any unsolicited AE during a 30-day follow-up period.
  - Occurrence of Serious AEs during a 30-day follow-up period.
  - Occurrence of any haematological (Leukocytes, Neutrophils, Lymphocytes, Eosinophils, Haemoglobin, Platelets) and biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen [BUN]) laboratory abnormalities at Day 8 and Day 31.

Secondary

- Occurrence of SAEs from vaccination up to Day 91 and up to Day 181 for all subjects, in all groups.
- Humoral immune response to the investigational vaccine at Day 8, Day 31, Day 61 and Day 91 for all subjects in each investigational RSV vaccine group
  - RSV-A neutralising antibody (Nab) titres;
  - RSVPreF3 immunoglobulin G (IgG) antibody concentrations

Tertiary

- Additional humoral response which may include but not limited to, RSVPreF3 specific IgG1 subclass antibody concentrations, RSV-B neutralising antibody titres, antibody competing for binding to specific epitopes on RSVPreF3 and antibody concentrations to residual host cell proteins in the RSVPreF3 vaccines.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of Covariance
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BLA	Biologicals License Application
BMI	Body Mass Index
BSH	Blood Sample for Humoral immunogenicity
BSS	Blood Sample for Safety
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CEPL	Clinical & Epidemiology Project Lead
CFR	Code of Federal Regulations
CI	Confidence Interval
CLS	Clinical Laboratory Sciences
CMO	Chief Medical Officer
CRDL	Clinical Research and Development Lead
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
eCRF	electronic Case Report Form
EGA	Estimated Gestational Age
EMA	European Medicines Agency
EoS	End of Study
ERD	Enhanced RSV Disease
ES	Exposed Set

eTDF	Electronic Temperature excursion Decision Form
FDA	Food and Drug Administration, United States of America
FI-RSV	Formalin-inactivated whole virus RSV vaccine
FTiH	First Time in Human
FU	Follow-up
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICD-10	International Classification of Diseases 10th Revision
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
IRB	Institutional Review Board
iSRC	Internal Safety Review Committee
LL	Lower limit
LMP	Last Menstrual Period
LRTI	Lower Respiratory Tract Infection
LSLV	Last subject last visit

MACDP	Metropolitan Atlanta Congenital Defects Program
MATEX	MATerial EXcellence
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
Nab	Neutralising antibodies
NIH	National Institute of Health
PCA	Palivizumab Competing Antibodies
PCD	Primary Completion Date
PP	Per Protocol
PPS	Per Protocol Set
RNA	Ribonucleic Acid
RSV	Respiratory syncytial virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR	Source Database for Internet Randomisation
SDV	Source Document Verification
SD	Standard Deviation
SE	Safety event
SPM	Study Procedures Manual
SRT	Safety Review Team
TBD	To be determined
UL	Upper Limit
UP	Urine Pregnancy test
VSMB	Vaccines Safety Monitoring Board

WBC	White Blood Cells
WHO	World Health Organization

GLOSSARY OF TERMS

Active Phase (of a clinical trial): Active phase is defined as the time period in a clinical trial during which all study visits involving the main study activities (e.g. vaccination or study medication/ product administration; main blood collection) take place; this excludes follow-up periods aimed at monitoring the safety of a subject over a long period of time or checking long-term immunity persistence.

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- combined oestrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etonogestrel or levonorgestrel,
- contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- current bilateral tubal ligation,
- male partner sterilisation (i.e. vasectomy) prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records and interview with the subject on her medical history.
- male condom and progesterone alone oral contraceptive.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and progesterone alone oral contraceptive.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners only.

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 5.3 for details on observer-blinded studies). The method of blinding in this study is further defined in Section 1.5.6.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolment:	Enrolment is defined as the point that a subject is determined as eligible to participate in the study and has been randomized to a treatment group.
End of Study: **(Synonym of End of Trial):**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints or LSLV, whichever comes later. EoS must be achieved no later than 8 months after LSLV.

Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are screening visits, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the Per Protocol (PP) analysis (see Sections 6.6.2, 6.7and 10.5 for details on criteria for evaluability).
Investigational vaccine: **(Synonym of Investigational Medicinal Product):**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Internal Safety Review Committee (iSRC):	The iSRC is a group of experts (a GSK Biologicals' Safety Physician, a CRDL/CEPL and a Biostatistician), external to the on-going study/project and with lack of conflicts of interest in the outcome of the study, who assess the safety data in an unblinded (on a subject level or treatment group level) fashion. They may also assess other parameters (e.g. immunogenicity), if requested. Based on its review, the iSRC gives recommendations to the Clinical Project Team regarding study modification, continuation or termination.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Safety Review Team (SRT):	Includes as core members, the GSK Biologicals' Central Safety Physician, Central Safety Scientist, the Clinical and Epidemiology Project Lead (CEPL), Epidemiologist, Clinical Regulatory Affairs representative and the Biostatistician of the project.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.

Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vaccines Safety Monitoring Board (VSMB):	Internal GSK Biologicals governance with the mandate for oversight of safety information for GSK vaccines.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines/products and/or medications will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Synagis (MedImmune LLC.)	Recombinant humanized monoclonal anti-RSV antibody

1. INTRODUCTION

1.1. Background

RSV is a negative-strand, ribonucleic acid (RNA) virus of which two antigenically distinct subgroups exist, referred to as RSV-A and RSV-B. RSV is a highly contagious human pathogen that causes respiratory tract infections in people of all ages. In temperate climates throughout the world, RSV predictably causes fall-winter epidemics whereas viral activity is more endemic in tropical regions and outbreaks are less seasonally focused.

The virus causes respiratory tract infections at all ages, but young infants below 1 year of age have the highest incidence of severe disease (bronchiolitis, pneumonia), peaking at 1-3 months of age [Hall, 2013] and with a continuing burden of disease through the second year of life [EMA/CHMP, 2017]. Severe disease often leads to hospitalisation and may be life threatening. The majority of children become infected with RSV within 2 years of birth [Hall2001; Nyiro, 2017; Kutsaya, 2016]. The impact continues into later life, specifically, episodes of wheezing and asthma during the first decade of life are more common in children who were hospitalized for RSV bronchiolitis during infancy than those who were not hospitalized [Wu, 2011].

The risk for severe RSV-induced lower respiratory tract infection is highest in infants below 6 months of age and it is the most common cause of hospitalisation in this age group. About 45% of the estimated 3.2 million hospital admissions for RSV –associated acute lower respiratory tract infections that occurred globally in 2015, occurred in infants younger than 6 months of age. Additionally, it was estimated globally that hospital deaths due to RSV-associated lower respiratory infection were approximately 59,600 in children younger than 5 years and 27, 300 in children <6 months of age [Shi, 2017]. Approximately 2% of children < 1 year of age are hospitalized for RSV-associated lower respiratory tract infections each year in industrialized countries [Blais, 2017; Boyce, 2000; Deshpande, 2003; Hall, 2009; Holman, 2004; Iwane, 2004; Madhi, 2006; Nair, 2010; Paramore, 2004; Vicente, 2003; Shi, 2017; Stein, 2017].

Previous infection with RSV does not prevent subsequent infections. Re-infection with RSV occurs throughout an individual's lifetime [Simoes, 1999; Kapikian, 1969; Krilov, 2011]. These re-infections generally go undiagnosed because they usually present as common acute upper respiratory tract infections. In more vulnerable populations (e.g., immunocompromised individuals or older adults), re-infections can also lead to severe disease and result in mortality [Graham, 2011].

1.2. Current Management of RSV Disease in Infants

To date, no licensed vaccine is available for RSV and treatment for RSV disease is limited to supportive care. Palivizumab (*Synagis*, MedImmune), an RSV specific- recombinant humanised monoclonal antibody, is indicated for the prevention of severe LRTI requiring hospitalisation caused by RSV in children at high risk for RSV disease, such as infants who were born prematurely or with bronchopulmonary dysplasia,

as well as with hemodynamically significant congenital heart disease. *Synagis* is only effective as prophylaxis and is not indicated or recommended in the general, healthy infant population, due to high cost and the need for monthly administration throughout the RSV season [Buck, 2004].

1.3. Maternal Immunization

Maternal immunization, and the protective effect of maternally transferred antibodies was initially demonstrated with the small pox vaccination in 1879 [Rasmussen, 2014]. Effective immune responses to vaccines and transmission of specific antibodies to infants through the placenta are observed when pregnant women are vaccinated [Vojtek, 2018]. Currently, the Advisory Committee on Immunization Practices recommends the inactivated influenza and Tdap (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis) vaccines for pregnant women [CDC, 2017].

In a study evaluating maternal vaccination with influenza, there was a 63% reduction in laboratory proven influenza illness in infants up to 6 months of age and 29% and 36% reductions in rates of respiratory illness with fever in infants and mothers, respectively [Zaman, 2008]. Additionally, in a retrospective cohort study, it was concluded that infants with pertussis whose mothers received Tdap during pregnancy had a significantly lower risk of hospitalization and intensive care unit admission and shorter hospital stays [Winter, 2017]. Following maternal tetanus toxoid vaccination, neonatal tetanus mortality has been reduced by 92% in combination with improved hygienic birthing practices [Healy, 2012].

Based on the results seen with previous maternal vaccines, vaccinating mothers with an RSV vaccine could reduce RSV-associated morbidity and mortality in infants less than 6 months of age.

It was shown that most of the RSV neutralizing activity present in serum from previously infected individuals is directed to the pre-fusion conformation of RSV F protein [Ngwuta, 2015]. In addition, antibodies specific for the RSV F pre-fusion conformation are typically more potent than those which are common to both the post- and pre-fusion forms [Kwakkenbos, 2010].

Administration of an RSV vaccine to adults (pregnant women in this case), all of whom can be assumed to have been naturally infected with RSV before, is expected to boost the immunological memory induced by previous natural infections [Anderson, 2013]. High titers of maternally derived RSV-neutralizing antibodies have been shown to be associated with subsequent serologic protection against RSV infection and lower incidence of RSV-associated acute lower respiratory tract infection during the first 6 months of life [Roca, 2002; Stensballe, 2009; Chu, 2014].

Enhanced respiratory disease (ERD) was seen in clinical trials of a formalin-inactivated whole virus RSV vaccine (FI-RSV) in seronegative children. Among seronegative children in those trials, the FI-RSV vaccine did not protect against RSV disease and more importantly led to more severe clinical symptoms upon subsequent natural infection of RSV [Chin, 1969; Kapikian, 1969; Kim, 1969]. In contrast, clinical data demonstrate a

decrease in severity of RSV infection among the non-naïve population following repeat exposure and the lack of ERD in the seropositive children who participated in the FI-RSV studies [Roberts, 2016]. With the transfer of vaccine-induced neutralizing antibodies from the mother to the infant, the risk of ERD in the infants is considered negligible. In support of this hypothesis, ERD has not been observed with the use of *Synagis*, nor with the transfer of serum from FI-RSV vaccinated animals to recipient animals [Kwon, 2014].

1.4. GlaxoSmithKline (GSK) Biologicals' Investigational RSV maternal vaccine

The RSV maternal vaccine is composed of the lyophilized RSVPreF3 antigen (Refer to the Investigational Medicinal Product (IMP) Dossier and Section 3.2.S.1.2 of the Investigational New Drug (IND). The vaccine is being developed for prevention of RSV LRTI disease in infants by transfer of maternal antibodies.

Refer to the Investigator Brochure (IB) for more information on the RSV maternal vaccine

1.5. Rationale for the study and study design

1.5.1. Rationale for the study

GSK is developing a new investigational RSV maternal vaccine against RSV disease in infants through a maternal immunization program.

The purpose of this study is to evaluate the safety, reactogenicity and immunogenicity of three dose levels (30 µg, 60 µg and 120 µg) of the investigational RSV maternal vaccine antigen compared to placebo administered as a single intramuscular injection.

1.5.2. Rationale for the study design

To assess the impact of the investigational RSV maternal vaccine in terms of safety, reactogenicity and immune response, four treatment groups will be evaluated:

Group Name (Product):

- RSV MAT 30 (RSVPreF3 30 µg)
- RSV MAT 60 (RSVPreF3 60 µg)
- RSV MAT 120 (RSVPreF3 120 µg)
- Control (Saline Placebo)

Healthy, non-pregnant women aged 18 - 45 years will be enrolled in this study, a population of the same gender and age of the vaccine's target population.

1.5.3. Rationale for dose selection

GSK previously evaluated a different candidate RSV maternal vaccine at dose levels of 30, 60, and 120 µg in a similar population, non-pregnant women 18-45 years of age. Building on this experience, the RSV MAT-001 study will evaluate 3 dose levels (30, 60 or 120 µg) of the new investigational unadjuvanted RSV maternal vaccine administered intramuscularly as a single dose. Clinical experience with the previously evaluated vaccine candidate indicated that unadjuvanted formulations induced Nab levels similar to those of alum-adjuvanted formulations in adults [Langley, 2017; Beran, 2018]. Therefore, only unadjuvanted formulations will be used in RSV MAT-001.

The highest proposed dose level (120 µg) for RSV MAT-001 was well tolerated when given alone, 3 times at 2-week intervals, in a GLP toxicology study. Additionally, previous pharmacology studies of the RSVPreF3 antigen conducted in a bovine model demonstrated that the molecule is able to boost Nab titres. Refer to the Investigator Brochure for a summary of the nonclinical studies.

This is a single-dose study so the maximum dose to be administered will be the dose to which the subject is randomised.

1.5.4. Rationale for the use of placebo

The placebo group is included as a control for both the safety/reactogenicity and the immunogenicity assessments.

1.5.5. Safety considerations

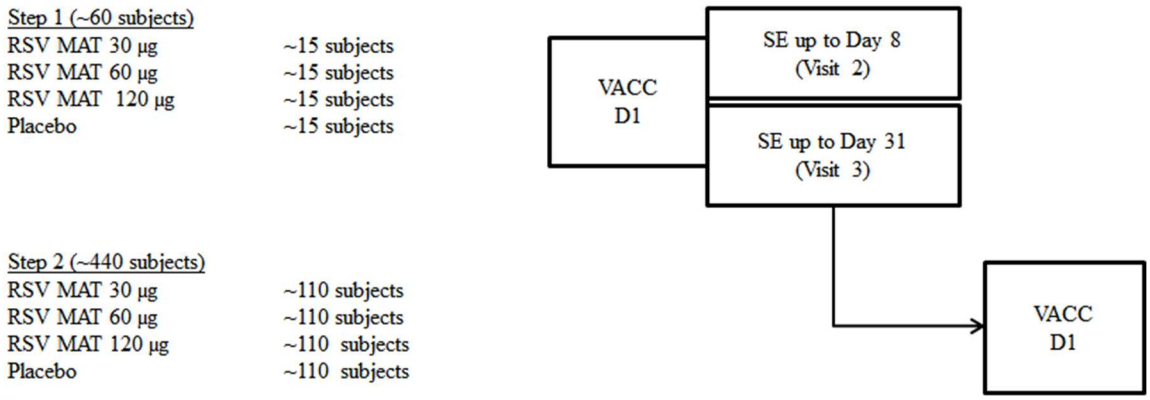
As this will be the first time that the GSK investigational RSV maternal vaccine will be administered in humans, the study will enrol subjects in 2 steps with randomisation to all dose levels (30, 60 and 120 µg) from the start, (See Figure 1). Step 1 (~ 60 subjects) will be conducted at sites in the United States only and additional countries will be added in Step 2.

During Step 1, until the first 30 subjects have been vaccinated, vaccination will be limited to 10 subjects per day across sites. These subjects will be vaccinated sequentially and at least 60 minutes apart across all sites. During the remainder of Step 1 and in Step 2, vaccination will continue without limitations to the number of subjects vaccinated per day or time lag between vaccination of consecutive subjects.

Refer to Sections 5.6.13 and 5.6.14 for more information on vaccine administration and subject monitoring.

Refer to Section 8.10.1 and 8.10.2 for more information on the Safety Review Team (SRT) and the internal Safety Review Committee (iSRC) evaluations, respectively.

Figure 1 Overview of staggered enrolment/vaccination and safety evaluation



Safety Events (SE) up to Day 8 visit = safety evaluation by iSRC based on all available safety data from subjects up to at least 7 days post-vaccination (including Day 8 haematology/ biochemistry parameters).
SE up to Day 31 visit = safety evaluation by iSRC based on all available safety data from subjects up to 30 days post-vaccination (Including Day 31 haematology/biochemistry parameters).

1.5.6. Study blinding

Given the different presentation of the placebo and the investigational RSV vaccine, a double-blinded study design is not possible. This study will be conducted in an observer-blind manner up to Day 91, after which it will be conducted in a single-blind manner.

Observer-blind, means that during the course of the study, the vaccine recipient, those responsible for the evaluation of any study endpoint (e.g. safety and reactogenicity), and the sponsor will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

Single-blind, means that GSK statistician and data management staff will be unblinded (i.e. will have access to the individual subject treatment assignments), but individual listings will not be provided until the study report at the completion of the study. In addition, site staff involved in the clinical evaluation of study participants will not be aware of individual treatment assignments until the study report.

Please refer to Section 5.3 for further details regarding the methods of blinding used in this study.

1.6. Benefit: Risk Assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of the investigational RSV maternal vaccine.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.6.1. Risk Assessment

Risks, Contraindications and Warnings	Data/Rationale for Risk	Mitigation Strategy
All Study Vaccines		
Hypersensitivity including allergic reactions such as anaphylaxis	Acute allergic reactions, such as an anaphylactic event, may occur with any vaccine administration. These are serious, but rare occurrences, estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Rueggeberg, 2007].	The onset of vaccine-related allergic symptoms is typically quite prompt. In order to treat subjects with a serious allergic reaction to vaccination, all subjects will need to remain under observation (i.e. visibly followed; no specific procedure) at the vaccination centre for at least 60 minutes after vaccination with appropriate medical treatment readily available, in case needed.
Syncope	Syncope (fainting) can occur following or even before any vaccination as a psychogenic or vasovagal response to the needle injection.	All subjects will remain under observation at the vaccination centre for at least 60 minutes after vaccination.
Intramuscular Injection site reaction	Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, redness, and swelling.	Solicited local AEs will be collected and reviewed up to 7 days post-vaccination
RSV maternal vaccine		
Due to the lack of experience in human subjects to date, there is currently not enough information available to identify the risks of adverse events (AE) related to administration of the RSV maternal vaccine		Any untoward symptoms experienced by the subject after receiving the vaccine should be reported to the investigator. Ongoing safety monitoring will be performed in a blinded fashion by the Safety Review Team, and unblinded review will be performed by the internal Safety Review Committee (independent from the RSV program). Established holding rules will be applied. In step 1, for the first 30 subjects there will be a minimum interval of 60 minutes between vaccinations and vaccination will be limited to 10 subjects per day across all sites. In addition to the above, all subjects will remain under observation at the vaccination centre for at least 60 minutes

Risks, Contraindications and Warnings	Data/Rationale for Risk	Mitigation Strategy
		after vaccination.
Study Procedures – Venipuncture		
Pain and bruising	Pain or bruising at the site where blood is drawn.	A topical analgesic may be applied to the site where blood will be taken.
Syncope	Syncope (fainting) can occur following or even before any blood draw as a psychogenic or vasovagal response to the needle injection.	All subjects will remain under observation, post venepuncture, through completion of the applicable study visit.

1.6.2. Benefit Assessment

Benefits linked to the investigational RSV maternal vaccine

RSV infections in healthy adults generally go undiagnosed because they usually present as mild acute upper respiratory tract infections. Moreover, vaccine efficacy has not been assessed yet and it is not known whether the investigational RSV maternal vaccine is effective in protecting against RSV infection in infants.

As the proposed indication of the vaccine is to prevent RSV-associated lower respiratory tract illness (LRTI) in infants by transfer of maternal antibodies, the subjects in RSV MAT-001 (healthy, non-pregnant women) receiving the investigational RSV maternal vaccine are not expected to directly benefit from this vaccination.

1.6.3. Overall Benefit: Risk Conclusion

This is a FTiH study evaluating an investigational RSV maternal vaccine. The investigational RSV maternal vaccine is currently in an early stage of clinical development and although no vaccine efficacy has been demonstrated, the vaccine has been shown to boost Nab to both RSV serotype A and RSV serotype B in animal models (refer to the IB).

2. OBJECTIVE(S)

2.1. Primary objective

- To evaluate the safety and reactogenicity of three dose levels (30, 60, 120 µg) of the RSV maternal investigational vaccine administered as a single intramuscular injection, as compared to placebo up to 1 month post vaccination (Day 31).

Refer to Section 10.1 for the definition of the primary endpoint(s).

2.2. Secondary objectives

- To evaluate the safety of three dose levels (30, 60, 120 µg) of the RSV maternal investigational vaccine compared to placebo up to 6 months post vaccination (Day 181).
- To evaluate the humoral immune response to three dose levels (30, 60, 120 µg) of the RSV maternal investigational vaccine compared to placebo up to 3 months post vaccination (Day 91).

Refer to Section 10.2 for the definition of the secondary endpoint(s).

2.3. Tertiary objective

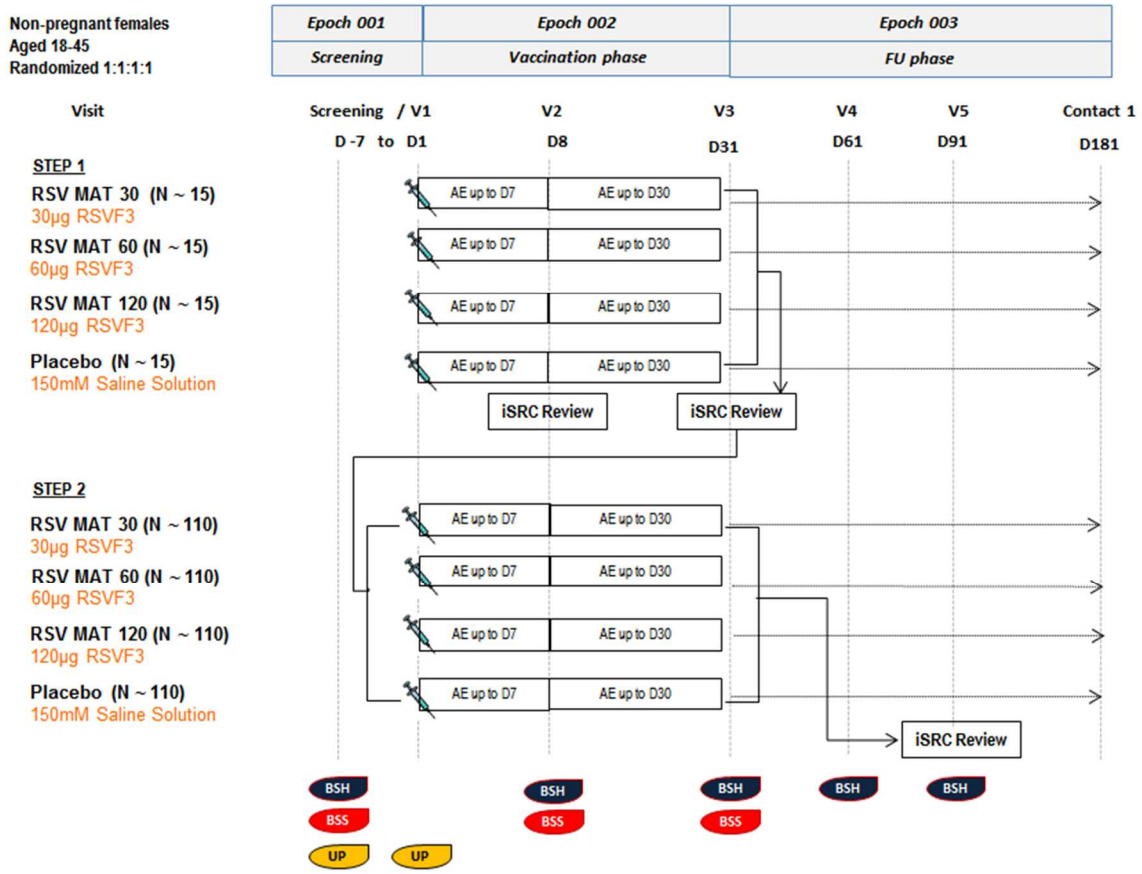
- To further evaluate the humoral immune response to the RSV maternal vaccine.

Refer to Section 10.3 for the definition of the tertiary endpoint(s).

3. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), is essential and required for study conduct.

Figure 2 Study Design Overview



AE – Adverse Events: solicited (Day 1 to Day 7); unsolicited (Day 1 to Day 30) and serious (Enrolment to Study conclusion)
BSS – Blood samples for haematology/biochemistry will be collected (~5.5 mL) from all subjects at Screening, Visit 2 (Day 8), and Visit 3 (Day 31).
BSH – Blood samples for humoral immunogenicity will be collected (~30 mL) from all subjects at Screening, Visit 2 (Day 8) Visit 3 (Day 31), Visit 4 (Day 61), and Visit 5 (Day 91).
iSRC – Internal Safety Review Committee (See Section 8.10.2).
Contact 1- will be completed for all subjects at Day 181 (preferred contact is Phone Call).
RSV MAT 30/60/120 – RSV maternal 30/60/120µg, respectively, of the RSV maternal vaccine.
Screening can occur ≤ 7 days prior to Visit 1 or on the same day, when possible.
UP – Urine Pregnancy test (or serum pregnancy test if country/local specific regulation) from all subjects (if Screening and Visit 1 are on the same day UP will not be repeated).

- **Experimental design**: Phase I/II, randomised, observer-blind, placebo control, multicentre study with four parallel groups.
- **Duration of the study** for each subject enrolled will be approximately 6 months from Visit 1:
  - Epoch 001: Screening Visit (Day -7 to Day 1)
  - Epoch 002: Active Vaccination phase starting at (Day 1) and concluding at, and including, Visit 3 (Day 31).

– Epoch 003: Long Term Follow-up starting after Visit 3 (Day 31) and concluding at Contact 1 (Day 181).

Any safety data collected beyond Day 31 will be collected in Epoch 003.

- **Primary Completion Date**: Visit 3 (Day 31) or last visit of Epoch 002.

Refer to GLOSSARY OF TERMS for the definition of PCD

- **End of Study:** Last testing results released for samples collected at Visit 5 (Day 91) or LSLV (i.e. last Contact 1), whichever comes last.

Refer to GLOSSARY OF TERMS for the definition of EoS

Study groups:

Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min - Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
RSV MAT 30	~125	18 - 45 years	x	x	x
RSV MAT 60	~125	18 - 45 years	x	x	x
RSV MAT 120	~125	18 - 45 years	x	x	x
Placebo	~125	18 - 45 years	x	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups			
		RSV MAT 30	RSV MAT 60	RSV MAT 120	Placebo
RSVPreF3 30	RSVPreF3 low dose	•			
RSVPreF3 60	RSVPreF3 mid dose		•		
RSVPreF3 120	RSVPreF3 high dose			•	
Control	NaCl				•

- Control: placebo control
- Vaccination schedule: Single intramuscular injection at Visit 1 (Day 1)
- Treatment allocation: Subjects will be randomised using a centralized randomisation system on internet (SBIR) at Visit 1 (Day 1). The randomisation algorithm will use a minimization procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.
- Blinding:

Table 3 Blinding of study epochs

Study Epochs	Blinding
001	N/A
002	observer-blind
003	single-blind *

* The study will be conducted in an observer-blind fashion through Day 91. After this day, the study will continue in a single-blind fashion. For more details about blinding see Section(s) 1.5.6, 5.3, 10.11.1**.**

- Sampling schedule:
  - **Blood samples for haematology/biochemistry**: will be collected (~5.5 mL) from all subjects at Screening, Visit 2 (Day 8), Visit 3 (Day 31) and any Unscheduled Visit(s).
  - **Blood samples for humoral immunogenicity:** will be collected (~30 mL) from all subjects at Screening, Visit 2 (Day 8),Visit 3 (Day 31), Visit 4 (Day 61) and Visit 5 (Day 91).
- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)
- Safety monitoring: This study will be monitored by a blinded SRT and by an unblinded iSRC.

Refer to Section(s) 1.5.5 and 8.10 for detailed description of holding rules and safety monitoring.

4. STUDY COHORT

4.1. Number of subjects/centres

This will be a multi-centre, multi-country study. It is planned that enrolment will be equally distributed to the participating countries.

The target is to enrol approximately 500 eligible women (~125 per group).

Refer to Section 10.4 for a detailed description of the criteria used in the estimation of the sample size.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who the investigator believes will comply with the requirements of the protocol (e.g. completion of the diary cards/questionnaires, return for follow-up visits, have regular contact to allow evaluation during the study);
- Written informed consent obtained from the subject;
- Healthy female subjects; as established by medical history and clinical examination, aged 18 to 45 years at the time of the vaccination;
- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination, and
  - has agreed to continue adequate contraception until 90 days after vaccination

Please refer to the GLOSSARY OF TERMS for the definition of adequate contraception.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding vaccination or any planned use during the study period;
- Concurrently participating in the active phase of another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device);
- Chronic administration (defined as more than 14 days in total) of immunosuppressant or other immune-modifying drugs, as well as administration of long acting immune modifying drugs (e.g. infliximab), within 6 months prior to the vaccine dose (for corticosteroids, this will mean prednisone ≥ 5 mg/day, or equivalent). Inhaled and topical steroids are allowed;
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the study vaccination, or planned administration until 90 days post-vaccination;
- Planned administration/administration of a vaccine not foreseen by the study protocol within the period starting 30 days before and ending 30 days after study vaccination, with the exception of any licensed influenza vaccine which may be administered ≥ 15 days before or after study vaccination;

- Previous experimental vaccination against RSV;
- Presence of neurological or psychiatric diagnoses which, although stable, are deemed by the investigator to render the potential subject unable/unlikely to provide accurate safety reports;
- Family history of congenital or hereditary immunodeficiency;
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required);
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine;
- Any acute or chronic, clinically significant disease, as determined by physical examination, laboratory screening tests, subject personal report and/or health care provider information. The following conditions will be exclusionary:
  - Diabetes mellitus,
  - Respiratory diseases, such as:
    - Chronic Pulmonary diseases, including COPD,
    - Bronchopulmonary dysplasia (note: history of past bronchopulmonary dysplasia as a neonate/infant will not be exclusionary),
    - Uncontrolled asthma or asthma necessitating treatment with chronic systemic glucocorticoids (please refer to the exclusion criterion on use of immunosuppressants or other immune-modifying drugs for the definition of chronic corticoids use)
  - Significant and/or uncontrolled psychiatric illness:
    - hospitalization for psychiatric illness, history of suicide attempt(s) or confinement for danger to self or others within 10 years
    - clinically significant depression (as deemed by the investigator)
  - Major neurological disease including:
    - seizure or adulthood epilepsy (note: history of febrile convulsion in childhood is not exclusionary)
    - myasthenia gravis
    - history of repetitive migraine mal/status migrainosus (i.e. severe or debilitating migraine attack that lasts for more than 72 hours)
  - Significant cardiovascular disease, including:
    - Uncontrolled arterial hypertension,
    - Congenital heart disease (with the exception of corrected atrial or ventricular septal defects),
    - Previous myocardial infarction,
    - Valvular heart disease or history of rheumatic fever,

  - Previous bacterial endocarditis,
  - History of cardiac surgery (with the exception of corrected atrial or ventricular septal defects),
  - Personal or family history of cardiomyopathy or sudden adult death.
- Known or suspected Hepatitis B or Hepatitis C infection,
- Any other significant uncontrolled medical illness (acute or chronic), defined as any illness requiring new medical and/or surgical treatment or significant modification of treatment dose due to uncontrolled symptoms or drug toxicity, within 3 months prior to study vaccination.

- History of or current autoimmune disease;
- Body mass index (BMI) > 40 kg/m^2;
- Pregnant or lactating female;
- Female planning to become pregnant or planning to discontinue contraceptive precautions (if of childbearing potential);
- Hypersensitivity to latex;
- Lymphoproliferative disorder or malignancy within previous 5 years (excluding effectively treated non-melanotic skin cancer);
- Acute disease and/or fever at the time of enrolment;
  - Fever is defined as temperature ≥ 38°C/100.4°F
  - For subjects with acute disease and/or fever at the time of enrolment, Visit 1 will be rescheduled within the allowed window for the visit (see Table 5).
  - Subjects with fever at screening may be re-screened 1 time at a later date.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Any clinically significant or any ≥ Grade 2* haematological (haemoglobin level, white blood cell, lymphocyte, neutrophil, eosinophil, and platelets) and biochemical (alanine aminotransferase [ALT] aspartate aminotransferase [AST], creatinine, blood urea nitrogen [BUN]) laboratory abnormality detected at the last screening blood sampling;

  *Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" [APPENDIX C].

  For Grade 1 laboratory abnormalities, the investigator should use clinical judgement to decide which ones are clinically relevant.

  Subjects with haematological/biochemical values out of normal range at screening which are expected to be temporary, may be re-screened 1 time at a later date.
- Any other condition that the investigator judges may interfere with study procedures (e.g. drawing blood) or findings (e.g. immune response);

- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe;
- Alcoholism, drug abuse and/or use disorder within the past two years (as defined in DSM-5 Diagnostic Criteria) [Hasin, 2013];
- Planned move to a location that will prohibit participating in the trial until study end.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject as appropriate, prior to participation in the study.

GSK will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to

GSK and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.

In order to allow for proper control of recruitment as per the Step 1 and Step 2 recruitment targets, consented subjects will be registered in the SBIR application.

5.2.2. Randomisation of treatment

5.2.2.1. Randomisation of supplies

The randomisation of supplies within blocks will be performed at GSK, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK. Entire blocks will be shipped to the study centres/ warehouse(s).

To allow GSK to take advantage of greater rates of recruitment than anticipated at individual centres in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Study group and treatment number allocation

The target will be to enrol approximately 500 eligible subjects who will be randomly assigned to four study groups in a (1: 1: 1: 1) ratio (~125 subjects in each group).

Allocation of each subject to a study group at the investigator site will be performed using SBIR. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre. Minimisation factors will have equal weight in the minimisation algorithm.

At Visit 1, after having fully checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon selecting the subject identification number previously entered in the application, the randomisation system will determine the study group and will provide the treatment number to be used for vaccination.

The number of the administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.3. Method of blinding

Given the different presentation of the placebo and the investigational RSV vaccines, a double-blinded study design is not possible. Refer to Section 1.5.6 for more information on study blinding.

Data will be collected in an observer–blinded manner up to Day 91 (Visit 5). During this time, vaccine recipients and those responsible for the evaluation of any study endpoints will be unaware of which vaccine was administered. To achieve this, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluations. Additionally, vaccine recipients will receive the same volume (0.5 mL) of the study product on Day 1.

Analyses for the iSRC review will be performed by an independent statistician to ensure that the study team remains blinded to individual subject listings. Refer to Section 10.11 for more information on analyses.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5. Outline of study procedures

Table 4 List of study procedures

Epoch	001	002			003			
Type of contact	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Contact 1	Unsch Visit
Time point (s)	Day -7 to Day 1	Day 1	Day 8	Day 31	Day 61	Day 91	Day 181	
Sampling time point(s)	Pre-Vacc	Vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc	
Informed consent	●							
Assign subject number	●							
Register subject in SBIR	O							
Check inclusion/exclusion criteria	●	O[1]						
Collect demographic data	●[2]							
Medical history	O	●						
Physical examination[3]	●	●[1]	●	O *	O *	O *		O *
Urine pregnancy test[4]	●	●[1]						
Pre-vaccination body temperature		●						
Distribution of subject card	O							
Blood sampling for humoral immune response (~30 mL)[5]	●		●	●	●	●		
Blood sampling for haematology/ biochemical analysis (~5.5 ml)[5]	●		●	●				●
Study group and treatment number allocation (SBIR)		O						
Vaccine administration		●						
Recording of administered treatment number		●						
60 minutes post vaccination observation period		O						
Training on use of diary cards		O	O					
Distribution of diary cards[6]		O	O					
Collection of diary cards			O	O				
Diary card transcription by investigator			●	●				
Recording of solicited adverse events		●	●					
Recording of unsolicited adverse events		●	●	●				●
Recording of AE leading to withdrawal		●	●	●	●	●	●	●
Recording of serious AE[7]	●	●	●	●	●	●	●	●
Recording of pregnancies		●	●	●	●	●	●	●
Recording of concomitant medications/vaccinations		●	●	●	●[8]	●[8]	●[8]	●[8]

Epoch	001	002			003			
Type of contact	Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Contact 1	Unsch Visit
Time point (s)	Day -7 to Day 1	Day 1	Day 8	Day 31	Day 61	Day 91	Day 181	
Sampling time point(s)	Pre-Vacc	Vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc	
Record any intercurrent medical conditions			●	●	●	●	●	●
Check for interest in participating in future booster study	O						●	
Screening conclusion	●							
Investigator sign-off on eCRF before analysis						●	●	
Study Conclusion							●	

Vacc: vaccination.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF

[1] When Screening Visit and Visit 1 are performed on the same day, Inclusion and Exclusion Criteria check, Physical examination and Urine pregnancy test will not be repeated.

[2] Date of birth (month and year or year only, as per local regulations), race, ethnicity and childbearing potential (if subject not of childbearing, the specific reason should be documented in the eCRF: hysterectomy, ovariectomy, post-menopause, pre-menarche or other)

[3] Physical examination including resting vital signs (blood pressure, heart rate and respiratory rate, temperature) after at least 10 minutes of rest. Weight, height and BMI will only be collected at Screening. * Physical examination at Visits 3, 4 and 5, as well as any unscheduled visit, will be performed only if deemed necessary by the investigator

[4] Only for women of childbearing potential. Urine pregnancy test is sufficient to determine the eligibility to enter the study. Serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.

[5] Method, cut-off, and laboratory locations are defined in Section 5.7.

[6] Two diary cards will be distributed. The first one will be distributed at the day of vaccination and will be used for recording solicited and unsolicited AEs, and concomitant medications/products on the day of vaccination and for 6 subsequent days. The second one will be distributed at Visit 2 (Day 8) and will be used for recording unsolicited AEs and concomitant medications/products and vaccinations from Day 8 to Day 30.

[7] For Screening and Visit 1 (prior to study vaccine administration), only those SAEs that are considered related to study participation need to be recorded.

[8] Recording of Concomitant medications/vaccinations/products as described in Section 6.6.

Note:

The dashed line border between Screening and Visit 1 indicates the ability for investigator/subject to be screened and vaccinated on the same day, when possible. Prior to vaccination all study procedures in the screening visit must be recorded in eCRF and signed by investigator.

Table 5 Intervals between study visits

Interval	Optimal length of interval[1]	Allowed interval[2]
Screening Visit → Visit 1 (Day 1)	≤7 days	0 – 7 days
Visit 1 (Day 1) → Visit 2 (Day 8)	7 days	7 - 10 days
Visit 1 (Day 1) → Visit 3 (Day 31)	30 days	30 - 45 days
Visit 1 (Day 1) → Visit 4 (Day 61)	60 days	56 – 70 days
Visit 1 (Day 1) → Visit 5 (Day 91)	90 days	86 - 100 days
Visit 1 (Day 1) → Contact 1 (Day 181)	180 days	165 - 195 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] For a study visit where a sample is collected, subjects will not be eligible for inclusion in the Per Protocol (PP) cohort for analysis of immunogenicity if the visit takes place outside this interval.

5.6. Detailed description of study procedures

5.6.1. Study procedure timings

When the Screening Visit and Visit 1 are performed on the same day, the following study procedures will not be repeated:

- Physical Examination (note: temperature [including pre-vaccination temperature] will only be measured once but recorded twice).
- Urine (or serum, if required) Pregnancy test.

5.6.2. Informed consent

During the Screening Visit the signed/witnessed/ thumb printed informed consent of the subject must be obtained before study participation.

Refer to Section 5.1 for the requirements for informed consent, as appropriate.

5.6.3. Subject number allocation and Registration in SBIR- “subject planning” module

Upon signature of the ICF and a first check on eligibility, the subject will be assigned a subject number (refer to section 5.2.1).

The assigned subject number must be recorded in the eCRF.

In addition, the site staff will register the subject into the SBIR application. This will allow to properly control recruitment per the established Step 1 and Step 2 recruitment targets.

5.6.4. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 during the Screening Visit and verify prior to randomisation.

5.6.5. Collect demographic data

During the Screening Visit, record demographic data such as date of birth (month and year or year only, as per local regulations), race and ethnicity as well as information on subject's childbearing potential (if subject is not of childbearing potential, the specific reason should be documented: hysterectomy, ovariectomy, post-menopause, pre-menarche or other) in the subject's eCRF.

5.6.6. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in the subject prior to the study vaccination (Visit 1) in the eCRF.

5.6.7. Physical examination

During the Screening Visit, Visit 1 and Visit 2, perform a physical examination of the subject, including assessment of resting vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate and temperature, after at least 10 minutes of rest. In addition, at Screening only, collect height, weight and BMI. Collected information needs to be recorded in the eCRF.

At subsequent study visits, perform a physical examination only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.8. Pregnancy test

Female subjects of childbearing potential are to have a pregnancy test during the Screening Visit and Visit 1 (prior to study vaccine administration). The study vaccines may only be administered if the pregnancy test is negative.

Urine pregnancy test is sufficient to determine the eligibility to enter the study, however, serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.

Note: The pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

5.6.9. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.10. Assess pre-vaccination body temperature

Record the body temperature of the subject prior to study vaccination. The preferred route for recording temperature in this study will be oral using the provided GSK thermometers.

If the subject has fever (defined as temperature ≥ 38.0°C/100.4°F regardless of the location of measurement) on the day of vaccination, Visit 1 can be rescheduled within the allowed interval for this visit (see Table 5).

If meeting the allowed interval between Screening and Visit 1 in such cases is not possible, subject may be re-screened at a later date (per investigator's discretion).

5.6.11. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of the administered treatment must be recorded in the eCRF.

5.6.12. Blood sampling for safety or immune response assessments

A volume of ~5.5 mL of whole blood should be drawn from all subjects for analysis of the haematology/biochemistry parameters at Screening, Visit 2, Visit 3 and Unscheduled Visits (if any). In the event any re-test is needed; as per investigator discretion, (e.g. laboratory abnormalities) the volume required will also be ~5.5mL. Haematology and biochemistry assessments will be performed in the investigator's laboratory as per local practice (see Table 8 and Table 9).

A volume of ~30 mL of whole blood should be drawn from all subjects at Screening, Visit 2, Visit 3, Visit 4 and Visit 5 for analysis of humoral immune responses (see Table 7 and Table 10).

Refer to the SPM for details on blood sample handling.

5.6.13. Study Vaccine administration

After completing all prerequisite procedures prior to vaccination, administer one dose of study vaccine intramuscularly in the deltoid of the non-dominant arm. In case of anatomical features, medical indication or skin colouration (e.g. tattoos) preventing vaccination in the non-dominant arm, the vaccine may be administered in the dominant arm. Refer to Section 6.3 for information on the dosage and administration of the vaccine.

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccines administration, the vaccination visit will be rescheduled within the allowed interval (refer to Table 5).

Vaccination in Step 1 will be limited to 10 subjects a day for the first 30 subjects. These subjects should be vaccinated sequentially and at least 60 minutes apart.

5.6.14. 60 minutes post-vaccination observation

All subjects across all steps will be observed closely at least 60 minutes following study vaccination, with appropriate medical treatment readily available in case of anaphylaxis and syncope related issues/injuries.

5.6.15. Distribution of Subject Card

For information regarding the Subject Card, please refer to Section 8.9.

5.6.16. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.6.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.7.

5.6.17. Recording of AEs, SAEs and pregnancies

- Refer to Section 8.3 for procedures for the investigator to record AEs, SAEs and pregnancies, as well as the time period for detecting and recording of the different events. Refer to Section 8.4 for guidelines and how to report SAE and pregnancy reports to GSK.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- At the vaccination visit (Visit 1), the first diary card will be provided to the subjects. The subject will be instructed to measure and record body temperature at home (using GSK supplied thermometers) and any solicited local/general AEs, as well as unsolicited AEs and concomitant medications/products/vaccinations as from the time of vaccination up to Day 7. The subject will be instructed to return the diary card to the investigator at the next study visit (Visit 2).
- A second diary card will be provided to the subject at Day 8 (Visit 2) to record any unsolicited AEs and concomitant medications/products/vaccinations from Day 8 until Day 30. The subject will be instructed to return the completed diary card to the investigators at the next study visit (Visit 3).
- The investigator will collect and verify completed diary cards during discussion with the subject and transcribe the information into the eCRF (in English) at Visit 2 and Visit 3.
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure.

5.6.18. Extension/Booster study

It is likely that the RSV antibodies elicited by the vaccine may wane during the period between pregnancies, therefore there may be a need to administer the vaccine during each pregnancy to achieve optimal anti-RSV antibody levels in the neonate. In order to assess whether a booster dose might induce a higher reactogenicity or immune-tolerance, subjects who participated in the study RSV MAT-001 study may be invited to participate in a booster study.

The investigator will ask each subject, at the time of informed consent, if she is interested in participating in a booster study and will document this in the source documents only. At study conclusion (Day 181 contact), the investigator will confirm subject's interest and report it in the eCRF.

If a subject is not interested in participating in the booster study, the reason for refusal will also be documented in the subject's eCRF. Refusal to participate in the extension study will not prevent subjects from enrolling in the RSV MAT-001 study.

5.6.19. Day 181 Contact

Contact should be preferably performed via telephone, or alternatively, if phone contact is not possible, through email/other means where the information can be fully collected. When the contact is not done by telephone, if questions remain, the study site may follow-up with the subject via telephone.

During this contact, the investigator (or delegate) will ask the subject if she has experienced any serious adverse events and/or any AEs leading to study withdrawal since Visit 5 and/ or whether she has become pregnant. The investigator (or delegate) will also ask the subject for concomitant vaccinations/products/medications that she has received since Visit 5.

Subject's interest in participating in a booster study will also be re-confirmed at Day 181 contact, and the corresponding information will be reported in the eCRF (refer to Section 5.6.18).

Please refer to the SPM for further guidance.

5.6.20. Study conclusion

The investigator will:

- Review all data collected from all source documents (e.g. ICF, Diary Cards, etc.) to ensure accuracy and completeness.
- Complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study contact), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK.

5.7.1. Use of specified study materials

When materials are provided by GSK, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the Per Protocol (PP) analysis (See Section 10.5 for the definition of cohorts to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK does not provide material for collecting and storing clinical samples, appropriate

materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Table 6 Biological samples

Sample type	Time point	Cohort	N° of subjects	Quantity	Unit
Blood for haematology/biochemical analysis	Screening Visit	All screened subjects	≥500	~5.5	ml
	Visit 2 (Day 8)	All enrolled subjects	~500	~5.5	ml
	Visit 3 (Day 31)	All enrolled subjects	~500	~5.5	ml
	Unsch Visit	All enrolled subjects	Event driven	~ 5.5	ml
Blood sampling for humoral immune response	Screening Visit*	All screened subjects	≥500	~30	ml
	Visit 2 (Day 8)	All enrolled subjects	~500	~30	ml
	Visit 3 (Day 31)	All enrolled subjects	~500	~30	ml
	Visit 4 (Day 61)	All enrolled subjects	~500	~30	ml
	Visit 5 (Day 91)	All enrolled subjects	~500	~30	ml
Urine[1]	Screening Visit	All screened subjects	≥500		
	Visit 1 (Day 1)	All enrolled subjects	~500		
Total quantity of blood for each subject				~167¥	ml

*Humoral blood sample will not be tested and will be discarded if subject fails screening
¥Volume of blood sample collected at the unscheduled visits is not taken into account
[1] Serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the serological assays performed in the study.

Serological assays described in Table 7 will be performed at a GSK laboratory or in a laboratory designated by GSK and those in Table 8 will be performed at the investigator's laboratory.

Please refer to APPENDIX B for the address(es) of the laboratories used for assessment of humoral immunity analysis.

Table 7 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Serum	Anti-RSV A Neutralizing Antibody	NEUTRALIZATION	In house	ED60	TBD**	GSK Biologicals*
Serum	RSVPreF3 IgG antibody concentrations	ELISA	In house at Neomed Labs	ELU/ mL	TBD**	Neomed Labs

ELISA = Enzyme-linked immunosorbent assay; **ELU** laboratory units; **ED60** = serum dilution inducing 60% inhibition in plaque forming units; **TBD** = to be determined; **IgG** = immunoglobulin G
*GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium
** Assay cut-offs could be subject to change and will be described in the statistical analysis plan (SAP).
NA = not applicable

Table 8 Haematology, Serum Chemistry, Urine tests

System	Discipline	Component	Method	Scale	Laboratory
Whole blood	Haematology	Leukocytes (White Blood Cells)	As per local practice	Quantitative	At investigator's laboratory
		Lymphocytes			
		Eosinophils			
		Haemoglobin			
		Platelets			
		Neutrophils			
Serum	Biochemistry	Alanine Aminotransferase (ALT)	As per local practice	Quantitative	
		Aspartate Aminotransferase (AST)			
		Creatinine			
		Blood Urea Nitrogen (BUN)/urea]*			
Urine[1]		Pregnancy	As per local practice; dipstick provided by GSK Biologicals	Ordinal	At investigator's laboratory

* Sites not able to directly test for BUN, will test for urea and then convert urea values into BUN using the applicable established conversion factor(s). Only BUN values will be entered into the eCRF.
[1] Serum pregnancy test (instead of urine test) may be performed if required by country, local or ethics committee regulations.

Additional Testing

Additional exploratory testing on serum samples to characterise the immune response to the RSV infection or the investigational RSV maternal vaccine, such as but not limited to, RSVPreF3 IgG1 subclass antibody concentrations, RSV-B neutralising antibody titres, antibodies competing for binding to specific epitopes on RSVPreF3, and antibody concentrations to residual host cell proteins in the RSVPreF3 vaccines may be performed if deemed necessary for accurate interpretation of the data or should such test(s) become available in the GSK laboratory or a laboratory designated by GSK.

The GSK's clinical laboratories have established a Quality System supported by procedures. The activities of GSK's clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

5.7.4.1. Haematology/Blood Chemistry

Table 9 Haematology/Blood Chemistry

Blood sampling time point		Sub-cohort Name	No. subjects	Component
Type of contact (time point)	Sampling time point			
Screening	Pre-vaccination	All Subjects	~500	Haematology (Leukocytes, Neutrophils, Lymphocytes, Eosinophils, Haemoglobin, Platelets) Biochemistry (ALT, AST, Creatinine, and BUN/Urea*)
Visit 2 (Day 8)	Post-vaccination	All subjects	~500	
Visit 3 (Day 31)	Post- vaccination	All subjects	~500	
Unscheduled Visit	Post-vaccination	All subjects	event driven	

ALT = Alanine Amino-transferase; **AST** = Aspartate Amino-transferase; **BUN** = Blood Urea Nitrogen

* Sites not able to directly test for BUN, will test for urea and then convert urea values into BUN using the applicable established conversion factor(s). Only BUN values will be entered into the eCRF.

5.7.4.2. Immunological read-outs

Table 10 Immunological read-outs

Blood sampling time point		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and time point	Sampling time point				
Screening Visit	Pre-Vacc	All subjects	~500	RSV-A neutralising antibody RSVPreF3 IgG antibody concentrations	1 2
Visit 2 (Day 8) Visit 3 (Day 31) Visit 4 (Day 61) Visit 5 (Day 91)	Post-vaccination				

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 10.

5.7.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been established so far for the antigen used in the investigational RSV vaccine.

6. STUDY VACCINES ADMINISTRATION

6.1. Description of study vaccine

All candidate vaccines to be used have been developed and manufactured by GSK.

The Quality Control Standards and Requirements for the candidate vaccines are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Table 11 Study vaccine

Treatment name	Vaccine/product name	Formulation	Presentation	Volume to be administered	Number of doses
RSVPreF3 30	RSVPreF3 low dose	RSVPreF3=30µg	Freeze-dried Antigen (174µg/vial)	0.5 ml	1
	NaCl	NaCl=150mM	Clear liquid in monodose ampule or vial		
RSVPreF3 60	RSVPreF3 mid dose	RSVPreF3=60µg	Freeze-dried Antigen (174µg/vial)	0.5 ml	1
	NaCl	NaCl=150mM	Clear liquid in monodose ampule or vial		
RSVPreF3 120	RSVPreF3 high dose	RSVPreF3=120µg	Freeze-dried Antigen (174µg/vial)	0.5 ml	1
	NaCl	NaCl=150mM	Clear liquid in monodose ampule or vial		
Control	NaCl	NaCl=150mM	Clear liquid in monodose ampule or vial	0.5 ml	1

6.2. Storage and handling of study vaccine

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. For the observer-blind part of this study (up to Day 91), access to the storage space by study personnel is further detailed in the guidance on observer-blind studies in the SPM. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the storage, the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccines.

6.3. Dosage and administration of study vaccine

Table 12 Dosage and administration

Type of contact and time point	Study group	Treatment name	Volume to be administered	Route	Site	
					Location	Laterality
Visit 1 (Day 1)	RSV MAT 30 RSV MAT 60 RSV MAT 120 Placebo	RSVPreF3 30 RSVPreF3 60 RSVPreF3 120 Control	0.5 ml	IM	Deltoid	Non-dominant*

IM = intramuscular
*In case of anatomical features, medical indication or skin colouration (e.g. tattoos) that prevents vaccination in the non-dominant arm, the vaccine may be administered in the dominant arm.

6.4. Replacement of unusable vaccine

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 10% additional vaccine doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement number. The replacement numbers will be allocated by dose. The system will ensure, in a blinded manner, that the replacement vial matches the formulation the subject was assigned to by randomisation.

6.5. Contraindications to vaccination

The following events constitute contraindications to administration of the study vaccine. The subject may be vaccinated at a later date, within the time window specified in the protocol (See Table 5) or the subject may be re-screened or withdrawn at the discretion of the investigator:

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C / 100.4°F by any route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered the study vaccine.

6.6. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator should question the subject about any medications/products taken and vaccinations received.

6.6.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medications/vaccinations/products, except vitamins and dietary supplements, administered as of study vaccination and up to 29 days after vaccination (Day 1 to Day 30).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (Fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement).
- Any concomitant medications/products/vaccines listed in Section 6.6.2 during the period specified in that section.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol requirements or administered during the study period for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.

6.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from Per Protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the PP analysis. See Section 10.5 for cohorts to be analysed**.**

- The use of any investigational or non-registered product (drug or vaccine) other than the study vaccine up to study completion (Contact 1 [Day 181]).
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) or any long-acting immune-modifying drugs (e.g. infliximab) administered any time up to 90 days post-vaccination. For corticosteroids, this will mean ≥ 5mg/day prednisone or equivalent. Inhaled and topical steroids are allowed.
- A vaccine not foreseen by the study protocol administered during 30 days following vaccination*, with the exception of seasonal influenza vaccine which may be administered ≥ 15 days after the dose of study vaccine.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Products Characteristics/Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered up to 90 days post-vaccination.

6.7. Intercurrent medical conditions that may lead to elimination of a subject from Per Protocol analyses

At each study visit subsequent to vaccination and up to study end it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the Per Protocol Set (PPS) for immunogenicity if, during the study period up to Day 91 (Visit 5), they incur a condition that has the capability of altering their immune response or if they are diagnosed with an immunological disorder.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine(s) administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

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

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

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

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other

outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 13 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 14 Solicited general adverse events

Fatigue
Fever *
Gastrointestinal symptoms †
Headache

* Fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement (oral is preferred)
†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the diary card and eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). All Grade ≥ 3* abnormal laboratory findings should be reported as AE/SAE. Abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. If a diagnosis is associated with the abnormal findings, the diagnosis should be reported as AE/SAE.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

**Grading will be based on the Food & Drug Administration (FDA) Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" [APPENDIX C].*

8.2. Events or outcomes not qualifying as adverse events or serious adverse events (pregnancy)

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator, but will be followed to determine the outcome of the pregnancy.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.4.1 and 8.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2017]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccines will be reported to GSK as described in Section 8.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

8.3. Detecting and recording adverse events, serious adverse events and pregnancies

8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs starting within 30 days following administration of the study vaccine (Day 1 to Day 30) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the receipt of the study vaccine and will end at the contact at Day 181. See Section 8.4 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the receipt of the study vaccine.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of the study vaccine and will end at the contact at Day 181. See section 8.4 for instructions on reporting of pregnancies.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 15.

Table 15 Reporting periods for collecting safety information

Event	Screening	Visit 1	Day 7	Visit 2	Day 30	Visit 3	Visit 4	Visit 5	Contact
		Day 1	end of 7-day FU	Day 8	end of 30-day FU	Day 31	Day 61	Day 91	Day 181 Study conclusion
Solicited local and general AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
Serious adverse events									
SAEs related to study participation* or concurrent GSK medication/vaccine									
Pregnancies									

*i.e. SAEs related to study participation will be collected as from informed consent signing. AE = Adverse event; FU = Follow-up; SAE = Serious adverse event

Type	Solicited adverse events /Unsolicited adverse events/ Serious adverse events
Method of 'solicited' follow-up	Diary cards
Method of 'unsolicited' follow-up	Diary cards/Questioning at study visits
Method for reporting SAEs	Electronic Expedited Adverse Events Report

8.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 15. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccines, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.3. Evaluation of adverse events and serious adverse events

8.3.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as: '*Have you felt different in any way since receiving the vaccine(s) or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 16 Intensity scales for solicited adverse events

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever(defined as temperature ≥ 38°C /100.4°F)*		Record temperature in °C/°F Temperature will be analysed in 0.5°C increments from ≥ 38.0°C /100.4°F) Grade 3 fever is defined as > 39.0°C /102.2°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

* Fever is defined as temperature ≥ 38.0°C/100.4°F [Marcy, 2004] regardless of the location of measurement (oral is preferred)

The maximum intensity of local injection site (redness and swelling) will be scored at GSK Biologicals as follows:

0 : ≤ 20 mm
1 : > 20 mm to ≤50 mm
2 : > 50 mm to ≤100 mm
3 : >100 mm

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. Such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccines and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccines will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccine administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question: *Is there a reasonable possibility that the AE may have been caused by the investigational vaccine?*

YES:	There is a reasonable possibility that the study vaccination contributed to the AE.
NO:	There is no reasonable possibility that the AE is causally related to study vaccination. There are other, more likely causes and study vaccination is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine(s), if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.3.3.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if she received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.4. Reporting of serious adverse events, pregnancies and other events

8.4.1. Prompt reporting of serious adverse events, pregnancies and other events to GSK

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pregnancy.

Table 17 Timeframes for submitting serious adverse event and pregnancy to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	Electronic SAE report	24 hours*	Electronic SAE report
Pregnancies	2 weeks*	Electronic pregnancy report	2 weeks*	Electronic pregnancy report

*Timeframe allowed after receipt or awareness of the information.
‡The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.4.2. Contact information for reporting serious adverse events and pregnancies

Study Contact for Reporting SAEs and pregnancies
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs and pregnancies
24 hour and 7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US sites: Fax: PPD or PPD Email address: PPD US sites only: Fax: PPD

8.4.3. Completion and transmission of SAE reports to GSK

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.4.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Event Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.4.4. Completion and transmission of pregnancy reports to GSK

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery should be estimated by ultrasound examination and recorded in the pregnancy report.

8.4.5. Updating of SAE and pregnancy information after removal of write access to the subject's eCRF

When additional SAE or pregnancy information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 17.

8.4.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for (a) SAE(s) that is/are both attributable to the study vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.5. Follow-up of adverse events, serious adverse events, and pregnancies

8.5.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK (within 24 hours for SAEs; refer to Table 17).

All AEs/SAEs documented at a previous visit and designated as either on-going, not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits until the end of the study.

8.5.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

8.5.3. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as a SAE.

8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 6.6)

8.7. Unblinding

GSK's policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the investigational vaccines, prior to regulatory reporting. The GSK's Central Safety Physician is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 8.4.1).

8.8. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK On-call Central Safety Physician (or Backup) if he/she needs medical advice or needs the support of GSK to perform the unblinding (i.e. he/she cannot access SBIR).

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK.

GSK Biologicals' Contact information for Emergency Unblinding 24/24 hour and 7/7 day availability
GSK Biologicals' Central Safety Physician: Outside US: PPD (GSK Biologicals Central Safety Physician on-call) For US Only: PPD (GSK Biologicals Central Safety Physician on-call) **GSK Biologicals' Central Safety Physician Back-up:** Outside US: PPD For US Only: PPD **Emergency Unblinding Documentation Form transmission:** Outside US Fax: PPD or PPD For US Only: Fax: PPD

8.9. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the clinical study. The investigator (or designate) must therefore provide a "subject card" to each subject.

In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times during the study duration.

8.10. Holding rules and safety monitoring

8.10.1. Safety review team (SRT)

The SRT includes as core members the GSK's Central Safety Physician, Central Safety Scientist, the Clinical and Epidemiology Project Lead (CEPL), Epidemiologist, Clinical Regulatory Affairs representative and the Biostatistician of the project. The SRT is responsible for on-going safety monitoring of the entire project and will meet on a regular basis. In order to keep all people involved in the conduct, cleaning and final analysis of the study blinded, the SRT will monitor safety in a **blinded** manner.

In addition to the existing SRT, unblinded safety evaluations will be performed by an iSRC at regular intervals and *ad hoc* as needed. The SRT will inform the iSRC about any potential safety concern relevant to the study and vice versa.

8.10.2. Internal Safety Review Committee (iSRC) Evaluation

As this will be the first time that the RSV maternal vaccine will be administered in humans, the study will enrol subjects in two steps with randomisation to all dose levels from the start (see also Figure 1). Safety monitoring will be performed by an iSRC, authorised by the GSK's Vaccines Safety Monitoring Board (VSMB), and holding rules have been established to ensure the safety of the subjects in the study.

The iSRC will include the following GSK personnel: a Safety Physician (Vaccines Clinical Safety and Pharmacovigilance representative), a Clinician (CEPL or CRDL), and a Statistician, all external to the study/project and with no conflicts of interest in the outcome of the study. The GSK Safety Physician will act as the Chair of the iSRC. Additionally, the iSRC will have (a) *ad hoc*, non-voting member(s): (an) independent statistician(s) in charge of providing unblinded data to the iSRC.

This study has 3 planned iSRC reviews.

Only if no safety signal is observed during each of the 2 (Day 8 and Day 31) planned safety evaluations after the first 12% of subjects have been enrolled (Step 1) [See Figure 1 and Figure 2], the screening and enrolment/vaccination of the remaining subjects (Step 2) can start.

Another iSRC review is planned to review the safety data up to at least Day 91 and immunogenicity data up to at least Day 31 for all subjects (Step 1 and Step 2) enrolled in the study.

In addition to the above planned iSRC evaluations, *ad hoc* iSRC reviews can be organized, as deemed necessary at any time during the study.

During the planned (and any *ad-hoc*, if applicable) iSRC safety evaluations, the iSRC will review all available safety data in an **unblinded** manner, while taking into account any other findings that could have an impact on the safety of the subjects, and will determine whether there is a safety signal or not.

Favourable outcome of the safety reviews will be documented and provided in writing to the RSV study team and investigator(s).

If a safety signal is observed during the planned safety evaluations or during *ad hoc* reviews, the iSRC Chair is responsible for urgent communication and escalation of the concern to the GSK's Chief Medical Officer (CMO), who may choose to involve the VSMB or VSMB sub-team, and will communicate the outcome to the study team. The CMO will then decide during an *ad hoc* meeting whether to suspend, modify or continue the conduct of the study.

Already vaccinated subjects will continue with all planned visits, including the capture of all safety data. However, further enrolment/vaccination cannot proceed until CMO (with or without the involvement of VSMB) review and corresponding outcome is available.

The decision of the GSK's iSRC will be documented and provided in writing to the Primary Contact for the study (study CRDL) who will ensure further communication of the outcome to investigator(s). Ethics Committees and Competent Authorities will also be notified, as applicable.

Details about the working procedures of the iSRC will be documented in an iSRC Charter.

8.10.3. Holding rules

The safety holding rules 1a through 1d, as defined in Table 18, will be applied throughout the enrollment period of the study. In addition, the safety holding rules 2a through 2c will be applied for the iSRC reviews.

Table 18 Study holding rules

Holding Rule	Event	Number of Subjects per group/ % of subjects per group
1a	Death or any life-threatening **SAE**	≥ 1
1b	Any non-life threatening SAE that cannot reasonably be attributed to a cause other than vaccination	≥ 1
1c	Any **withdrawal** from the study (by investigator or subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination	≥ 1
1d	Any local or general solicited AE leading to **hospitalization**, or **fever > 40°C** (104°F) that cannot reasonably be attributed to a cause other than vaccination, or **necrosis** at the injection site, within the 7-day (day 1-7) post-vaccination period	≥ 1
2a	Any **Grade 3 solicited local** AE lasting 48h or more in an investigational group, within the 7-day (day 1-7) post-vaccination period	≥3 AND ≥20%
2b	Any **Grade 3 solicited general** AE lasting 48h or more in an investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (day 1-7) post-vaccination period	≥3 AND ≥20%
2c	Any **Grade 3 unsolicited** AE in an investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (day 1-7) post-vaccination period OR Any Grade 3 abnormality in pre-specified hematological or biochemical **laboratory parameters** in an investigational group, that cannot reasonably be attributed to a cause other than vaccination, at day 8 post-vaccination [1]	≥3 AND ≥20%

[1] Grading of laboratory parameters will be based on the FDA Guidance for Industry [APPENDIX C]"Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

8.10.4. Risk assessment

Figure 3 Risk assessment curve for one formulation based on the proposed safety holding rules after 15 subjects/group at step 1

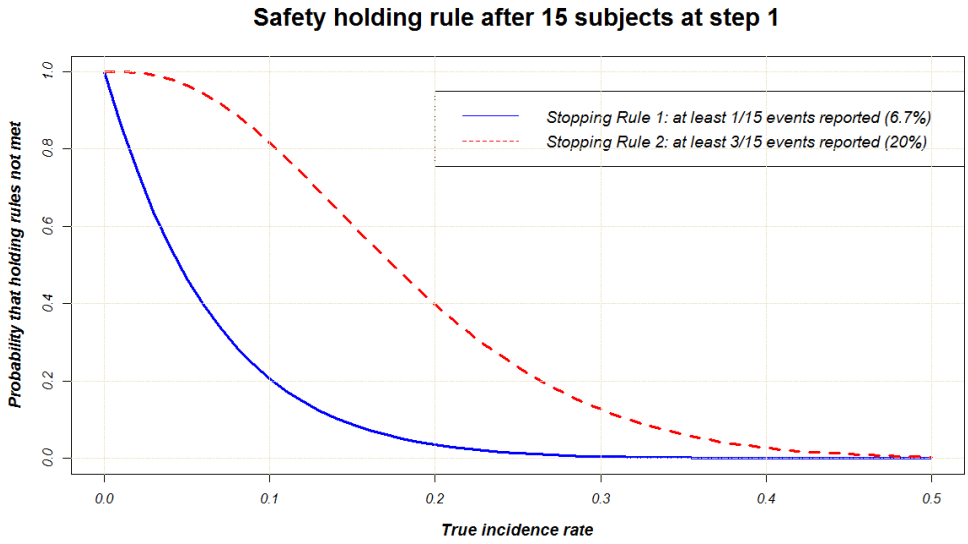


Figure 3 above illustrates that, with 15 subjects per group:

- Each holding rule 1 (a-d) has more than 40% chance of not being met for a vaccine with a true incidence rate below 5% and has more than 90% chance of being met for a vaccine with a true incidence rate above 20%.
- Each holding rule 2 (a-c) has more than 80% chance of not being met for a vaccine with a true incidence rate below 10% and more than 80% chance of being met for a vaccine with a true incidence rate above 30%.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who is available for Contact 1 at Day 181 foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who is not available for Contact 1 at Day 181 foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make at least 3 documented attempts (e.g. 2 phone calls and a letter sent by certified mail to the last known address) to contact those subjects who do not return for scheduled visits and/or are not available for Contact 1 at Day 181.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.

- Lost to follow-up.
- Sponsor study termination.
- Other (specify).

*In case a subject is withdrawn from the study because she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as a result of a SAE/AE until resolution of the event (see Section 8.5.2).

9.3. Screening Failures

Screening failures are defined as subjects who are withdrawn from the study after giving informed consent, but who do not meet the inclusion and exclusion criteria.

The following information will be collected for screening failures:

- Informed consent.
- Inclusion/Exclusion Criteria.
- Demographic Data.
- Physical Examination.
- Blood Sample for haematology/biochemistry.
- Pregnancy test results.
- SAEs related to study participation or any fatal SAE.
- Screening conclusion.

In order to allow a proper control of recruitment and not jeopardize the enrolment of eligible subjects into the study, as soon a subject is identified as being a screening failure, the site staff will access SBIR and withdraw that subject from the application.

9.4. Extension study

During the study conclusion contact (Contact 1 / Day 181) the investigator will re-confirm a subject's interest to participate in a booster /re-vaccination study and the corresponding information will be reported in the eCRF.

If a subject is not interested in participating in the booster study the reason for refusal will be documented in the subject's eCRF (refer to Section(s) 5.6.18 and 5.6.19).

10. STATISTICAL METHODS

10.1. Primary endpoints

- Occurrence of any adverse events (AEs) from vaccination during a 30-day follow-up period, for all subjects in all groups:
  - Occurrence of each solicited local and general symptom during a 7-day follow-up period.
  - Occurrence of any unsolicited AE during a 30-day follow-up period.
  - Occurrence of Serious AEs during a 30-day follow-up period.
  - Occurrence of any haematological (Leukocytes, Neutrophils, Lymphocytes, Eosinophils, Haemoglobin, Platelets) and biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen [BUN]) laboratory abnormalities at Day 8 and Day 31.

10.2. Secondary endpoints

- Occurrence of SAEs from vaccination up to Day 91 and up to Day 181 for all subjects, in all groups.
- Humoral immune response to the investigational vaccine at Day 8, Day 31, Day 61 and Day 91 for all subjects in each investigational RSV vaccine group
  - RSV-A neutralising antibody (Nab) titres
  - RSVPreF3 IgG antibody concentrations

10.3. Tertiary endpoints

Additional humoral response which may include but not limited to, RSVPreF3 specific IgG1 subclass antibody concentrations, RSV-B neutralising antibody titres, antibody competing for binding to specific epitopes on RSVPreF3 and antibody concentrations to residual host cell proteins in the RSVPreF3 vaccines

10.4. Determination of sample size

This section provides justification of sample size in terms of safety and immunogenicity.

Table 19 illustrates the precision with exact 95% confidence interval on the percentage of subjects with AEs following vaccination with 125 subjects per group. If an AE is not observed in a given treatment group, we are 95% confident that the true incidence rate of an AE is less than or equal to 2.9%, in the treatment group. Furthermore, a sample size of 125 subjects per group provides a probability of 80% or 90% to observe at least one AE if the true incidence rate is 1.3% or 1.8% respectively.

Table 19 Exact 95% confidence interval on the percentage of subjects with adverse events following vaccination for 125 subjects per group

Number (%) of subjects with an AE	Exact 95% Confidence Interval	
	Lower Limit (%)	Upper Limit (%)
0 (0%)	0.00	2.9
13 (10%)	5.4	16.6
25 (20%)	13.4	28.1
38 (30%)	22.1	38.8
50 (40%)	31.3	49.1
63 (50%)	40.9	59.1
75 (60%)	50.9	68.7
88 (70%)	61.2	77.9
100 (80%)	71.9	86.6
113 (90%)	83.4	94.6
125 (100%)	97.1	100

CI = confidence interval; LL/UL = lower/upper limit
Exact 95% CI computed based on Clopper/Pearson formula

Based on the results of Day 30 analysis from previous RSV vaccine studies, the standard deviation (SD) of RSV-A Nab titre is approximately 0.4 on its log10 transformation.

Table 20 (below) presents the precision estimation on fold increases in RSV-A Nab titres between two investigational RSV vaccine dose groups, when the sample size is 125 subjects/group, with a range of SD 0.3-0.5 and 95% confidence interval for assumed fold increases of 1.3-2.

Assuming a 2-fold increase of RSV-A Nab between the high and low dose groups, with 125 subjects per group, the 95% confidence interval on the fold increase will be (1.5, 2.67) if a standard deviation of log10 transformed RSV-A Nab of 0.5 is assumed. There is a very small (0.3%) chance that the SD will be larger than 0.5 assuming a chi-square distribution with degree of freedom 124 and mean 0.4.

The power to detect 1.5 fold increase between two groups using one-sided Z test with 2.5% significant level will be at least 90% with SD 0.4 and 80% with SD 0.5 assumed.

The power to detect 1.3 fold increase between two groups using one-sided Z test with 2.5% significant level will be 85% with SD 0.3 and 62% with SD 0.4 assumed.

Table 20 Precision Estimation

Fold increase btw 2 groups	No. of Subjects per group	SD**	Precision*	95% CI LL	95% CI UL
1.3	125:125	0.3	0.075	1.09	1.55
1.3	125:125	0.4	0.1	1.03	1.64
1.3	125:125	0.5	0.125	0.97	1.73
1.5	125:125	0.3	0.075	1.26	1.78
1.5	125:125	0.4	0.11	1.19	1.89
1.5	125:125	0.5	0.125	1.12	2
2	125:125	0.3	0.075	1.68	2.38
2	125:125	0.4	0.1	1.59	2.52
2	125:125	0.5	0.125	1.5	2.67

*Precision estimation using PASS 12.0.2 (Confidence Interval for two means), LL: Lower Limit, UL: Upper Limit
**Standard deviation of $\log_{10}$ of RSV-A Nab titre. The highest standard deviation observed 30 days after vaccination in a previous GSK RSV study was 0.4.

10.5. Cohorts for Analyses

In order to align to ICH and CDISC terminology, the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per Protocol Set (PPS) respectively. Two cohorts will be defined for the purpose of the analysis: the ES and the PPS for analysis of immunogenicity. All analyses will be performed per treatment actually administered.

10.5.1. Exposed Set (ES)

The ES will include all subjects with study vaccine administration documented:

- A **safety** analysis based on the ES will include all vaccinated subjects.
- An **immunogenicity** analysis based on the ES will include all vaccinated subjects for whom immunogenicity data are available.

10.5.2. Per-protocol set (PPS) for analysis of immunogenicity

The PPS for immunogenicity will be defined by time-point and will include all vaccinated subjects:

- Meeting all eligibility criteria (i.e. no protocol violation linked to the inclusion/ exclusion criteria, including age).
- Who received the study vaccine according to protocol procedures.
- Who did not receive a concomitant vaccination/medication/product leading to elimination from the PPS analysis up to the corresponding time-point as described in Section 6.6 of the Protocol.

- Who did not present with an intercurrent medical condition leading to elimination from the PPS analysis up to the corresponding time-point, as described in Section 6.7 of the Protocol.
- Who complied with the post-vaccination immunogenicity blood sampling schedule at the corresponding time-point, as specified in Table 6 of the Protocol.
- For whom post-vaccination immunogenicity results are available for at least 1 assay at the corresponding time-point, as specified in Table 10 of the Protocol.

When presenting different time-points, the PPS for immunogenicity will be adapted for each time-point (Day 8, Day 31, Day 61 and Day 91).

10.6. Derived and transformed data

The study groups will be defined by treatment actually administered.

For a given subject and a given demographic variable, missing measurements will not be replaced.

Safety

- For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed).
- For analysis of unsolicited adverse events (including SAEs) categorized by primary Medical Dictionary for Regulatory Activities (MedDRA) term, all vaccinated subjects will be considered. Subjects who did not report the event will be considered as subjects without the event.
- For the analysis of concomitant medications, all vaccinated subjects will be considered and analysis will be performed on the ES. Subjects who did not report the concomitant medication will be considered as subjects without concomitant medication.

Immunogenicity

- For a given subject and given immunogenicity measurements, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- A seronegative subject is a subject whose antibody titre/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titre/concentration is greater than or equal to the cut-off value of the assay.
- The Geometric Mean Titres/Concentrations(GMT/GMCs) calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. The cut off values are defined by the laboratory before the analysis and will be described in the Statistical Analysis Plan (SAP).

- In order to compute fold increase of antibody titres/concentrations (ratio) between post-vaccination and pre-vaccination titres/concentrations, antibody titres/concentrations below the assay cut-off will be given an arbitrary value of half the cut-off.
- The handling of data below the assay cut offs for GMT/GMC calculations will be described in the SAP.

10.7. Analysis of demographics

The analysis of demographics will be performed on the ES and on the PPS for immunogenicity.

Demographic characteristics such as age at vaccination in years, race, ethnicity, vital signs and cohort description will be summarised by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as race.
- Mean, median, standard error and range will be provided for continuous data such as age.

The distribution of subjects will be tabulated as a whole and per group and for each age category (18 - 32 years and 33 - 45 years).

Withdrawal status will be summarised by group using descriptive statistics:

- The number of subjects enrolled into the study as well as the number of subjects excluded from PPS analyses will be tabulated.
- The number of withdrawn subjects will be tabulated according to the reason for withdrawal.

10.8. Analysis of safety

10.8.1. Within groups assessment

The primary analysis of safety will be performed on the ES. The percentage of subjects with at least one **local AE** (solicited and unsolicited), with at least one **general AE** (solicited and unsolicited) and with any AE during the 7-day or 30-day follow-up period after vaccination will be tabulated with exact 95% CI. The same computations will be done for any ≥ Grade 2 AEs, for any AEs considered related to vaccination, for any Grade 3 AEs considered related to vaccination and for AEs resulting in medically attended visit.

The percentage of subjects reporting each individual **solicited local AE** (any, each grade, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be tabulated based on maximum intensity per subject for each study vaccine group. The percentage of subjects reporting each individual **solicited general AE** (any, each grade, any related, any Grade 2 related, any Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period after vaccination will be based on maximum intensity per subject for each study vaccine group.

For fever during the 7-day follow-up period after vaccination, the number and percentage of subjects reporting any fever (i.e., temperature ≥38 °C) and fever by half degree (°C) cumulative increments will be reported. Similar tabulations will be performed for causally related fever, Grade 3 causally related fever and fever resulting in a medically attended visit. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after vaccination.

The percentage of subjects with any **unsolicited** symptoms within 30 days after vaccination with its exact 95% CI will be tabulated by group and by MedDRA preferred term. Similar tabulation will be done for Grade 3 unsolicited symptoms, for any causally related unsolicited symptoms, for Grade 3 causally related unsolicited symptoms and for unsolicited symptoms resulting in a medically attended visit (the verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term).

SAEs reported throughout the study will be described in detail.

Pregnancy exposures throughout the study and pregnancy outcomes will be described in detail (if applicable).

The percentage of subjects using **concomitant medication** (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (Day 1 - 7), 30 days follow-up (Day 1 – 30), between Day 1 – Day 91 and between Day 1- Day 181 after vaccination will be summarized by group. For all subjects in each group and each **haematology and biochemistry** parameter:

- The percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated for each time point.
- The maximum grading post-vaccination (from Day 8 to Day 31) versus baseline (Screening) and the percentage of subjects with laboratory parameters above or equal to Grade 1, Grade 2, Grade 3 and Grade 4 will be tabulated (Grades will be based on the FDA Guidance for Industry “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”, see APPENDIX C of the Protocol: FDA toxicity grading scale. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

10.9. Analysis of immunogenicity

The analysis will be performed on the applicable PPS cohort for immunogenicity and, if in any group the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is ≥5%, a second analysis will be performed on the ES.

10.9.1. Within groups assessment

Humoral Immune response to RSV vaccine

For each group, at each time point that blood samples are collected and for each assay (Anti-RSV-A Nab and RSVPreF3 IgG) (unless specified otherwise):

- GMTs/GMCs will be tabulated with 95% CI based on log-transformed values and represented graphically.
- Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.
- Pre- and Post- Nab titres/concentrations will be displayed using reverse cumulative curves.
- The distributions of Nab titres (Percentage of subjects greater than or equal to specified thresholds) will be tabulated.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using *scatt*er plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody titres/concentrations post-vaccination over pre-vaccination will be tabulated with 95% CI.
- Distribution of the fold increase of the antibody titres will be tabulated.
- The kinetics of individual antibody titres/concentrations will be plotted as a function of time for subjects with results available at all time points.
- An analysis of variance model for repeated measures will be fitted to assess the mean profile in each group.

If deemed necessary, the same analyses may be performed by age category (18 - 32 years and 33 - 45 years).

Fold increase of RSVPreF3 immunoglobulin G (IgG) antibody concentrations over fold increase of RSV-A Nab titres will be calculated. This analysis will include calculation on:

- Geometric mean ratios with corresponding 95% CIs of RSVPreF3 immunoglobulin G (IgG) antibody concentration over anti-RSV-A plaque reduction Nab titres at pre-vaccination for each group and
- Geometric mean ratios with corresponding 95% CIs of fold increase post/pre (Day 8, Day 31, Day 61 and Day 91/Day 1) between RSVPreF3 immunoglobulin G (IgG) antibody concentration and anti-RSV-A plaque reduction Nab titres for each group.

Details of statistical analysis on exploratory endpoints will be described in Statistical Analysis Plan (SAP).

10.9.2. Between groups assessment

Exploratory comparisons will be performed for RSV-A Nab titres and RSVPreF3 IgG antibody concentrations between the different RSV vaccine groups at Day 31. If deemed necessary this exploratory comparisons may also be done at other time-points.

- The three RSV formulations will be first compared to the Placebo in order to identify groups whose means are significantly different from the mean of the Placebo group, (alpha=2.5%, Dunnett's adjustment test for multiplicity).
- Estimation of GMT/GMC ratios between groups with corresponding 95% CI using an ANCOVA model on the logarithm10 transformation of the titres/concentrations. This model includes:
  - The vaccine group as the fixed effect
  - The pre-vaccination titre/concentration as the covariate
  - Age groups (18 - 32 years and 33 - 45 years) and/or centre as the categorical covariate if deemed necessary
- GMT/GMC ratios with corresponding 95% CI will be computed between the RSV vaccine groups
- Linear and quadratic trend of dose response will be tested using appropriate contrasts.

10.10. Interpretation of analyses

All comparative analyses will be descriptive with the aim to characterise the difference in reactogenicity/immunogenicity between groups. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

10.11. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.11.1. Sequence of analyses

In preparation of the three planned iSRC evaluations, analyses of all available safety data, and if applicable all available immunogenicity data will be performed (see Section 8.10.2 for more information). These analyses will be done by an unblinded statistician outside GSK to maintain the study blinding, and will be documented in the statistical analysis report. Only the outcome of the iSRC review will be communicated to the RSV study team (no safety signal or safety signal). No clinical study report will be written at this time.

In order to obtain early immunogenicity data of the different formulations of the investigational RSV Maternal vaccine, an interim analysis will be performed when immunogenicity data up to Day 31 for the Step 1 subjects becomes available. This analysis will be performed on data as available (i.e partially clean or non-clean data).

To ensure the study team remains blinded, the analysis will be performed by an unblinded statistician outside GSK and the iSRC will act as a firewall team, to review the aggregated summaries for risk of unblinding of individual subjects, before these are released to the team.

For this analysis only a statistical report will be prepared

The final statistical analyses will be performed in 2 steps:

- A first analysis will be performed when all safety and immunogenicity data up to at least Day 91 is available in all subjects. At this point, the study statistician will be unblinded (i.e. will have access to the individual subject treatment assignments), but no individual listings will be provided to investigators until the study report. However, summary results may lead to the unblinding of some specific subjects in case an event occurred only in one group; steps will be taken to minimize this risk.
- The final analysis covering all primary and secondary endpoints as well as any evaluated tertiary endpoint(s) will be performed when all data up to study conclusion are available. A clinical study report will only be written at this stage and individual listings will be provided as part of it.

If the data for tertiary endpoints becomes available at a later stage, (an) additional analysis/analyses will be performed. These data will be documented in annex(es) to the study report and will be made available to the investigators at that time.

10.11.2. Statistical considerations for interim analyses

All analyses are descriptive. Therefore, the conduct of interim analyses has no impact on interpretation of study results.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, public disclosure requirements and publications must be fulfilled.

11.1. Case Report Form/electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database

or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 30 years after completion of the study report.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date and to have

secondary endpoint disclosed at latest 12 months after the last subject last visit as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures and relevant reports, and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

12. COUNTRY SPECIFIC REQUIREMENTS

12.1. Requirements for Germany

Explanatory statement concerning Gender Distribution (Article 7, paragraph 2 (12) of the German GCP ORDER)

GSK's investigational RSV maternal vaccine (GSK3888550A) is developed for prevention of severe RSV disease in infants by transfer of maternal antibodies following active single dose immunisation of pregnant women between 28 and 34 weeks of gestation. Therefore, only women will be recruited in the RSV MAT-001 study.

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APPENDIX A LABORATORY ASSAYS

Descriptions of available assays are provided below. Assay descriptions could be subject to change, due to assay re-development and/or qualification. Assay Standard Operating Procedures and characterization/qualification reports will be submitted to FDA upon availability.

RSV A/B neutralization assay

The serum neutralization assay is a functional assay that measures the ability of serum antibodies to neutralize RSV entry and replication in a host cell line.

First, virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long) or RSV-B strain (B18537) with serial dilutions of the test serum. Then, the serum-virus mixture is transferred onto a monolayer of Vero cells (African Green Monkey, kidney, *Cercopitheus aethiops*, ATCC CCL-81) and incubated for three days to allow infection of Vero cells by non-neutralized viruses and the formation of plaques in the cell monolayer. Following the fixation period, RSV-infected cells are detected using a primary antibody directed against RSV (anti-RSV IgG) and a secondary antibody conjugated horse-radish peroxidase (HRP), allowing the visualization of plaques after coloration with TrueBlue™ peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with Axiovision software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at that dilution and the number of plaques in the virus control wells (no serum added). The serum Nab titres is expressed in ED60 (Estimated Dilution 60) and corresponds to the inverse of the interpolated serum dilution that yields a 60% reduction in the number of plaques compared to the virus control wells as described by others [Barbas, 1992; Bates, 2014].

RSVPreF3 ELISA

The RSVPreF3 IgG and IgG1 ELISA's are under development. The assays will be based on an indirect ELISA allowing the detection and the quantification of total IgG or IgG1 antibodies directed against RSVPreF3 in human serum samples.

The principle of this assay will be as follows: RSVPreF3 antigen will be adsorbed onto a 96-well polystyrene microplate. After a washing and a blocking step, dilutions of serum samples, controls and standards will be added to the coated microplate. A reference standard curve will be prepared using a pool of commercial human serum containing anti-RSV antibodies. After incubation, the microplate will be washed to remove unbound primary antibodies. Bound IgG or IgG1 will be detected by the addition of a secondary anti-human antibody conjugated to HRP. Bound antibodies are quantified by the addition of the HRP substrate, tetramethylbenzidine and hydrogen peroxide, whereby a colored product develops proportionally to the amount of anti-RSVPreF3 IgG or IgG1 antibodies present in the serum sample. The optical density of each sample dilution is then interpolated on the reference standard. The corresponding antibody concentration, corrected for the dilution factor, is expressed in arbitrary ELISA Laboratory Units per milliliter (ELU/mL).

Epitope specific competition assay

Epitope specific competition assays are based on the competitive binding between a labelled epitope-specific monoclonal antibody and non-labelled antibodies present in serum samples and targeting the same epitope on a coated antigen. A competition assay specific for the site 0 epitope, using RSVPreF3 protein as coating antigen, is under development.

The principle of competition assays is as follows: The RSVPreF3 protein antigen will be coated onto an assay plate. After blocking, dilutions of control serum or sample, as well as labelled, epitope-specific, monoclonal antibody, are added to the coated plate. If epitope-specific antibodies are present in serum samples, they will compete with the monoclonal antibody for binding to the epitope on the antigen-coated plate. After washing, the bound, labelled antibody is then quantitated using a validated chromogenic detection system. The intensity of the detected signal is inversely proportional to the concentration of the epitope-specific antibodies present in the sample.

The antibody concentrations are calculated for each control and sample by transforming the OD values corresponding to the dilutions into a % competition value, and from this, the epitope-specific antibody concentration of the samples and controls is calculated.

References:

Barbas, C. F., J. E. Crowe et al. “Human Monoclonal Fab Fragments Derived from a Combinatorial Library Bind to Respiratory Syncytial Virus F Glycoprotein and Neutralize Infectivity.” Proceedings of the National Academy of Sciences of the United States of America 89, no. 21 (November 1, 1992): 10164–68.

Bates, John T., Christopher J. Keefer et al. “Escape from Neutralization by the Respiratory Syncytial Virus-Specific Neutralising Monoclonal Antibody Palivizumab Is Driven by Changes in on-Rate of Binding to the Fusion Protein.” Virology 454–455 (April 2014): 139–44.

APPENDIX B CLINICAL LABORATORIES

The samples for Haematology and Biochemistry assessment as well as the pregnancy status of the subject will be tested locally at the investigators' laboratory.

The samples for immunogenicity assessment will be tested at GSK Biologicals' laboratories or at outsourced laboratories designated by GSK.

Table 21 GSK Biologicals' laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	**Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart – Belgium**
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	**Avenue Fleming, 20 - B-1300 Wavre - Belgium**

Table 22 Outsourced laboratories

Laboratory	Address
NÉOMED-LABS Inc.	525, Cartier Ouest Laval Quebec Canada H7V 3S8

APPENDIX C FDA GUIDANCE FOR INDUSTRY: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS (SEPTEMBER 2007)

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

- **INTRODUCTION**

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs) (see, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of AEs, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.

- **BACKGROUND**

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

- **TOXICITY GRADING SCALE TABLES**

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, and 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorise adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

- **Tables for Clinical Abnormalities**

Note from the sponsor: The tables in this section of the guidance will not be used in this particular study. Instead, the parameters as provided in the study protocol are to be used.

- **Tables for Laboratory Abnormalities**

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

Only those parameters that will be assessed as part of the study have been maintained in the tables below.

Table 23 FDA toxicity grading scales for hematology/biochemistry parameters

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	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

ULN = upper limit of the normal range.
* 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.
** 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.

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
WBC Increase - cell/mm3	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm3	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm3	650 – 1 500	1 501 - 5 000	> 5 000	Hypereosinophilic
Platelets Decreased - cell/mm3	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.

- **REFERENCES for the Appendix C**

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)
2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)
3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)
4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)
5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)
6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.