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

Primary Study vaccine(s)/product(s) and number(s)	GlaxoSmithKline (GSK) Biologicals' investigational respiratory syncytial virus (RSV) vaccine (GSK3003891A)
Other Study vaccine(s)/product(s)	Placebo
eTrack study number and Abbreviated Title	204812 (RSV F-021)
Investigational New Drug (IND) number	15487
EudraCT number	2016-001135-12
Date of protocol	Final Version 3 16 August 2016
Date of protocol amendment	Amendment 1 Final 21 August 2017
Title	An observer-blind study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A) administered to healthy women.
Detailed Title	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 - 45 years.
Co-ordinating author(s) **(Amended 31 July 2017)**	• PPD (XPE Pharma & Science for GSK Biologicals) • PPD, ***Senior Science Writer***
Contributing authors **(Amended 31 July 2017)**	• PPD and PPD, Clinical & Epidemiology Project Lead • PPD, PPD, and PPD, Clinical Research & Development Leads • PPD, Lead Statistician • PPD, Project Statistician

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PPD • PPD , , and PPD , Study Delivery Leads

- PPD ***(Aixial for GSK Biologicals) and*** PPD (CVO-Europe for GSK Biologicals), Vaccine Supply Coordinator
- PPD , Clinical Read-Out Team Leader

GSK Biologicals' Protocol DS v 14.1.1

Protocol Amendment 1 Sponsor Signatory Approval

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Sponsor signatory	***Alexander Schmidt*** Clinical & Epidemiology Project Lead
Signature	
Date	

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Protocol Amendment 1 Rationale

Amendment number: Amendment 1

Rationale/background for changes:

The following minor changes and clarifications have been made

- The kit used for multiplex respiratory viral panel testing has been changed.
- Changes to study personnel have been included on the protocol cover page.

Protocol/Protocol Amendment 1 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' investigational vaccines 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, 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.**

eTrack study number and Abbreviated Title	204812 (RSV F-021)
IND number	15487
EudraCT number	2016-001135-12
Date of protocol amendment	Amendment 1 Final 21 August 2017
Detailed Title	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 - 45 years.
Investigator name	_____
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

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 II, randomised, observer-blind, controlled, multi-country study to rank different formulations of GSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 - 45 years.
Indication	Active immunisation of pregnant women during the third trimester of pregnancy to prevent respiratory syncytial virus (RSV) (subtypes A and B)-associated severe lower respiratory tract infection (LRTI) in infants by transfer of maternal antibodies.
Rationale for the study and study design	• **Rationale for the study** The safety/reactogenicity and immunogenicity of 6 different formulations of the PreF-based investigational RSV vaccine (10, 30 and 60 µg of PreF antigen, non-adjuvanted or adjuvanted with aluminium [500 µg]) have been evaluated in a Phase I study in healthy men, aged 18-44 years (study RSV F-001; NCT01905215). No safety signal associated with the investigational RSV vaccines was identified which would preclude further clinical development. Based on data from that Phase I study, the safety/reactogenicity and immunogenicity of 30 µg of non-adjuvanted PreF and 60 µg of non-adjuvanted and aluminium-adjuvanted PreF formulations are currently being evaluated further in non-pregnant women aged 18-45 years (study RSV F-020; NCT02360475). The RSV F-020 study is still ongoing but safety/reactogenicity and immunogenicity data up to 90 days post vaccination are already available for all subjects. Based on these results, the non-adjuvanted 30 µg and 60 µg PreF formulations were selected for further evaluation in the current RSV F-021 study. In addition, the RSV F-021 study will also evaluate a formulation containing 120µg of PreF antigen. This will allow evaluation of a wider antigen dose range to determine if there is a dose response relationship in terms of antibody response at the higher dose range that was not present at the lower range. The purpose of this study is to rank the different vaccine formulations based on safety/reactogenicity and immunogenicity data. The formulations eliciting strong immune responses while maintaining an acceptable safety profile will be considered for further evaluation, including in studies vaccinating pregnant women.

- **Rationale for the study design**

Healthy, non-pregnant women aged 18 - 45 years will be enrolled in this study:

- Women aged 18 - 45 years are selected to match the vaccine's target population, i.e. pregnant women, as closely as possible (gender, age).
- Non-pregnant women are selected to avoid unnecessarily exposing a vulnerable population (pregnant women and the foetuses/children) to a higher dose of the vaccine that has not previously been studied in non-pregnant women.

- **Rationale for the use of placebo**

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

Objectives

Primary

- To rank different formulations of the investigational RSV vaccine based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination (Day 30).

Secondary

- To evaluate the reactogenicity and safety of a single intramuscular dose of the RSV investigational vaccines up to study conclusion.
- To evaluate the immunogenicity of a single intramuscular dose of the RSV investigational vaccines up to 90 days after vaccination (Day 90).
- To further assess the safety of the investigational RSV vaccines by evaluating whether a single dose of the vaccines induces antibodies against the residual host cell protein neogenin (NEO) up to 1 month post-vaccination (Day 30)
- To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion.

Tertiary

- If deemed necessary, to further characterise the immune response of a single intramuscular dose of the RSV investigational vaccines.

Study design

- **Experimental design**: Phase II, observer-blind, randomised, controlled, multi-country, study with four parallel groups.
- **Duration of the study**: the intended duration of the study will be approximately 1 year from Visit 1 to study conclusion (Day 360).
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 5 (Day 90).
  - Epoch 002 : Follow-up phase starting one day after Day 90 and ending at Day 360 contact.
- **Primary completion Date (PCD)**:Visit 3 (Day 30).
- **End of Study (EoS)**: Last testing results released of samples collected at Visit 5 (i.e. last testing results released for the assays related to the primary and secondary endpoints).
- **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
30 PreF	~100	18 - 45 years	x	x
60 PreF	~100	18 - 45 years	x	x
120 PreF	~100	18 - 45 years	x	x
Control	~100	18 - 45 years	x	x

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/ Product name	Study Groups			
		30 PreF	60 PreF	120 PreF	Control
30 µg PreF	PreF-30	X			
	NaCl				
60 µg PreF	PreF-60		X		
	NaCl				
120 µg PreF	PreF-120			X	
	NaCl				
Placebo	Formulation buffer S9b				X

- **Control**: placebo control
- **Vaccination schedule**: One intramuscular vaccination at Day 0.
- **Treatment allocation**: Subjects will be randomisedusing a centralised randomisation system on internet (SBIR) at Day 0. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.

- **Blinding**: Observer-blind in Epoch 001 and single-blind in Epoch 002.

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	single-blind

- **Sampling schedule**:
  - Blood samples for haematology/biochemistry will be collected (~10 mL) from all subjects at Visit 1 (Day 0), Visit 2 (Day 7) Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - Blood samples for humoral immune response evaluation will be collected (~17 mL) from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60) and at Visit 5 (Day 90).
  - Nasal swabs will be collected from subjects in case of a medically attended respiratory tract infection from enrolment (Visit 1) until Contact 3.
- **Type of study**: self-contained
- **Data collection:** Electronic Case Report Form (eCRF).
- **Safety monitoring**: When the first 25% of subjects (i.e. ~100 subjects; ~25 subjects per study group) have been vaccinated, enrolment will be paused until completion of an unblinded review by a GSK internal Safety Review Committee (iSRC). Continuation of study enrolment will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post-vaccination (including Day 7 haematology and biochemistry parameters). In addition, the blinded safety data will be reviewed by GSK Biologicals' Safety Review Team (SRT) on a regular basis throughout the study.

Refer to Section 8.10 for description of safety monitoring.

Number of subjects The target is to enrol approximately 400 eligible women (~100 per group).

Endpoints **Primary**

- Occurrence of AEs from vaccination up to Day 7, for all subjects in each investigational RSV vaccine group:
  - Occurrence of any Grade 2 and Grade 3 general AE

(solicited and unsolicited);

- Occurrence of Grade 2 and Grade 3 fever;
- Occurrence of any vaccine-related SAE.

- Functional antibody titres against RSV at Day 0 and Day 30, for all subjects in each investigational RSV vaccine group.
  - Neutralising antibody titres against RSV-A
- PCA concentrations at Day 0 and Day 30 for all subjects in each investigational RSV vaccine group.

Secondary

- Occurrence of AEs from vaccination up to study conclusion:
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days), for all subjects in all groups;
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days), for all subjects in all groups;
  - Occurrence of any haematological (haemoglobin level, White Blood Cells [WBC], lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (alanine amino-transferase [ALT], aspartate amino-transferase [AST] and creatinine) laboratory abnormality at Day 0, Day 7, Day 30, Day 60 and Day 90 for all subjects in all groups;
  - Occurrence of any SAE, for all subjects in all groups.
- Functional antibody titres against RSV for all subjects in all groups:
  - Neutralising antibody titres against RSV-A at Day 0, Day 30, Day 60 and Day 90;
  - Neutralising antibody titres against RSV-B at Day 0, Day 30, Day 60 and Day 90.
- PCA concentration at Day 0, Day 30, Day 60 and Day 90 for all subjects in all groups.
- Humoral immune response to the residual host cell protein NEO in the investigational RSV vaccine at pre-vaccination (Day 0), and 1 month post-vaccination (Day

30) for all subjects in all groups.

  - Neutralising antibody titres against NEO

- Occurrence of medically attended RSV-associated RTIs up to study conclusion.

Tertiary

See section 5.7.3 for additional testing proposed to further characterise the immune response to the investigational RSV vaccine.

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LIST OF ABBREVIATIONS

AE:	Adverse Event
AIDS:	Acquired Immunodeficiency Syndrome
ANCOVA:	Analysis of Covariance
ALT:	Alanine Aminotransferase
AST:	Aspartate Aminotransferase
ATP:	According-to-Protocol
BLA:	Biologicals License Application
BMI:	Body Mass Index
CEPL:	Clinical and Epidemiology Project Lead
CHO:	Chinese Hamster Ovary
CI:	Confidence Interval
CFR:	Code of Federal Regulations
CLS:	Clinical Laboratory Sciences
CRA:	Clinical Research Associate
CRDL:	Clinical Research and Development Lead
CTR:	Clinical Trail Register
eCRF:	electronic Case Report Form
EGA:	Estimated Gestational Age
EMA:	European Medicines Agency
EoS:	End of Study
ERD:	Enhanced RSV Disease
eTDF:	Electronic Temperature excursion Decision Form
FDA:	Food and Drug Administration, United States of America
FI-RSV:	Formalin-inactivated whole virus RSV vaccine

GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titre
GP:	General Practitioner
GSK:	GlaxoSmithKline
HIV:	Human Immunodeficiency Virus
HRP:	Horse Radish Peroxidase
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on 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
LLOQ:	Lower Limit of Quantification
LMP:	Last Menstrual Period
LRTI:	Lower Respiratory Tract Infection
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MA-RTI:	Medically Attended Respiratory Tract Infection
MedDRA:	Medical Dictionary for Regulatory Activities
NEO:	Neogenin

NIH:	National Institute of Health
pIMD:	Potential Immune-Mediated Disease
PCA:	Palivizumab Competing Antibodies
PCR:	Polymerase Chain Reaction
PreF:	Purified recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation
PCD:	Primary Completion Date
RNA:	Ribonucleic Acid
RSV:	Respiratory syncytial virus
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SAS:	Statistical Analysis System
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SPM:	Study Procedures Manual
SRT:	Safety Review Team
TMB:	Tetramethylbenzidine
TVC:	Total Vaccinated Cohort
VSMB:	Vaccine Safety Monitoring Board
WBC:	White Blood Cells

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 estrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- bilateral current 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; or 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, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

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). In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
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. EoS must be achieved no later than 8 months after LSLV.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are 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 According-to-Protocol (ATP) analysis (see Sections 6.6.2 and 10.5 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
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.
iSRC:	The internal Safety Review Committee is a group of experts (a GSK Biologicals' Safety Physician, a CRDL and a Biostatistician), external to the ongoing study/project and with lack of conflicts of interest in the outcome of the study, who assess the progress of the study and the safety and efficacy data in an unblinded (on a subject level or treatment group level) fashion. 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, the larche. 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.

Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
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.
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.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects.
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.
VSMB:	Vaccine Safety Monitoring Board: an internal GSK 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 and/or medications will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks not owned by the GSK group of companies	Generic description
Synagis (MedImmune LLC.)	Recombinant humanized monoclonal anti-RSV antibody
Allplex (Seegene)	***Respiratory panel assay***

1. INTRODUCTION

1.1. Background

1.1.1. Disease burden

RSV is a 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 temporally focused.

During the first year of life, 50-70% of infants are infected with RSV and essentially all children have had an RSV infection by their third birthday [Hall, 2004]. The risk for *severe* RSV-induced LRTIs is highest in infants below 6 months of age and it is the most common cause of hospitalisation in this age group. Approximately 2% of children < 1 year of age are hospitalized for RSV-associated LRTIs each year in industrialized countries [Boyce, 2000; Deshpande, 2003; Hall, 2009; Holman, 2004; Iwane, 2004; Madhi, 2006; Nair, 2010; Paramore, 2004; Vicente, 2003].

In the early months of life, infants may have protection against RSV through the maternal antibodies transferred to them during pregnancy. High titres of maternally derived RSV-neutralising antibodies [Roca, 2002] have been shown to be inversely associated with the incidence of RSV associated-acute LRTI during the first 6 months of life, whereas incomplete transfer of maternally derived RSV-neutralising antibodies has been implicated in the increased risk of severe RSV infection in preterm infants [de Sierra, 1993].

Previous infection with RSV does not prevent subsequent infections. Re-infection with RSV occurs throughout an individual's lifetime and is common in all age groups [Simoes, 1999; 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 elderly), re-infections can however also lead to severe disease and result in excess mortality [Graham, 2011].

Please refer to the current Investigator Brochure (IB) for information regarding the pre-clinical and clinical studies with the investigational RSV vaccine.

1.1.2. Current management of RSV disease in infants

To date, no vaccine is available for RSV and treatment for RSV disease is administered largely to alleviate symptoms.

The antiviral drug ribavirin is currently the only approved therapy for treatment of RSV disease, but its use is restricted to severe hospitalized cases. Moreover, the efficacy of ribavirin against RSV disease in infants and young children is not well supported by strong evidence, [American Academy of Paediatrics Subcommittee on Diagnosis and Management of Bronchiolitis, 2006; Ventre, 2007].

There is currently no preventive measure available for children who do not present major risk factors for severe RSV disease. 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. *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; Committee on Infectious Diseases and Committee on Fetus and Newborn, 2003].

1.1.3. RSV vaccination strategies

In the late sixties, a formalin-inactivated whole virus RSV (FI-RSV) vaccine tested in clinical trials led to more severe clinical symptoms upon subsequent natural infection with RSV in children under the age of 2 years [Chin, 1969; Fulginiti, 1969; Kapikian, 1969; Kim,1969]. This so-called 'vaccine-induced enhanced RSV disease (ERD)' is believed to have been due to the formalin inactivation step during vaccine production, leading to the induction of low-quality, non-neutralising antibodies in RSV naïve infants [Delgado, 2004]. These antibodies did not neutralise RSV infectivity and contributed to the formation of immune complexes that may have contributed to the severe clinical symptoms and potentially immunopathology of FI-RSV ERD [Polack, 2002]. In addition, it is hypothesized that enhanced RSV disease may have been linked to the induction of a Th2-skewed CD4-T cell immune response [Castilow, 2008]. This experience has led to increased safety monitoring of clinical trials with RSV vaccines.

Another approach to protect young infants against severe RSV disease is by immunising pregnant women to increase the amount of protective RSV-neutralising antibodies transferred to the foetus to offer passive protection of the offspring. Administration of an RSV vaccine to adults (pregnant women in this case), all of whom will have been naturally infected with RSV before, is expected to boost the immunological memory induced by previous natural infections. The risk of vaccine-induced RSV disease is therefore considered negligible. Enhanced respiratory disease has not been observed with the use of *Synagis*.

1.1.3.1. GSK Biologicals' investigational RSV vaccine

GlaxoSmithKline (GSK) Biologicals is currently developing a new RSV investigational vaccine to protect infants against RSV-associated severe LRTI through maternal immunization during the third trimester of pregnancy. GSK Biologicals' RSV vaccine candidate is based on a recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation (PreF). Different formulations of this candidate vaccine, non-adjuvanted or adjuvanted with aluminium, have been evaluated in a Phase I study in healthy men aged 18-44 years (study RSV F-001; NCT01905215) and are currently being evaluated in a Phase II study in healthy non-pregnant women aged 18-45 years (study RSV F-020; NCT02360475). Based on safety and immunogenicity data from study RSV F-001 and up to 90 days post-vaccination from study RSV F-020, aluminium-adjuvanted formulations will not be evaluated further.

1.1.3.2. Other RSV investigational vaccines

Other investigational vaccines based on the RSV F protein have been and are currently tested in clinical trials. In 2014, Novavax, Inc. completed a dose-confirmatory Phase II trial (NCT01960686) in women of childbearing potential age receiving one dose of recombinant F protein micelles combined with aluminium. The candidate vaccine of Novavax, Inc. has been observed to be immunogenic with no safety signals reported. Further, Novavax Inc., has recently announced preliminary results of a Phase II clinical trial (NCT02247726) in healthy third-trimester pregnant women assessing safety and immunogenicity of the same candidate vaccine, as well as the impact of maternal immunization on infant safety through one year of life. The candidate RSV F vaccine was shown to be safe and well-tolerated by the vaccinated subjects. The study demonstrated robust anti-F, Palivizumab competing (PCA) and microneutralising antibody responses in mothers and efficient antibody transfer from mothers to infants. Based on these preliminary results, Novavax, Inc has initiated a Phase III trial (NCT02624947) for further evaluation of this vaccine in pregnant women [Novavax, press release, 2015].

In 2014, Novartis Vaccines & Diagnostics (now GSK Biologicals) started a Phase I clinical trial (NCT02298179) in 288 subjects to assess safety and immunogenicity of RSV F post-fusion protein subunit adjuvanted with aluminium or MF59. Results are expected by end 2017.

Other RSV F protein vaccines are currently in preclinical phase (Crucell, National Institutes of Health [NIH]).

Several other RSV vaccine candidates using different technologies (attenuated virus vaccines from NIH or Medimmune; adenovector-based vaccines from GSK or Crucell) are currently being evaluated in clinical trials. However, those technologies are not compatible with the maternal immunization approach and are tested in the context of paediatric or elderly vaccination.

Besides vaccines, new generation MedImmune monoclonal antibodies with increased potency and extended half-life are currently being evaluated and the most advanced candidate is currently in Phase II.

No RSV vaccine is licensed to date.

1.1.4. GSK Biologicals' investigational RSV vaccine composition

The antigen used in the investigational RSV vaccine is a purified recombinant RSV F protein, engineered to preferentially maintain the pre-fusion conformation (PreF). The F protein has been selected because it is a major surface antigen of the RSV virus that is well conserved among RSV-A and RSV-B subtypes. The RSV F protein pre-fusion conformation is the target of most RSV-neutralising activity in human sera [Corti, 2013]. Moreover, these pre-fusion-specific antibodies targeting antigen binding site ϕ, are substantially more potent compared to the prophylactic monoclonal antibody Palivizumab. Palivizumab targets antigenic site II which is present in both pre- and post-fusion conformations [Ngwuta, 2015].

Based on preclinical experiments and Phase I dose escalation study data (RSV F-001 study; NCT01905215), the PreF antigen has shown to boost neutralising antibodies, which are considered essential for protection against RSV-associated severe disease [Magro, 2012]. No safety signals whϕich would preclude further development were identified in any of the vaccine formulations containing different dosages of the PreF antigen evaluated in the Phase I study. Based on this Phase I data, vaccine formulations containing 10 µg of the PreF antigen were excluded from further development as they were less immunogenic. Boosting of pre-existing RSV-specific neutralising antibodies in adults was further confirmed by the Day 30 post-vaccination data of a Phase II study that evaluated the safety and immunogenicity of 30 µg of non-adjuvanted PreF and 60 µg of non-adjuvanted and aluminium-adjuvanted PreF formulations in non-pregnant women aged 18-45 years (study RSV F-020; NCT02360475). In addition, Day 90 post-vaccination immunogenicity data has recently become available indicating that, although there is a decline in the boosted RSV-specific neutralising antibodies as compared to D30, titres remain well above the baseline. No safety concerns which would preclude further development were identified in this Phase II study up to Day 90 post-vaccination. One SAE of diffuse panbronchiolitis, considered to be related to study vaccine as per investigator's opinion, has been reported. Please refer to the current IB for further details.

Since all adults have been naturally infected with RSV before, it was expected that a strong adjuvant was not needed in these primed individuals and that a non-adjuvanted or an aluminium-adjuvanted PreF antigen would sufficiently boost the pre-existing immune response. Data obtained from the Phase I study (study RSV F-001; NCT01905215) seemed to confirm this assumption because the study results did not show any difference between non-adjuvanted PreF formulations and aluminium-adjuvanted formulations with respect to immune response. In view of the limited number of subjects evaluated in RSV F-001 (~16/group), non-adjuvanted and aluminium-adjuvanted PreF formulations are being evaluated further in study RSV F-020 (NCT02360475) with ~125 subjects/group. The non-adjuvanted PreF antigen formulations have now been selected for further development because data from the RSV F-020 study up to 90 days post-vaccination showed a trend for higher reactogenicity in the aluminium-adjuvanted formulation group, while there was no significant difference in terms of immunogenicity between the different RSV PreF formulations evaluated.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

The main goal of this study is the selection of the final RSV vaccine formulation for potential further evaluation in pregnant woman.

The safety/reactogenicity and immunogenicity of 6 different formulations of the PreF-based investigational RSV vaccine (10, 30 and 60 µg of PreF antigen, non-adjuvanted or adjuvanted with aluminium [500 µg]) have been evaluated in a Phase I study in healthy men, aged 18-44 years (study RSV F-001; NCT01905215). No safety signal associated with the investigational RSV vaccines was identified which would preclude further clinical development. Based on data from that Phase I study, the safety/ reactogenicity and immunogenicity of 30 µg of non-adjuvanted PreF and 60 µg of non-adjuvanted and

aluminium-adjuvanted PreF formulations are currently being evaluated further in non-pregnant women aged 18-45 years (study RSV F-020; NCT02360475).

The RSV F-020 study is still ongoing but safety/reactogenicity and immunogenicity data up to 90 days post-vaccination are already available for all subjects. Based on these results, the non-adjuvanted 30 µg and 60 µg PreF formulations were selected for further evaluation in the current RSV F-021 study. These two formulations are also foreseen to be evaluated in the first study in pregnant women (RSV F-004). In addition, the RSV F-021 study will also evaluate a formulation containing 120µg of PreF antigen. This will allow evaluation of a wider antigen dose range to determine if there is a dose response relationship in terms of antibody response at the higher dose range that was not present at the lower range.

The purpose of this study is to rank the different vaccine formulations based on safety/reactogenicity and immunogenicity data. The formulations eliciting strong immune responses while maintaining an acceptable safety profile will be considered for further evaluation, including in studies vaccinating pregnant women.

It is likely that the RSV vaccine may need to be administered during each pregnancy to further boost immunogenicity in the pregnant woman and achieve protective anti-RSV 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 F-021 and who were part of the selected vaccine group or the control group may be invited to a booster study (study RSV F-021B).

1.2.2. Rationale for the study design

Healthy, non-pregnant women aged 18 - 45 years will be enrolled in this study:

- Women aged 18 - 45 years are selected to match the vaccine's target population, i.e. pregnant women, as closely as possible (gender, age).
- Non-pregnant women are selected to avoid unnecessarily exposing a vulnerable population (pregnant women and the foetuses/children) to a higher dose of the vaccine that has not previously been studied in non-pregnant women.

1.2.3. Rationale for the use of placebo

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

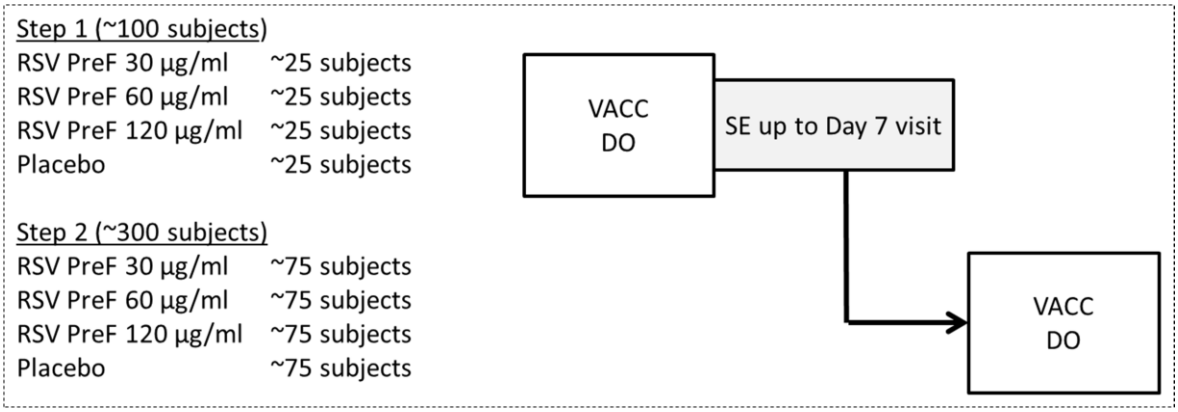
1.2.4. Safety considerations

Safety data for the non-adjuvanted and aluminium (500 µg)-adjuvanted 30 and 60 µg PreF formulations up to one year post-vaccination from study RSV F-001 as well as safety/reactogenicity data for the non-adjuvanted 30 and 60 µg formulations and the aluminium (500 µg)-adjuvanted 60 µg formulation up to 90 days post-vaccination from study RSV F-020 are currently available. No safety concern which would preclude further development has been identified for any of the RSV groups in either study.

Additional safety data for these vaccine formulations from study RSV F-020 or from other ongoing/planned studies might also be available, prior to the start of the current study (study RSV F-021).

As indicated above, safety information on the lower doses of the investigational RSV vaccines is already available from the clinical studies performed so far. However, this will be the first time that the 120 µg PreF antigen formulation will be administered in humans. Therefore, the RSV F-021 study will follow a 2-step staggered enrolment/vaccination with **unblinded** safety review in between (Figure 1):

Figure 1 Overview of staggered enrolment/vaccination and safety evaluation



SE up to Day 7 visit = safety evaluation by iSRC based on all available safety data from 25% of the vaccinated subjects [100 subjects] up to at least 7 days post-vaccination (including Day 7 haematology/ biochemistry parameters).

- **Step 1** will include the first 25% of subjects (i.e. ~100 subjects; ~25 subjects per study group) vaccinated in the study. When this cut-off is reached, further enrolment will be paused until completion of an unblinded review by a GSK internal Safety Review Committee (iSRC) not involved in the conduct of the study/project.
- Continuation of study enrolment of the remaining 75% of subjects (i.e. ~300 subjects; ~75 subjects per study group) in **Step 2** will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post vaccination (including Day 7 haematology and biochemistry parameters).

In addition to the unblinded review by iSRC after vaccination of the first 25% of subjects, the GSK Biologicals' Safety Review Team (SRT) will perform blinded safety reviews on a regular basis throughout the study

Refer to Sections 8.10.1 and 8.10.2 for more information on the SRT and the iSRC evaluation, respectively.

Furthermore, the iSRC outputs and review outcome will be provided to the Independent Data Monitoring Committee (IDMC) of the RSV F-004 study (first study in which the investigational RSV vaccine will be administered to pregnant women).

In case of a medically attended respiratory tract infection (MA-RTI) (e.g. visit to the General Practitioner [GP] for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the

Investigator to enable the collection of a nasal swab within 72h after the medical attendance. Following the visit, the MA-RTI section of the eCRF will be completed to document key aspects of the case including vital signs and evidence of increased work of breathing.

Should the 120µg PreF formulation be selected for further evaluation, an additional Phase II study will be initiated to evaluate the safety of the 120µg formulation in pregnant women and their infants before proceeding to Phase III studies.

1.2.5. Study blinding

Given the different presentation of the placebo and the investigational RSV vaccines, a double blinded study design is not possible. This study will be conducted in an observer-blind manner up to Day 90 post-vaccination after which it will be conducted in a single-blind manner.

Please refer to the glossary of terms for the definitions of observer-blind and single-blind study.

1.3. Benefit : Risk Assessment

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

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

1.3.1. Risk Assessment

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. These are however very rare and are estimated to occur once per 450 000 to once per 1 000 000 vaccinations for vaccines which do not contain allergens such as gelatine or egg protein [Zent, 2002]. In order to be able to treat subjects with an immediate systemic allergic reaction to vaccination, all subjects will need to remain under observation at the study site for at least 30 minutes after vaccination. All study sites will have resuscitation equipment available in case of a rare anaphylactic reaction.

Syncope (fainting) can occur following or even before, any vaccination as a psychogenic response to the needle injection. Therefore, it is important that procedures are in place to avoid injury from fainting.

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, redness, and swelling.

Risks linked to the investigational RSV vaccine

Non-adjuvanted and aluminium-adjuvanted investigational RSV vaccine formulations containing 10 to 60 µg PreF have previously been administered to a limited number of healthy men aged 18-44 years (~16/group) in the Phase I study RSV F-001 (116969) without any safety signals. The most frequently reported solicited local AE was pain at the injection site (up to 81.3%) and the most frequently reported solicited general AEs were fatigue and headache (both up to 43.8%). The most frequently reported unsolicited AE was headache (18.8%) after the solicited 7-day follow-up period. Overall, 4.2% of the subjects in the RSV vaccine groups (4 out of 95) reported Grade 3 AEs (solicited or unsolicited) in the 30-day follow-up period after vaccination compared to 6.1% (2 out of 33 subjects) in the placebo control group. For 3 subjects (2 in the RSV vaccine groups and one in the placebo control group), the reported Grade 3 AEs were considered to be related to vaccination by the investigator: Grade 3 fatigue was reported in the non-adjuvanted 10 µg PreF group, Grade 3 gastrointestinal symptoms in the control group and Grade 3 pain at injection site in the alum-adjuvanted 60 µg PreF group. Please refer to the current IB for more detailed information on the safety results from the study RSV F-001 (116969).

In the ongoing study RSV F-020 (NCT02360475), 30 µg of non-adjuvanted PreF and 60 µg of non-adjuvanted or aluminium (500 µg) adjuvanted PreF formulations have been administered to approximately 375 healthy women aged 18-45 years (~125/group). Data up to 90 days post-vaccination have not identified any safety concern that would preclude further development. A SAE of diffuse panbronchiolitis, considered by the investigator as being potentially related to the study vaccine, has been recently reported and is currently under further investigation. Please refer to the IB for further details on the case.

At the time of initiation of this study (RSV F-021), additional safety data from the ongoing RSV F-020 study or other ongoing/planned studies might also be available.

There is a potential risk of generating an immune response to neogenin (NEO), a host cell protein remaining in the purified antigen bulk. Release testing of vaccine lots used in studies RSV F-001 and RSV F-020 has detected residual host cell protein in a very low amount (below 0.1% of the amount of the purified PreF antigen bulk). The presence of residual host cell protein in the purified antigen bulk is not entirely unexpected as the PreF antigen is produced in the Chinese hamster ovary (CHO) cell line and current bioprocess technology cannot produce absolutely host cell protein-free material from cells [Wang, 2009]. Additional characterisation tests identified NEO as the main host cell protein. NEO is a cell surface trans-membrane protein that is ubiquitously expressed in all tissues and that serves as a multifunctional receptor [Meyerhardt, 1997]. NEO has been suggested to play a role in the regulation of diverse developmental processes, including the development of the central nervous system [De Vries, 2008; Hagihara, 2011; Hong, 2012; Lee, 2010].

Human and hamster NEO have ≅93% amino acid sequence homology. The amount of NEO per vaccine dose for the purified bulk lot used for the clinical trial material in studies RSV F-001 and RSV F-020 was initially estimated (by relative densitometry measurement of the SDS-PAGE gel) to be 0.48 µg per vaccine dose containing

60 µg PreF. Further exploration using mass spectrometry revealed a content of 0.26 µg of NEO per 60 µg vaccine dose. Although the risk of inducing anti-NEO antibodies that could cross-react with the endogenous antigen and affect its function was considered to be low, it could not be completely excluded that the hamster NEO present in the vaccine may induce an anti-NEO immune response in human. For this reason, anti-NEO antibody concentrations were assessed in the Phase I study RSV F-001 (116969) and have been assessed in RSV F-020. No evidence of a vaccine-induced anti-NEO response emerges from the available data up to Day 360 after vaccination from study RSV F-001 and up to Day 90 after vaccination from study RSV F-020. In parallel, every effort is being made to reduce the amount of NEO in the vaccine.

For RSV F-021 study, NEO-reduced lots will be used. However since the 120µg dose will be administered for the first time in human in the RSV F-021 study, as part of the safety assessment, the anti-NEO immune response will be evaluated again in this study, in order to be able to rule out that an immune response against NEO is induced by the investigational RSV vaccines.

1.3.2. Benefit Assessment

Benefits linked to the investigational RSV vaccine

The subjects receiving the investigational RSV vaccines may not directly benefit from this vaccination as RSV infections in healthy adults generally go undiagnosed because they usually present as common acute upper respiratory tract infections. Moreover, vaccine efficacy has not been assessed yet and it is hence not known whether the investigational RSV vaccines are effective in protecting against RSV infection.

An indirect benefit is that the information obtained in this study will aid the development of a maternal RSV vaccine, which is intended to prevent severe RSV disease in infants born to women vaccinated during pregnancy.

Other benefits

Subjects who are eligible and participate in the study will receive medical follow-up until the end of their participation in the study.

1.3.3. Overall Benefit:Risk Conclusion

The investigational RSV vaccine is currently in an early stage of clinical development and no vaccine efficacy has been demonstrated. However, no safety concerns which would preclude further development were identified in the completed or ongoing Phase I/II studies. Furthermore, the vaccine has been demonstrated to induce an immune response capable of boosting neutralising antibodies to both RSV serotype A and RSV serotype B. Given the measures taken to minimise the risk to subjects participating in this study, the potential risks are justified by the potential benefits linked to the development of a maternal RSV vaccine.

2. OBJECTIVES

2.1. Primary objective

- To rank different formulations of the investigational RSV vaccine based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination (Day 30).

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

- To evaluate the reactogenicity and safety of a single intramuscular dose of the RSV investigational vaccines up to study conclusion.
- To evaluate the immunogenicity of a single intramuscular dose of the RSV investigational vaccines up to 90 days after vaccination (Day 90).
- To further assess the safety of the investigational RSV vaccines by evaluating whether a single dose of the vaccines induces antibodies against the residual host cell protein neogenin (NEO) up to 1 month post-vaccination (Day 30).
- To estimate the incidence of medically attended RSV-associated RTIs up to study conclusion.

Refer to Section 10.2 for the definition of the secondary endpoints.

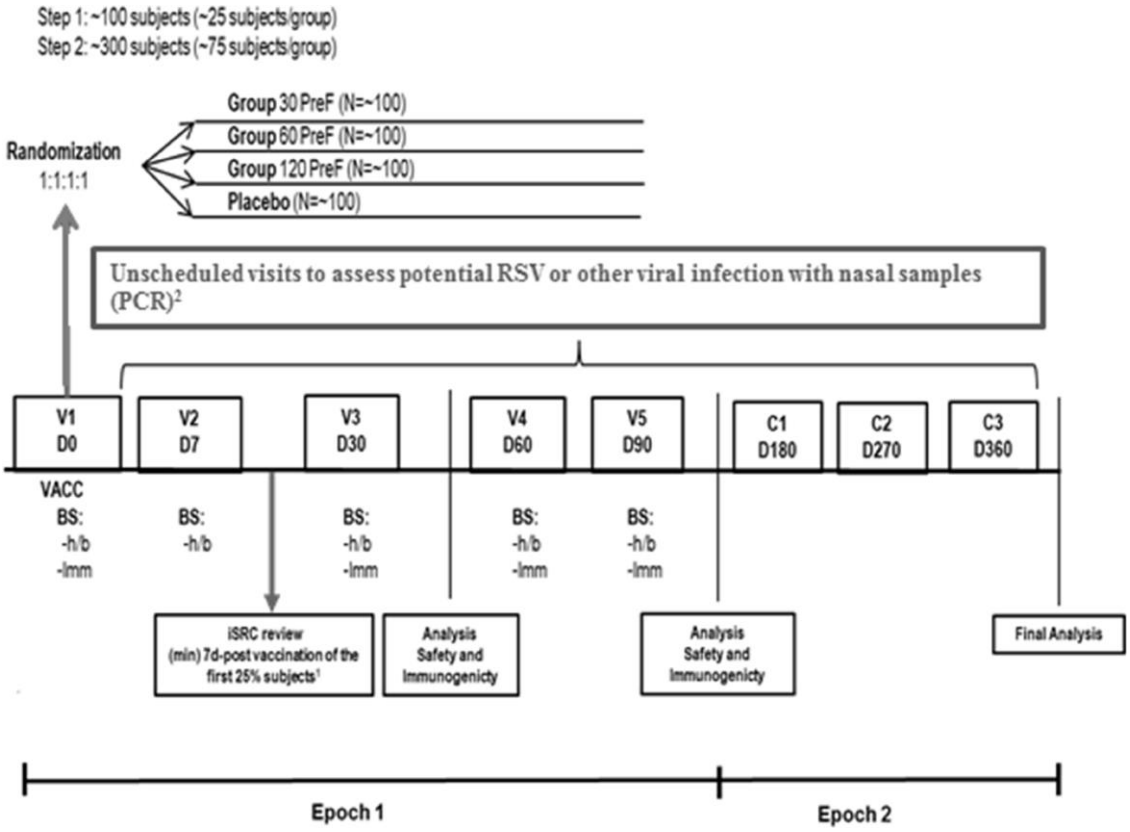
2.3. Tertiary objective

- If deemed necessary, to further characterise the immune response of a single intramuscular dose of the RSV investigational vaccines.

Refer to 5.7.3 for additional testing proposed to further characterise the immune response to the investigational RSV vaccine.

3. STUDY DESIGN OVERVIEW

Figure 2 Study design overview



V = Visit; **D** = Day; **VACC** = vaccination; **BS** = blood sample**; h/b** = blood sample for haematology/biochemistry; **Imm** = blood sample for immunogenicity; **C** = contact; **RSV** = Respiratory Syncytial Virus; **PCR** = Polymerase Chain Reaction.
[1] Safety data up to (minimum) 7 days post-vaccination (including Day 7 haematology and biochemistry parameters) of the first 25% of subjects vaccinated in the study will be reviewed by iSRC.
[2] In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable completion of the MA-RTI section of the eCRF and the collection of a nasal swab within 72h after the medical attendance.
Vertical lines stand for analysis on all subjects.

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), are essential and required for study conduct.

- **Experimental design**: Phase II, observer-blind, randomised, controlled, multi-country, study with four parallel groups.
- **Duration of the study**: the intended duration of the study will be approximately 1 year from Visit 1 to study conclusion (Day 360).
  - Epoch 001: Primary starting at Visit 1 (Day 0) and ending at Visit 5 (Day 90).

– Epoch 002 : Follow-up phase starting one day after Day 90 and ending at Day 360 contact.

- **Primary completion Date**: Visit 3 (Day 30).

Refer to glossary of terms for the definition of PCD.

- **End of Study (EoS)**: Last testing results released for samples collected at Visit 5 (i.e. last testing results released for the assays related to the primary and secondary endpoints).

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
30 PreF	~100	18 - 45 years	x	x
60 PreF	~100	18 - 45 years	x	x
120 PreF	~100	18 - 45 years	x	x
Control	~100	18 - 45 years	x	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/ Product name	Study Groups			
		30 PreF	60 PreF	120 PreF	Control
30 µg PreF	PreF-30 NaCl	X			
60 µg PreF	PreF-60 NaCl		X		
120 µg PreF	PreF-120 NaCl			X	
Placebo	Formulation buffer S9b				X

- **Control**: placebo control
- **Vaccination schedule**: One intramuscular vaccination at Day 0.
- **Treatment allocation**: Subjects will be randomised using a centralised randomisation system on internet (SBIR) at Day 0. The randomisation algorithm will use a minimisation procedure accounting for age (18 - 32 years or 33 - 45 years) and centre.
- **Blinding**: Observer-blind in Epoch 001 and single-blind in Epoch 002.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch 002	single-blind

- **Sampling schedule:**
  - **Blood samples for haematology/biochemistry** will be collected (~10 mL) from all subjects at Visit 1 (Day 0), Visit 2 (Day 7), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).

  - **Blood samples for humoral immune response evaluation** will be collected (~17 mL) from all subjects at Visit 1 (Day 0), Visit 3 (Day 30), Visit 4 (Day 60) and Visit 5 (Day 90).
  - **Nasal swabs** will be collected from subjects in case of a MA-RTI from enrolment (Visit 1) until Contact 3.

- **Type of study**: self-contained
- **Data collection**: Electronic Case Report Form (eCRF).
- **Safety monitoring**: When the first 25% of subjects are vaccinated in the study, enrolment will be paused until completion of an unblinded review by a GSK iSRC. Continuation of study enrolment will be conditional to a favourable outcome of the iSRC evaluation of all available safety and reactogenicity data collected up to at least 7 days post-vaccination (including Day 7 haematology and biochemistry parameters). In addition, the blinded safety data will be reviewed by GSK Biologicals' SRT on a regular basis throughout the study.

Refer to Section 8.10 for description of safety monitoring.

- In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the investigator to enable the collection of a nasal swab within 72 hours after the medical attendance.

Refer to Section 5.6.11 for more information on the procedure of nasal swabbing.

4. STUDY COHORT

4.1. Number of subjects/centres

This will be a multi-centre, multi-country study.

The target is to enrol approximately 400 eligible women (~100 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 of the study, regulatory acceptability 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, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of Diary Cards, return for follow-up visits).
- Written informed consent obtained from the subject prior to performance of any study specific procedure.

- Non-pregnant female between, and including, 18 and 45 years of age at the time of study vaccination.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study
  - Non-childbearing potential is defined as pre-menarche, hysterectomy, ovariectomy or post-menopause.

  Refer to the glossary of terms for the definition of menarche and menopause.
- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - Has practiced adequate contraception for 30 days prior to study vaccination, and
  - Has a negative pregnancy test on the day of study vaccination, and
  - Has agreed to continue adequate contraception up to 90 days after vaccination

  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 of the study, regulatory acceptability 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 vaccines within 30 days prior to study vaccination (Day -29 to Day 0), or 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).

  Refer to glossary of terms for the definition of active phase.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs, as well as administration of long-acting immune-modifying drugs [e.g. infliximab]), within 6 months prior to study vaccination, or planned administration until 90 days post-vaccination. For corticosteroids, this will mean prednisone ≥ 10 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.
- History of any neurological disorders or seizures (subjects with a history of febrile convulsion may be enrolled).
- 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 or current autoimmune disease(for a list of potential immune mediated diseases, please refer to APPENDIX A. Note that this list should be used as a guidance to identify diseases that could be autoimmune in nature. However, not all reported diseases in the appendix will be autoimmune in nature and therefore represent an exclusion criterion. This will be based on the opinion of the investigator and/or specific available diagnostic data).
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality as determined by physical examination and/or Medical History (including any previously performed laboratory tests).
- Lymphoproliferative disorder or malignancy within previous 5 years (excluding effectively treated non-melanotic skin cancer).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study vaccine.
- Hypersensitivity to latex.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Current alcohol and/or drug abuse.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
  - For subjects with acute disease and/or fever at the time of enrolment, Visit 1 will be rescheduled within the allowed recruitment period.
- Body mass index (BMI) > 40 kg/m².
- Pregnant or lactating female.
- Planned move to a location that will prohibit participating in the trial until study conclusion.

- Any other condition that the investigator judges may interfere with study procedures (e.g. drawing blood) or findings (e.g. immune response).

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 Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals 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 Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation of treatment

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.

5.2.2. Randomisation of treatment

5.2.2.1. Randomisation of supplies

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

To allow GSK Biologicals 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 400 eligible subjects who will be randomly assigned to four study groups in a (1: 1: 1: 1) ratio (approximately 100 subjects in each group).

Allocation of the 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.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for the first dose.

The number of each 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. This study will be conducted in an observer blind manner up to Day 90 post-vaccination after which it will be conducted in a single-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. safety and reactogenicity) 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.

Please refer to the glossary of terms for the definition single-blind study.

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	Epoch 001					Epoch 002			Epoch 001/002
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Contact 1[8]	Contact 2[8]	Contact 3[8]	Unscheduled visit
Timepoint(s)	Day 0	Day 7	Day 30	Day 60	Day 90	Day 180	Day 270	Day 360	-
Sampling timepoints	Pre-vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc				Unscheduled nasal swab
Informed consent	●								
Check inclusion/exclusion criteria	●								
Record demographic data	●[1]								
Medical history including review of respiratory symptoms*	●								
Physical examination [2]	●	●	O	O	O				●
Pregnancy test [3]	●								
Pre-vaccination body temperature	●								
Distribution of subject card	O								
Laboratory Assays									
Blood sampling for haematology/ biochemical analysis (~10 ml)	●[4]	●	●	●	●				
Blood sampling for humoral immune responses including anti-neo antibody assay (~17 mL)	●[4]		●	●	●				
Nasal swab									●[9]
Vaccine									
Randomization and treatment number allocation	O								
Vaccination	●								
Recording of administered treatment number	●								
30 minutes post-vaccination observation period	O								
Distribution of diary cards and instruction on how to complete them [5]	O	O							
Return of diary cards		O	O						
Diary card transcription by investigator		●	●						
Recording of solicited adverse events (Day 0-Day 6)	●	●							
Recording of unsolicited adverse events (Day 0-Day 29)	●	●	●						
Recording of adverse events related to MA-RTIs	●	●	●	●	●	●	●	●	
Recording of adverse events leading to withdrawal	●	●	●	●	●	●	●	●	

Epoch	Epoch 001					Epoch 002			Epoch 001/002
Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Contact 1[8]	Contact 2[8]	Contact 3[8]	Unscheduled visit
Timepoint(s)	Day 0	Day 7	Day 30	Day 60	Day 90	Day 180	Day 270	Day 360	-
Sampling timepoints	Pre-vacc	Post-Vacc	Post-Vacc	Post-Vacc	Post-Vacc				Unscheduled nasal swab
Recording of serious adverse events	●	●	●	●	●	●	●	●	
Recording of pregnancies	●	●	●	●	●	●	●	●	
Recording of concomitant medications/products/vaccinations [6]	●	●	●	●	●	●	●	●	
Recording of intercurrent medical conditions		●	●	●	●				
Completion of MA-RTI case details									●
Check for interest in participating in future booster study [7]					O			●	
Investigator sign-off on eCRF before analysis			●		●			●	
Study Conclusion								●	

Vacc = vaccination; **MA-RTIs** = Medically Attended Respiratory Tract Infections; **eCRF** = electronic Case Report Form.

● 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

***** In addition to the medical history, a full respiratory review of symptoms (including shortness of breath, chest pain, symptoms of upper respiratory tract infection,including cough, sputum production, sore throat, nasal congestion, personal and family history of pulmonary illnesses including asthma, chronic obstructive pulmonary disease, cystic fibrosis, autoimmune diseases affecting the lungs and smoking, personal history of recurrent infections, pneumonia, sleep apnea and occupational exposure) should be completed and recorded in the eCRF**.**

[1] Date of birth (year only), geographic ancestry, ethnicity and childbearing potential (if subject not of childbearing, the specific reason should be documented in the CRF: hysterectomy, ovariectomy, post-menopause, pre-menarche or other)

[2] Complete physical examination including resting vital signs (blood pressure, heart rate and respiratory rate) after at least 10 minutes of rest. In addition, a pulmonary examination, including measurement of blood oxygen saturation and chest auscultation should be performed at Visit 1 and Unscheduled visit. Weight, height and BMI will also only be collected at Visit 1. Physical examination at Visit 3, 4 and 5 will be performed only if deemed necessary by the investigator.

[3] 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.

[4] Blood sampling for haematology/biochemical analysis and for immunogenicity assays **must be done before** vaccination at Visit 1. Refer to Table 7 and Table 8 for the list of parameters to be tested.

[5] 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 and vaccinations on the day of vaccination and for 6 subsequent days. The second one will be distributed at Visit 2 (Day 7) and will be used for recording unsolicited AEs and concomitant medications/products and vaccinations from 7 to 29 days after vaccination.

[6] Concomitant medications/products/vaccinations as described in Section 6.6 need to be recorded in the eCRF.

[7] It is likely that the RSV vaccine may need to be administered during each pregnancy to further boost immunogenicity in the pregnant woman and achieve protective anti-RSV 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 F-021 and who were part of the selected vaccine group or the control group may be invited to a booster study (study RSV F-021B).

[8] 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.
[9] In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable the collection of a nasal swab within 72h after the medical attendance. Refer to Table 9 for sequence and method of testing for respiratory viruses of collected samples.
Note: The double-line border following Day 30 and Day 90 indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Day 30 and Day 90 respectively.

Table 5 Intervals between study visits

Interval	Optimal length of interval[1]	Allowed interval
Visit 1 (Day 0) → Visit 2 (Day 7)	7 days	7 - 9 days
Visit 1 (Day 0) → Visit 3 (Day 30)	30 days	30 - 44 days[2]
Visit 1 (Day 0) → Visit 4 (Day 60)	60 days	56 - 70 days[2]
Visit 1 (Day 0) → Visit 5 (Day 90)	90 days	86 - 100 days[2]
Visit 1 (Day 0) → Contact 1 (Day 180)	180 days	150 -210 days
Visit 1 (Day 0) → Contact 2 (Day 270)	270 days	240 - 300 days
Visit 1 (Day 0) → Contact 3 (Day 360)	360 days	330 - 390 days

[1]Whenever possible the investigator should arrange study visits within this interval.
[2]Subjects will not be eligible for inclusion in the ATP cohort for analysis of immunogenicity if they make the study visit outside this interval.

5.6. Detailed description of study procedures

5.6.1. Informed consent

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

Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. Collect demographic data

Record demographic data such as date of birth (year only), geographic ancestry* and ethnicity* as well as information on subject's childbearing potential (if subject is not of childbearing potential, the specific reason be documented: pre-menarche, hysterectomy, ovariectomy, post-menopause or other) in the subject's eCRF.

* Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013;Pérez-Losada, 2009; Kollmann, 2013], have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g. genetics, metabolism, elimination), extrinsic factors (e.g. diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both geographic ancestry and ethnicity will be collected for all subjects participating in the RSV F-021 study.

5.6.4. 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 a

subject prior to the study vaccination in the eCRF. In addition to the medical history, a full respiratory review of symptoms (including shortness of breath, chest pain, symptoms of upper respiratory tract infection, including cough, sputum production, sore throat, nasal congestion, personal and family history of pulmonary illnesses including asthma, chronic obstructive pulmonary disease, cystic fibrosis, autoimmune diseases affecting the lungs, and smoking, personal history of recurrent infections, pneumonia, sleep apnea and occupational exposure) should be completed and recorded in the eCRF**.**

5.6.5. Physical examination

At Visit 1, Visit 2 and unscheduled visits, perform a physical examination of the subject, including assessment of resting vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate after at least 10 minutes of rest. In addition, a pulmonary examination, including measurement of blood oxygen saturation and chest auscultation should be performed at Visit 1 and unscheduled visits. Also at Visit 1 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.

5.6.6. Pregnancy test

Female subjects of childbearing potential are to have a pregnancy test prior to any 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.

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.

5.6.7. 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 Section 6.5 for more details.

5.6.8. Assess pre-vaccination body temperature

Record the axillary, oral or tympanic body temperature of the subject prior to study vaccination. The preferred route for recording temperature in this study will be oral.

If the subject has fever (fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route) on the day of vaccination, Visit 1 can be rescheduled within the allowed recruitment period.

5.6.9. 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 each administered treatment must be recorded in the eCRF.

5.6.10. Blood sampling

A volume of ~10 mL of whole blood should be drawn from all subjects for analysis of the haematology/biochemistry parameters at each study visit. Haematology and biochemistry assessments will be performed in a central laboratory (Q^2 solutions).

A volume of ~17 mL of whole blood (to provide ~6 mL of serum) should be drawn from all subjects at study visits 1, 3, 4 and 5, for analysis of humoral immune responses, including anti-NEO antibody assay which is only performed at Visits 1 and 3. Refer to Table 6 and Table 11.

Refer to the SPM for details on blood sample handling.

5.6.11. Collection of nasal swab samples

In case of a MA-RTI (e.g. visit to the GP for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable the collection of a nasal swab within 72h after the medical attendance.

Investigator will decide if nasal swab is collected through subject visiting the site or through home visit by qualified site staff (or delegated to a third party).

The nasal swab will be used to assess a potential intercurrent infection with RSV and other respiratory viruses.

Cells and secretions from the nose will be collected using sterile swabs. Refer to the SPM for more details about nasal swabbing.

Note: For cases that are hospitalised and treated for an LRTI, it is recommended to take an **additional specimen** for testing at the local laboratory in order to establish a fast and accurate diagnosis for the SAE.

5.6.12. 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 detailed description of the vaccine administration procedure.

If the subject's health on the day of vaccination temporarily precludes vaccine administration, Visit 1 can be rescheduled within the allowed recruitment period.

5.6.13. 30 minutes post-vaccination observation

Closely observe the subject for at least 30 minutes following study vaccination, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.14. Distribution of Subject Card

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

5.6.15. 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.

5.6.16. 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 Biologicals.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious or if they have visited a health care professional for a respiratory tract infection.
- At the vaccination visit (Visit 1), a first diary card will be provided to the subject. The subject will record body (oral preferred) temperature, any solicited local/general AEs, any unsolicited AEs and concomitant medications/products/vaccination as from the day of vaccination and during the next 6 days. The subject will be instructed to return the completed diary card to the investigator at the next study visit (Visit 2).
- A second diary card will be provided to the subject at Day 7 (Visit 2) to record any unsolicited AEs and concomitant medications/products/vaccination from Day 7 until Day 29. The subject will be instructed to return the completed diary card to the investigator at the next study visit (Visit 3).
- Collect and verify completed diary cards during discussion with the subject on Visit 2 and 3.

- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

- From Visit 1 until Contact 3, all medically attended visits for a respiratory tract infection will need to be recorded in the subject's eCRF to document key aspects of the case including vital signs and evidence of increased work of breathing.

5.6.17. Extension/Booster study

It is likely that the RSV vaccine may need to be administered during each pregnancy to further boost immunogenicity in the pregnant woman and achieve protective anti-RSV 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 F-021 and who were part of the selected vaccine group or the control group may be invited to a booster study (study RSV F-021B).

For this purpose, at Visit 5, the investigator will ask each subject if she is interested in participating in a booster study and will document this in the source documents only. Then, at study conclusion for each subject (D360 contact), the investigator will check again to 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.

5.6.18. D180, D270 and D360 Contacts

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 was not done by telephone, if questions remain, the study site may follow up with the subject via telephone. During these contacts, 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/last contact (as applicable), as well as if she has become pregnant during the post-vaccination period. The investigator (or delegate) will also ask the subject for concomitant vaccinations/products/medications that she has received since Visit 5/ last contact (as applicable).

Subject's interest in participating in a booster study will also be re-confirmed at D360 contact, and the corresponding information will be reported in the eCRF (refer to section 5.6.17)

Please refer to the SPM for further guidance.

5.6.19. Study conclusion

The investigator will:

- review data collected 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 Biologicals.

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 5.7.4.2 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), 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 Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, 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 According-to-Protocol (ATP) 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 Biologicals 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	Timepoint	Cohort	N° of subjects	Quantity	Unit
Blood sample					
Blood for haematology/biochemical analysis	Visit 1 (Day 0)	All enrolled subjects	~400	~10	ml
	Visit 2 (Day 7)	All enrolled subjects	~400	~10	ml
	Visit 3 (Day 30)	All enrolled subjects	~400	~10	ml
	Visit 4 (Day 60)	All enrolled subjects	~400	~10	ml
	Visit 5 (Day 90)	All enrolled subjects	~400	~10	ml
Blood for Humoral immune responses including anti-NEO antibody assay*	Visit 1 (Day 0)	All enrolled subjects	~400	~17	ml
	Visit 3 (Day 30)	All enrolled subjects	~400	~17	ml
	Visit 4 (Day 60)	All enrolled subjects	~400	~17	ml
	Visit 5 (Day 90)	All enrolled subjects	~400	~17	ml
Total quantity of blood for each subject				~118	ml
Nasal swab					
Nasal swab	From Visit 1 until Contact 3	All subjects with a MA-RTI	Event-driven#	-	-

*Anti-NEO antibody assay will only be performed at visit 1 and visit 3.
#For each MA-RTI, a nasal swab will be collected within 72 hours at the investigator site or at the subject's home by qualified site staff (or delegated to a third party).

5.7.3. Laboratory assays

Please refer to APPENDIX B for a detailed description of the assays performed in the study. Please refer to APPENDIX C for the address of the clinical laboratories used for sample analysis.

Laboratory assays as described in Table 7, Table 8 and Table 9 will be performed at a GSK Biologicals' laboratory or in a laboratory designated by GSK Biologicals.

Table 7 Haematology/Serum Chemistry

System	Discipline	Component	Method	Scale	Laboratory
Whole blood	Haematology	Leukocytes (White Blood Cells)	As per local practice	Quantitative	Central laboratory (Q^2 Solutions)*
		Lymphocytes			
		Eosinophils			
		Haemoglobin			
		Platelets			
		Neutrophils			
Serum	Biochemistry	Alanine Aminotransferase (ALT)	As per local practice	Quantitative	
		Aspartate Aminotransferase (AST)			
		Creatinine			

* See APPENDIX Cfor address of the clinical laboratory used for sample analysis.

Table 8 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/ Manufacturer	Unit	Cut-off	Laboratory***
Serum	RSV-A neutralising Antibody	NEUTRALISATION	In house	ED60	TBD**	GSK Biologicals* or NÉOMED-LABS
Serum	PCA	ELISA	NA	µg/mL	TBD**	GSK Biologicals* or NÉOMED-LABS
Serum	RSV-B neutralising Antibody	NEUTRALISATION	In house	ED60	TBD**	GSK Biologicals* or NÉOMED-LABS
Serum	Anti-NEO antibody for safety assessment	ELISA	NA	ng/mL	55	GSK Biologicals* or NÉOMED-LABS

ELISA = Enzyme-linked immunosorbent assay**; ED60** = serum dilution inducing 60% inhibition in plaque forming units; **TBD** = to be determined; **PCA** = Palivizumab Competing Antibodies; anti-**NEO** = anti-neogenin; NA = not applicable

* 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).

*** See APPENDIX Cfor address of the clinical laboratories used for sample analysis.

Table 9 Molecular biology (PCR tests) (Amended 8 August 2018)

System	Component	Method	Unit	Laboratory
Nasal swab*	***Influenza A virus (Flu A)*** ***Influenza B virus (Flu B)*** ***Human respiratory syncytial virus A (RSV A)*** ***Human respiratory syncytial virus B (RSV B)*** ***Human influenza A virus subtype H1 (Flu A- H1)*** ***Human influenza A virus subtype H3 (Flu A-H3)*** ***Human influenza A virus subtype H1pdm09 (Flu A-H1pdm09)*** ***Human adenovirus (AdV)*** ***Human metapneumovirus (MPV)*** ***Human enterovirus (HEV)*** ***Human parainfluenza virus 1 (PIV1)*** ***Human parainfluenza virus 2 (PIV2)*** ***Human parainfluenza virus 3 (PIV3)*** ***Human parainfluenza virus 4 (PIV4)*** ***Human bocavirus 1/2/3/4 (HBoV)*** ***Human rhinovirus A/B/C (HRV)*** ***Human coronavirus 229E (229E)*** ***Human coronavirus NL63 (NL63)*** ***Human coronavirus OC43 (OC43)***	Multiplex PCR (PCRMTX) ***(Allplex Respiratory Panel or equivalent)****	Qualitative assay (positive/negative)	GSK Biologicals*** ***or designated laboratory***
Nasal swab*	RSV-A/B RNA	Quantitative ***Reverse Transcription*** PCR (QRTPCR) ****	Copies/ml	GSK Biologicals***

* In case of MA-RTI (e.g. visit to the General Practitioner [GP] for respiratory symptoms including but not limited to cough, sputum production, difficulty breathing), the subject will be asked to contact the Investigator to enable the collection of a nasal swab within 72h after the medical attendance.

** Respiratory Viruses Panel (Multiplex PCR) will be performed on all specimens. ***Refer to*** APPENDIX B ***for the laboratory addresses.***

*** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium.

****Additional testing with RSV-A/B RNA quantitative ***reverse transcription*** PCR may be performed.

(Amended 08-August-2017)

For subjects having a MA-RTI in the period from Visit 1 until Contact 3, a nasal swab will be collected.

For subjects admitted to hospital and treated for an LRTI, it is recommended to take an **additional specimen** for testing at the local laboratory in order to establish a fast and accurate diagnosis of the SAE.

Additional Testing

Additional testing on serum samples to characterise the immune response to RSV/ to the investigational RSV vaccines, such as, but not limited to, immunoglobulin G (IgG) antibody concentrations against the RSV F protein by subclass or further characterisation of the immune response against different protein F epitopes may be performed if deemed necessary for accurate interpretation of the data and/or should such test(s) become available in the GSK Biologicals laboratory or a laboratory designated by GSK Biologicals.

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 IRB/IEC has approved this research.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' 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 10 Haematology/Blood Chemistry

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component
Type of contact (timepoint)	Sampling timepoint			
Visit 1 (Day 0)	Pre-vaccination	All subjects	~400	Haematology (Leukocytes, Neutrophils, Lymphocytes, Eosinophils, Haemoglobin, Platelets) Biochemistry (ALT, AST, Creatinine)
Visit 2 (Day 7)	Post-vaccination	All subjects	~400	
Visit 3 (Day 30)	Post-vaccination	All subjects	~400	
Visit 4 (Day 60)	Post-vaccination	All subjects	~400	
Visit 5 (Day 90)	Post-vaccination	All subjects	~400	

ALT = Alanine Amino-transferase; **AST** = Aspartate Amino-transferase

5.7.4.2. Immunological read-out

Table 11 Immunological read outs

Blood sampling timepoint		Sub-cohort Name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Visit 1 (Day 0)	Pre-Vaccination	All subjects	~400	RSV-A neutralising antibody PCA RSV-B neutralising antibody Anti-NEO	1 2 3 4
Visit 3 (Day 30)	Post-vaccination				
Visit 4 (Day 60) Visit 5 (Day 90)	Post-vaccination	All subjects	~400	RSV-A neutralising antibody PCA RSV-B neutralising antibody	1 2 3

RSV = Respiratory Syncytial Virus; **NEO** = Neogenin; **PCA** = Palivizumab Competing Antibodies

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 11

5.7.4.3. Molecular biology

Table 12 Molecular biology tests (Amended 8 August 2017)

Nasal swab sampling timepoint		Group	No. Subjects	Component
Type of contact (timepoint)	Sampling timepoint			
Unscheduled visit for MA-RTI*	Unscheduled	All subjects	All subjects with a nasal swab sample*	***Influenza A virus (Flu A)*** ***Influenza B virus (Flu B)*** ***Human respiratory syncytial virus A (RSV A)*** ***Human respiratory syncytial virus B (RSV B)*** ***Human influenza A virus subtype H1 (Flu A- H1)*** ***Human influenza A virus subtype H3 (Flu A-H3)*** ***Human influenza A virus subtype H1pdm09 (Flu A-H1pdm09)*** ***Human adenovirus (AdV)*** ***Human metapneumovirus (MPV)*** ***Human enterovirus (HEV)*** ***Human parainfluenza virus 1 (PIV1)*** ***Human parainfluenza virus 2 (PIV2)*** ***Human parainfluenza virus 3 (PIV3)*** ***Human parainfluenza virus 4 (PIV4)*** ***Human bocavirus 1/2/3/4 (HBoV)*** ***Human rhinovirus A/B/C (HRV)*** ***Human coronavirus 229E (229E)*** ***Human coronavirus NL63 (NL63)*** ***Human coronavirus OC43 (OC43)***
				RSV-A/B RNA**

* For each MA-RTI, a nasal swab will be collected within 72 hours of the medical attendance either at the investigator site or at the subject's home by qualified site staff (or delegated to a third party).

Additional testing with RSV-A/B RNA quantitative ***reverse transcription* may be performed.

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 vaccines

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

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 13 Study vaccines

Treatment name	Vaccine/product name	Formulation	Presentation	Volume to be administered	Number of doses
30 µg PreF	PreF-30	PreF=30µg NaCl=150mM	Freeze-dried antigen in monodose vial Liquid in monodose, prefilled syringe	0.5 ml	1
60 µg PreF	PreF-60	PreF=60µg NaCl=150mM	Freeze-dried antigen in monodose vial Liquid in monodose, prefilled syringe	0.5 ml	1
120 µg PreF	PreF-120	PreF=120µg NaCl=150mM	Freeze-dried antigen in monodose vial Liquid in monodose, prefilled syringe	0.5 ml	1
Placebo	Formulation buffer S9b	Na_2HPO_4=1.3mg; KH_2PO_4=186µg; NaCl=3.85mg; KCl=100µg; $MgCl_2$=50µg	Clear liquid in monodose vial	0.5 ml	1

6.2. Storage and handling of study vaccines

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 Visit 5), 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. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

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 more details on actions to take.

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

6.3. Dosage and administration of study vaccines

Table 14 Dosage and administration

Type of contact and timepoint	Study group	Treatment name	Volume to be administered	Route	Site	Side
Visit 1 (Day 0)	30 PreF	30 µg PreF	0.5 ml	IM	Deltoid	Non-dominant*
	60 PreF	60 µg PreF	0.5 ml	IM	Deltoid	Non-dominant*
	120 PreF	120 µg PreF	0.5 ml	IM	Deltoid	Non-dominant*
	Control	Placebo	0.5 ml	IM	Deltoid	Non-dominant*

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

6.4. Replacement of unusable vaccine doses

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 at that point in time; if any of these events occur at the time scheduled for vaccination (Visit 1), Visit 1 will be rescheduled at a later date, within the allowed recruitment period, and the subject may be vaccinated at that time:

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥38.0°C for rectal 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 all vaccines.

6.6. Concomitant medications/products and concomitant vaccinations

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

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/products, except vitamins and dietary supplements, administered as of study vaccination and up to 29 days after vaccination (Day 0 to Day 29).
- Any concomitant vaccination, administered during the study period.
- 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 ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route].
- 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 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.
- Any prescribed treatment for the MA-RTIs as of study vaccination till end of study.

6.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP 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 ATP analysis. See Section 10.5 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period.
- 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 ≥10mg/day, 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 (SmPC)/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 ATP analyses

At each study visit subsequent to Visit 1 and up to Visit 5, 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 ATP cohort for immunogenicity if, during the study period up to Day 90 (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 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 15 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 local (injection-site) AEs will be solicited:

Table 16 Solicited general adverse events

Fatigue
Fever*
Gastrointestinal symptoms†
Headache

* Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.
† 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 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, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as 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. Clinically significant 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 D]*

8.1.5. Medically Attended Respiratory Tract Infections

A MA-RTI is defined as a subject's visit to a health care professional (e.g. GP) for any respiratory symptom, including (but not limited to) cough, sputum production and difficulty breathing.

All AEs related to MA-RTIs occurring during the period starting with the administration of study vaccine up to Contact 3 must be recorded in a specific eCRF form for MA-RTI, irrespective of intensity or whether or not they are considered administration-related.

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.

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, 2006]. 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, 1996] 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 Biologicals 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 30 days following administration of the dose of study vaccines (Day 0 to Day 29) 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 study vaccines and will end at the contact at Day 360 following administration of the dose of study vaccines for each subject. 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 study vaccines.

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 study vaccines and will end at the contact at Day 360 following administration of the dose of study vaccines. See section 8.4 for instructions on reporting of pregnancies.

An overview of the protocol-required reporting periods for AEs, SAEs, pregnancies is given in Table 17.

Table 17 Reporting periods for collecting safety information

Event	Visit 1 Day 0	Day 6 end of 7-day FU	Visit 2 Day 7	Day 29 end of 30-day FU	Visit 3 Day 30	Visit 4 Day 60	Visit 5 Day 90	Contact 1 Day 180	Contact 2 Day 270	Contact 3 Day 360 Study conclusion
Solicited local and general AEs										
Unsolicited AEs										
AEs/SAEs leading to withdrawal from the study										
SAEs										
SAEs related to study participation or concurrent GSK medication/vaccine*										
Pregnancies										
AEs related to MA-RTIs										

The double-bordered line indicates timing of vaccination.*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; **MA-RTI** = Medically Attended Respiratory Tract Infection.

Type	Solicited adverse events /Unsolicited adverse events/ Serious adverse events/ Adverse events related to MA-RTIs
Method of 'solicited' follow-up	Diary cards
Method of 'unsolicited' follow-up	Diary cards/ Questioning at study visits/ contacts up to D360
Method for reporting SAEs	Electronic Expedited Adverse Events Report
Method for reporting AEs related to MA-RTIs	Subject contacting Investigator

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 17. 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 vaccines 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) relative 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 Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

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 18 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*		Record temperature in °C
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 ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults:

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

The maximum intensity of fever will be scored at GSK Biologicals according to the standard GSK Biologicals' scoring system for adults (via the preferred route for recording temperature in this study which is oral):

0: < 37.5 °C
1: ≥ 37.5 °C to ≤ 38.5 °C
2: > 38.5 °C to ≤ 39.5°C
3: > 39.5°C

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 RSV maternal 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 Biologicals. 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 Biologicals. 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 vaccines, 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 Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 19, 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 19, once the investigator becomes aware of the pregnancy.

Table 19 Timeframes for submitting serious adverse event and pregnancy to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	Expedited Adverse Events Report	24 hours*	Expedited Adverse Events 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 24/24 hour and 7/7 day availability:
GSK Biologicals Clinical Safety & Pharmacovigilance Fax: +PPD or +PPD Email address: PPD

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

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 Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals 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 Biologicals

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 (EDD) 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, 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 Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 19.

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 Biologicals 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 investigational vaccines 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 of adverse events and serious adverse events

8.5.1.1. 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 Biologicals (within 24 hours for SAEs; refer to Table 19).

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

8.5.1.2. 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 Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals 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 Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5.2. 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 Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't 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 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 Biologicals' 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 Biologicals' 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 Biologicals' 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 Biologicals.

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

8.10. Safety monitoring

8.10.1. Safety review team

The SRT includes as core members the GSK Biologicals' Central Safety Physician, the Clinical & 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, an unblinded safety evaluation will be performed by an iSRC. 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

Since this will be the first time that the investigational RSV vaccine formulation containing 120 µg of the PreF antigen will be administered in humans, a staggered vaccination and monitoring by an iSRC, authorised by the GSK Biologicals' Vaccine Safety Monitoring Board (VSMB), have been established to ensure maximum safety of the subjects in the study.

The iSRC will include the following GSK personnel: a Safety Physician (Vaccines Clinical Safety & Pharmacovigilance representative [VCSP]), a Clinical Research and

Development Leader (CRDL), and a Biostatistician, 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 one *ad hoc*, non-voting member: an independent statistician in charge of providing unblinded data to the iSRC.

When the first 25% of the subjects are vaccinated in the study (Step 1), enrolment will be paused until completion of an unblinded iSRC review of all safety data collected up to (minimum) 7 days post-vaccination (including Day 7 haematology and biochemistry parameters).

It was deemed appropriate to place the sample size "cut-off" at the first 25% of subjects vaccinated based on the rate of Grade 3 AEs (solicited and unsolicited) during the 7-day post vaccination period observed in the RSV F-020 study with the non-adjuvanted 60µg PreF formulation, which was approximately 5%.

The table below shows that with 25% of subjects vaccinated (25 subjects per group) we have ~90% chance to observe a given Grade 3 event if the true incidence is 10% (i.e. ~2fold of what we would expect , based on RSV F-020 study data).

Table 20 Probability to observe at least one subject with an event of a given true incidence when looking after 25 enrolled subjects/group

True incidence	N = 25
1%	0.222
2%	0.397
5%	0.723
10%	0.928
15%	0.983
20%	0.996
30%	1

N = subjects per group

During the planned (and any *ad-hoc* iSRC safety evaluations, if applicable), 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.

If no safety signal is observed during the planned safety evaluation after the first 25% of subjects have been vaccinated (Step 1), the favourable outcome of the safety review will be documented and provided in writing to the RSV study team and investigator(s) and enrolment/vaccination of the remaining subjects (Step 2) can start.

If a safety signal is observed during the planned safety evaluation, the iSRC leader is responsible for urgent communication and escalation of the concern to the GSK Biologicals' VSMB and communication to the study team. The VSMB will then decide during an *ad hoc* meeting whether to suspend, modify or continue the conduct of the study. Already vaccinated subjects will continue all planned visits, including the capture of all safety data. However, further enrolment/vaccination cannot proceed until VSMB review and corresponding outcome is available.

The decision of the GSK Biologicals' VSMB will be documented and provided in writing to the investigator(s). Ethics Committees and Competent Authorities will also be notified, as applicable.

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

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

In addition to the above, the RSV F-021 iSRC outputs and review outcome will be provided to the Independent Data Monitoring Committee (IDMC) of the RSV F-004 study (first study in which the investigational RSV vaccine will be administered to pregnant women).

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who is available for the contact at Day 360 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 the contact at Day 360 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 the contact at Day 360.

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 herself, 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.
- 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 result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

10. STATISTICAL METHODS

10.1. Primary endpoints

- Occurrence of AEs from vaccination up to Day 7, for all subjects in each investigational RSV vaccine group:
  - Occurrence of any Grade 2 and Grade 3 general AE (solicited and unsolicited);
  - Occurrence of Grade 2 and Grade 3 fever;
  - Occurrence of any vaccine-related SAE.
- Functional antibody titres against RSV at Day 0 and Day 30, for all subjects in each investigational RSV vaccine group.
  - Neutralising antibody titres against RSV-A .
- PCA concentrations at Day 0 and Day 30 for all subjects in each investigational RSV vaccine group.

10.2. Secondary endpoints

- Occurrence of AEs from vaccination up to study conclusion:
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after vaccination (i.e. the day of vaccination and 6 subsequent days), for all subjects in all groups;
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after vaccination (i.e. the day of vaccination and 29 subsequent days), for all subjects in all groups;
  - Occurrence of any haematological (haemoglobin level, White Blood Cells [WBC], lymphocyte, neutrophil, eosinophil and platelet count) and biochemical

(alanine amino-transferase [ALT], aspartate amino-transferase [AST] and creatinine) laboratory abnormality at Day 0, Day 7, Day 30, Day 60 and Day 90 for all subjects in all groups;

  - Occurrence of any SAE, for all subjects in all groups.

- Functional antibody titres against RSV for all subjects in all groups:
  - Neutralising antibody titres against RSV-A at Day 0, Day 30, Day 60 and Day 90;
  - Neutralising antibody titres against RSV-B at Day 0, Day 30, Day 60 and Day 90.
- PCA concentration at Day 0, Day 30, Day 60 and Day 90 for all subjects in all groups.
- Humoral immune response to the residual host cell protein NEO in the investigational RSV vaccine at pre-vaccination (Day 0), and 1 month post-vaccination (Day 30) for all subjects in all groups.
  - Neutralising antibody titres against NEO
- Occurrence of medically attended RSV-associated RTIs up to study conclusion.

10.3. Tertiary endpoints

See section 5.7.3 for additional testing proposed to further characterise the immune response to the investigational RSV vaccine.

10.4. Determination of sample size

The main objective of the study is to rank different formulations of the investigational RSV vaccine based on immunogenicity and safety/reactogenicity data up to 1 month post-vaccination (Day 30).

The sample size was determined to allow reliable ranking of the investigational RSV vaccine formulations based on a desirability index (see details in APPENDIX E) combining the following endpoints:

- Incidence rate of any Grade 2 and any Grade 3 general AE (solicited and unsolicited) and any vaccine-related SAE during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
- Incidence rate of Grade 2 and Grade 3 fever during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
- Neutralising antibody titres against RSV-A at 1 month post-vaccination.
- PCA concentrations at 1 month post-vaccination.

Different plausible scenarios (2 for immunogenicity and 2 for reactogenicity) were simulated several times and the desirability analysis for formulation selection was applied on each simulated data package, as described below.

Immunogenicity

1. The functional antibody response covers a range from 10 log2 (30 PreF) to 12 log2 (120 PreF) for neutralising RSV-A titres, and from 100 to 200 for the PCA concentrations.
2. The functional antibody response covers a range from 10 log2 (30 PreF) to 11 log2 (120 PreF) for neutralising RSV-A titres, and from 100 to 150 for the PCA concentrations.

Reactogenicity

1. The incidence rate varies between 25% (30 PreF) and 30% (120 PreF) for the Grade 2/3 general AEs, and between 2% and 4% for Grade 2/3 fever.
2. The incidence rate varies between 25% (30 PreF) and 50% (120 PreF) for the Grade 2/3 general AEs, and between 4% and 10% for Grade 2/3 fever.

These four combinations of scenarios were simulated 10000 times in SAS, with a sample size of 95 evaluable subjects per group (see details in APPENDIX E). The percentages for ranking each formulation at the first place and for selecting the best formulation were computed.

Simulations in SAS shows that a sample size of 100 subjects enrolled per group (N=95 evaluable subjects) allows to reach a percentage >80% for selecting one of the best formulations, i.e. with a high immune response and acceptable reactogenicity. Moreover, this sample size will allow to have a small percentage (<5%) for selecting formulations with an unacceptable reactogenicity.

10.5. Cohorts for Analyses

Two cohorts will be defined for the purpose of the analysis: the Total Vaccinated Cohort (TVC) and the ATP cohort for analysis of immunogenicity. All analyses will be performed per treatment actually administered.

10.5.1. Total vaccinated cohort

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

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

10.5.2. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort 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 exclusion from an ATP analysis up to the corresponding timepoint as described in Section 6.6.2.
- Who did not present with an intercurrent medical condition leading to exclusion from an ATP analysis up to the corresponding timepoint, as described in Section 6.7.
- Who complied with the post-vaccination blood sampling schedule at the corresponding timepoint, as specified in Table 5.
- For whom post-vaccination immunogenicity results are available for at least 1 assay at the corresponding timepoint.

When presenting different timepoints, the ATP cohort for immunogenicity will be adapted for each timepoint (up to D30 and up to D90).

10.6. Derived and transformed data

The study groups will be defined by treatment actually administered.

Demography

- 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 during the 7-day follow-up period after vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects with documented safety data (i.e., symptom screen completed).
- For analysis of unsolicited AEs, SAEs and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report an event or concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

Immunogenicity

- Any missing or non-evaluable immunogenicity measurement will not be replaced:
  - For the within-group assessment, the descriptive analysis performed for each assay at each timepoint will exclude subjects with a missing or non-evaluable measurement.
  - For the between group assessments, the Analysis of covariance (ANCOVA) model will be fitted at each timepoint based on the subjects having a result at both the baseline and the considered timepoint.

- A seronegative subject will be defined as 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 (GMTs)/geometric mean concentrations (GMCs) will be computed by taking the anti-logarithm of the arithmetic mean of the log10 transformed titres/concentrations.
- Vaccine response in terms of RSV neutralising antibodies will be defined as:
  - At least a 4-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre <7 log2 (<128).
  - At least a 3-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in [7-8] log2 ([128-256]).
  - At least a 2.5-fold increase from pre-vaccination if pre-vaccination neutralising antibody titre in >8-10 log2 (>256-1024).
  - At least 1-fold from pre-vaccination if pre-vaccination neutralising antibody titre >10 log2 (>1024).
- The handling of data below the assay LLOQs for GMT/GMC calculations and evaluation of vaccine response will be described in the SAP.

10.7. Analysis of demographics

The analysis of demography will be performed on the TVC and on the ATP cohort for immunogenicity.

Demographic characteristics (age at vaccination in years, race, ethnicity, vital signs and BMI) 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 ATP analyses will be tabulated.
- The number of withdrawn subjects will be tabulated according to the reason for withdrawal.

10.8. Analysis for ranking RSV formulations

A desirability approach will be used to rank the formulations and guide the formulation selection, based on safety/reactogenicity and immunogenicity data up to 1 month post-vaccination.

This method is a multi-criteria decision making approach based on desirability functions. The main idea is to identify for each endpoint a desirability function that associates any value to another one between 0 and 1 depending on its desirability ('0' being considered as not desirable at all and '1' as the most desirable). An index with values between 0 and 1 will be created for each endpoint. An overall desirability index can be calculated by computing a weighted geometric mean of the endpoint indexes. By definition, this overall index also takes values between 0 and 1 and characterises the level of desirability of any candidate formulation by a single value [Dewé, 2015].

The desirability index calculations will include reactogenicity and safety data up to Day 7 post vaccination (on the TVC) and immunogenicity data at 30 days post-vaccination (on the ATP cohort for immunogenicity up to Day 30). The formulations will be ranked based on the values obtained with this overall desirability index. Refer to APPENDIX E for more details on the desirability analysis.

10.9. Analysis of safety

The analysis of safety will be performed on the TVC.

Within group evaluation

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

For fever during the 7-day follow-up period after vaccination, the number and percentage of subjects reporting fever will be reported by half degree (°C) cumulative increments. Similar tabulations will be performed for causally related fever, Grade 3 (> 39.5°C) 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 Medical Dictionary for Regulatory Activities (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) during the 7-day (Day 0 to Day 6) or 30-day (Day 0 to Day 29) follow-up period after vaccination will be summarised 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 timepoint.
- The maximum grading post-vaccination (from Day 7 to Day 90) versus baseline (Day 0) 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 D. Those laboratory parameters not included on FDA Toxicity Grading Scale will not be graded).

Assessment of anti-NEO immune response at Day 30 post-vaccination for each group:

- GMCs pre-and post-vaccination will be tabulated with 95% CI and represented graphically.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody concentrations at Day 30 over pre-vaccination will be tabulated with 95% CI.
- Distribution of the antibody concentrations pre-and post-vaccination and of fold increase after vaccination will be tabulated.

Between group evaluation

Exploratory comparisons between each investigational RSV vaccine group and (minus) the control group (*placebo*), and between the RSV vaccine groups (PreF-120 *minus* PreF 30, PreF-120 *minus* PreF-60, PreF-60 *minus* PreF 30) will be done in terms of the

percentage of subjects reporting any ≥ Grade 2, Grade 3 AE (solicited and unsolicited), and/or any fever > 38.5°C, and/or any vaccine-related SAE during the 7-day follow-up period after vaccination.

The standardised asymptotic 95% CI for the difference between the investigational RSV vaccine groups as well as between the investigational RSV groups and (minus) the control group will be computed.

10.10. Analysis of immunogenicity

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

Within group evaluation

Humoral Immune response to RSV vaccine

For each group, at each timepoint that blood samples are collected and for each assay (unless specified otherwise):

- GMTs/GMCs will be tabulated with 95% CI and represented graphically.
- Percentage of subjects above the seropositivity threshold will be tabulated with exact 95% CI.
- Pre- and post-vaccination antibody titres/concentrations will be displayed using reverse cumulative curves.
- The distributions of **neutralising** antibody titres will be tabulated.
- Percentage of responders in terms of **neutralising** antibody titres will be tabulated with exact 95% CI.
- Individual post-vaccination *versus* pre-vaccination results will be plotted using scatter plots. Results of the control group will be used as a reference.
- Geometric mean of ratios of antibody titres/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI.
- Distribution of the fold increase of **neutralising** antibody titres will be tabulated: by pre-vaccination titre category: < 7, 7-8, > 8-9, > 9-10, > 10-11, > 11-12, > 12 log2, and by cumulative categories: < 7, ≥ 7, ≥ 8, ≥ 9, ≥ 10, ≥ 11, ≥ 12 log2.
- The kinetics of individual antibody titres/concentrations will be plotted as a function of time for subjects with results available at all timepoints.
- 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 done by age category (18 - 32 years and 33 - 45 years).

Between group evaluation

Exploratory comparisons will be performed for **RSV neutralising** antibody titres and PCA concentrations post-vaccination (Day 30, Day 60 and Day 90) between the different RSV vaccine groups:

- Estimation of GMT/GMC ratios between groups with corresponding 95% CI using an ANCOVA model on the logarithm10 transformation of the titres/concentrations. The ANCOVA model will include the vaccine group as fixed effect and the pre-vaccination titre/concentration as regressor. If a statistically significant difference is found ($p < 0.05$), pairwise comparisons will be made using Tukey's multiple comparison adjustment.

10.11. Analysis of medically attended RTIs

The analysis will be performed on the TVC by study group.

The proportion of subjects with at least one medically attended RSV-associated RTI (with 95 % CI) will be calculated.

Descriptive analyses (mean, median, min, max) of viral load assessed by the quantitative PCR (RSV-A/B) of RSV-RTI cases will be tabulated for any cases where this assay is performed.

Medically attended RSV-associated RTI co-infected or colonised with another viral etiology identified by multiplex PCR will be described.

Medically attended RTI with any viral etiology identified by multiplex PCR will be described.

The proportion of subjects (with 95% CI) with at least one medically attended RTI (all causes) will be calculated by group.

10.12. 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.

10.13. 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.

10.13.1. Sequence of analyses

The statistical analyses will be performed in several steps:

- In preparation of the planned iSRC evaluation, analysis of safety and reactogenicity data up to at least 7 days post-vaccination of the first 25% of all subjects will be performed (see Section 8.10.2 for more information).
- The first main analysis on all subjects will be performed when all data up to 30 days post-vaccination are available (primary endpoints). In order to maintain the blind, this analysis by group will be performed by an independent statistician and the results which would lead to the unblinding of some subjects (e.g. a specific AE reported by one subject only) will be blinded (i.e. the group in which this event occurred will not be identified). No individual data listings will be provided.
- A second analysis will be performed when all data up to 90 days post-vaccination are available (secondary endpoints). At this point, the GSK statistician will be unblinded (i.e. will have access to the individual subject treatment assignments), but no individual listings will be provided. Given that summary results may unblind some specific subjects, the study will be conducted in a single-blind manner from this point onwards, with subjects remaining blinded up to study conclusion and the investigators will not have access to the treatment allocation up to study conclusion.
- The final analysis will be performed when all data up to study conclusion are available. All available tertiary endpoints will also be analysed in this step. Individual listings will only be provided at this stage.
- An integrated study report presenting all analyses will be written and made available to the investigators at that time.
- If data for tertiary endpoints become 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.

10.13.2. Statistical considerations for interim analyses

No interim analysis will be performed.

11. ADMINISTRATIVE MATTERS

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

11.1. 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 of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of 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 others, 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 monitor's and 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.

For eCRF, the monitor freezes completed and approved screens at each visit.

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 25 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 (PCD) and to

have secondary endpoint disclosed at latest 12 months after the Last Subject Last Visit (LSLV) 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.

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.

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 Biologicals' investigational RSV vaccine (GSK3003891A) is being 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 study RSV F-021.

12.2. Requirements for France

This section includes all the requirements of the French law (n° 2004-806 of 9th August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol and includes specifics GSK requirements.

1. Concerning the «STUDY POPULATION»

- In line with the local regulatory requirements, the following text about «PAYMENT TO SUBJECTS» is added:

  Subjects will be paid for the inconvenience of participating in the study. The amount of payment is stated in the informed consent form. Subjects not completing the study for whatever reason could be paid at the discretion of the Investigator, generally on a pro rata basis.

- In line with the local regulatory requirements, the following text about «NATIONAL FILE» is added:

  All subjects who will be paid, will be recorded into the "National File" by the investigator. They could be identified and monitored under the «Fichier national».

  The following details will be described:

  – Reference of the study
  – Surname and first name
  – Date and place of birth
  – Sex
  – Dates of beginning and termination of the study
  – Exclusion period
  – The total amount of allowance.

- In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS» is added:

  A subject will be eligible for inclusion in this study if he/she is either affiliated to or beneficiary of a social security category.

  It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

2. Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"

The expected number of patients to be recruited in France is declared to the French regulatory authority.

3. Concerning the "STUDY CONDUCT CONSIDERATIONS"

- In section "REGULATORY AND ETHICAL CONSIDERATIONS, INCLUDING THE INFORMED CONSENT PROCESS"
  - Concerning **the process for informing the patient** or his/her legally authorized representative, the following text is added:

    French Patient Informed Consent form is a document which summarizes the main features of the study and allows collection of the patient's written consent in triplicate. It also contains a reference to the authorisation of ANSM and the approval from the French Ethic committee and the maintenance of confidentiality of the returned consent form by GSK France.

  - Concerning **the management of the Patient Informed Consent forms**, the following text is added:

    The first copy of the Patient Informed Consent form is kept by the investigator. The second copy is kept by the Medical Direction of GSK France and the last copy is given to the patient or his/her legally authorized representative.

    The second copy of all the consent forms will be collected by the investigator under the Clinical Research Assistant's (CRAs) control, and placed in a sealed envelope bearing only:

    - the study number,
    - the identification of the Centre: name of the principal investigator and centre number,
    - the number of informed consents,
    - the date,
    - and the principal investigator's signature.

    Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.

- In section concerning the "NOTIFICATION TO THE HOSPITAL DIRECTOR" the following text is added:

  In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

- In section concerning the "INFORMATION TO THE HOSPITAL PHARMACIST" the following text is added:

  In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- In section "DATA MANAGEMENT" the following text is added:

  Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK Laboratory (Clinical Operations Department).

- In the section concerning "DEMOGRAPHIC DATA", the following text is added:

  In accordance with the data processing and freedom French law dated on 6th of January 1978 modified on the 6th of August 2004 - article 8, the ethnic origin can only be collected if the collection of this data is justified within the framework of this study.

- In the section concerning "TESTING OF BIOLOGICAL SAMPLES" the following text is added:

  In accordance with the Article L1211-2 of the French Public Health Code, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

4. Concerning the «SAE»

- In section "TRANSMISSION OF THE SAE REPORTS":

In case of paper CRF, the SAE Reports have to be transmitted to the GSK France Drug Safety Department, which name, address and phone number are:

Département de Pharmacovigilance

Laboratoire GlaxoSmithKline

100 Route de Versailles

78163 MARLY LE ROI

Tel: PPD

Fax: PPD

PPD

5. Monitoring visits

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GSK or of a service provider designated by GSK. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GSK or from a service provider designated by GSK. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GSK have direct access to all the data concerning the Study (test results, medical record, etc. …). This consultation of the information by GSK is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

6. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's eCRF use here below:

The Health Institution and the Investigator undertake:

i. That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GSK or by a company designated by GSK.

ii. That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.

iii. That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GSK.

iv. To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.

v. That the Investigator and the staff of the investigator center enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.

vi. That the Investigator resolves and returns to GSK the data queries issued by GSK or a service provider designated by GSK within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GSK and/or a company designated by GSK.

vii. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.

viii. To return at the end of the Study the IT Equipment and/or access codes to GSK or to any company designated by GSK and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

7. CTR publication

It is expressly specified that GSK and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GSK GROUP named Clinical Trial Register (CTR) including the registration of all the clinical trials conduct by the GSK Group and this before or after the publication of such results by any other process.

8. Data Protection French Law of 6 January 1978 (CNIL)

In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GSK to monitor and follow the implementation and the progress of the Study are declared with the CNIL by GSK. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GSK in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GSK Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

13. REFERENCES

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APPENDIX A LIST OF POTENTIAL IMMUNE-MEDIATED DISEASES

Please note that this list should be used as a guidance to identify diseases that could be autoimmune in nature. However, not all reported diseases in appendix will be autoimmune in nature and therefore represent an exclusion criterion. This will be based on the opinion of the investigator and/or specific available diagnostic data.

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome • Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)

Vasculitides	Blood disorders	Others
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyop athySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis • Celiac disease • Autoimmune pancreatitis	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease • Polyglandular autoimmune syndrome • Autoimmune hypophysitis

APPENDIX B DETAILED DESCRIPTION OF THE ASSAYS PERFORMED IN THE STUDY

Neutralisation assay

The serum neutralisation assay is a functional assay that measures the ability of serum antibodies to neutralise the cytopathic effects of RSV (for example, strains A and B) on the host cell line, hence RSV replication.

First, virus neutralization is performed by incubating a fixed amount of RSV-A long strain (ATCC No. VR-26) 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 with fluorescein isothiocyanate (FITC), allowing the visualization of plaques by immunofluorescence. 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 neutralizing antibody titer 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.

Anti-NEO ELISA

The anti-NEO ELISA assay is based on a direct ELISA format. This ELISA assay allows the quantification of NEO-specific IgG antibodies in human serum samples.

In summary, full-length recombinant human NEO is adsorbed onto a 96-well polystyrene microplate. After washing and blocking steps and dilutions of serum samples, controls and standards are added to the coated microplate. The standard curve is prepared with known concentrations of affinity purified rabbit anti-NEO polyclonal antibodies. After incubation, the microplate is washed to remove unbound primary antibodies. Bound primary antibodies are detected by the addition of a purified monoclonal mouse anti-human IgG antibody, conjugated to horse-radish peroxidase (HRP). This conjugated antibody cross-reacts with rabbit IgG (e.g. anti-NEO antibodies from rabbit used as positive control and standards) and detects human and rabbit IgG with a comparable sensitivity. Unbound HRP is removed by washing. Bound antibodies are quantified by the addition of the HRP substrate, tetramethylbenzidine (TMB), whereby a coloured product develops proportionally to the amount of anti-NEO antibodies present in the serum sample. The optical density (OD) of each sample dilution is then interpolated on a standard curve established with a non-weighted, 4-parameter logistic regression fitting algorithm and the corresponding antibody concentration, corrected for the dilution factor, is expressed in ng/mL.

PCA

The Palivizumab Competitive Assay is based on the competitive binding process between labelled antibody (Palivizumab-biotin) versus non-labelled antibody (Palivizumab-like antibodies in serum) targeting the same epitope on a coated antigen.

First, F protein antigens purified from CHO expression system are coated onto 96-well microplates. Then, after a washing and a blocking step, serial two-fold dilutions of test sera, positive control serum, and Palivizumab antibody reference standard are added in sequence with competitor antibodies (HRP-conjugated Palivizumab) and incubated to allow specific binding of antibodies directed against the F protein antigens. If Palivizumab-like antibodies are present in serum samples, they will compete with the HRP-conjugated Palivizumab antibodies for binding to the F protein coated antigen. After a washing step, the HRP substrate solution (TMB/H2O2) is added and a coloured product develops in a manner that is inversely proportional to the amount of Palivizumab-like antibodies contained in the test serum. The colour is quantified by reading the optical densities at 450-620 nm using a spectrophotometer. Antibody concentrations of individual serum and control samples are determined after interpolation from the ELISA standard curve using a four-parameter equation and are expressed as Palivizumab-equivalent antibodies in microgram per millilitre (µg/mL).

***PCR* (Amended 31 July 2017)**

Quantitative PCR able to discriminate RSV-A and RSV-B subtypes

Briefly, RSV A and RSV B RNA extraction from the nasal/throat swabs are detected in a duplex PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process involves nucleic acids extractions, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real-time PCR reaction using a calibration curve (absolute quantiation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

Qualitative multiplex PCR for detection of a panel of viruses:

A qualitative PCR multiplex assay is used for the detection and identification of multiple respiratory virus nucleic acid in nasal/throat swab from subjects with an assessment visit for MA-RTI. The following virus types and subtypes can be indentified in the assay

- **Influenza A virus (Flu A)**
- **Influenza B virus (Flu B)**
- **Human respiratory syncytial virus A (RSV A)**
- **Human respiratory syncytial virus B (RSV B)**
- **Human Influenza A virus subtype H1 (Flu-A-H1)**
- **Human Influenza A virus subtype H3 (Flu-A-H3)**

- **Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09)**
- **Human adenovirus (AdV)**
- **Human metapneumovirus (MPV)**
- **Human entrovirus (HEV)**
- **Human parainfluenza virus 1 (PIV1)**
- **Human parainfluenza virus 2 (PIV2)**
- **Human parainfluenza virus 3 (PIV3)**
- **Human parainfluenza virus 4 (PIV4)**
- **Human bocavirus 1/2/3/4 (HBoV)**
- **Human rhinovirus A/B/C (HRV)**
- **Human coronavirus 229E (229E)**
- **Human coronavirus NL63 (NL63)**
- **Human coronavirus OC43 (OC43)**

Following total nucleic acids extraction, viruses are detected by multiplex real-time RT-PCR assays targeting the avove mentioned viruses. A comparative analysis of the fluorescence intensities of each target is preformed to detect the viruses present in the sample.

APPENDIX C CLINICAL LABORATORIES

Table 21 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Clinical Laboratory Sciences, Rixensart	Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals 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, Québec Canada H7V 3S8
Q^2 Solutions Clinical Trials	***The Alba Campus (Rosebank)*** Livingston West Lothian, EH54 7EG Scotland, UK

APPENDIX D 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 categories 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
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
Hematology* **				
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

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.

*** 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 D**

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.

APPENDIX E DESIRABILITY APPROACH

- **DERIVED ENDPOINTS**

The following endpoints will be computed and taken into account in the desirability analysis:

1. Incidence rate of any Grade 2 and any Grade 3 general AE (solicited and unsolicited) and any vaccine-related SAE during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
2. Incidence rate of Grade 2 and Grade 3 fever during the 7-day follow-up period after vaccination for each investigational RSV vaccine formulation.
3. Geometric mean of neutralising antibody titres against RSV-A at Day 30 adjusted for pre-vaccination titres.
4. Geometric mean of PCA concentrations at Day 30 adjusted for pre-vaccination titres.

- **STATISTICAL COMPUTATION**

Reactogenicity

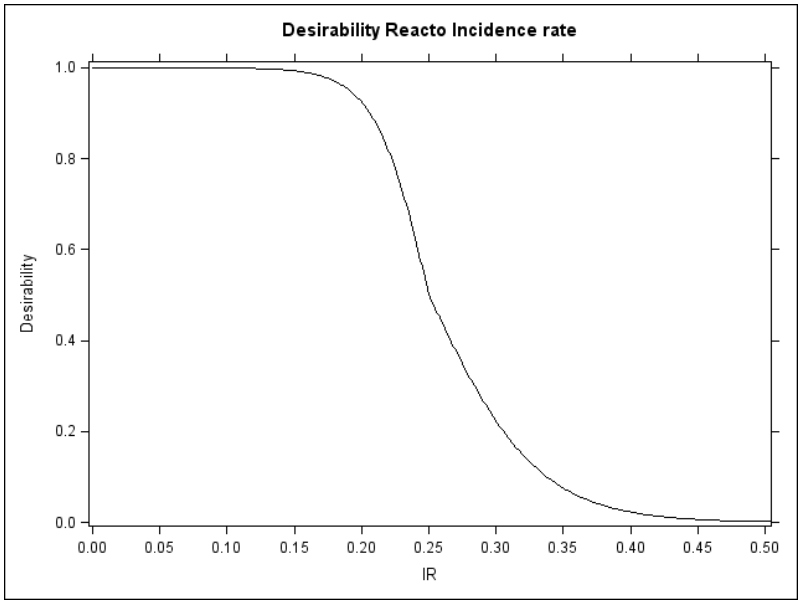
A logistic regression model will be fitted on each reactogenicity endpoint (any Grade 2/3 general AE and any related SAE, Grade 2/3 fever) reported during the 7-day follow-up period after vaccination, including all RSV formulations.

For any Grade 2/3 general AEs and any related SAEs, the incidence rate estimate (HR) will be transformed in a [0,1] desirability index using the following function:

$$DR1 = \begin{cases} \dfrac{1}{1 + \exp\left(-50 * (0.25 - HR)\right)}, & \text{if } HR \leq 0.25 \\ \dfrac{1}{1 + \exp\left(-25 * (0.25 - HR)\right)}, & \text{if } IR \geq 0.25 \end{cases}$$

where HR is the incidence rate estimated by the model. This function will allocate a desirability value of 1, 0.5 and 0 to incidence rate equal to 0.1, 0.25 and 0.5 respectively (see Figure 3).

Figure 3 Desirability function for the incidence rate of Grade 2/3 general AEs and related SAEs - for each investigational RSV vaccine formulation

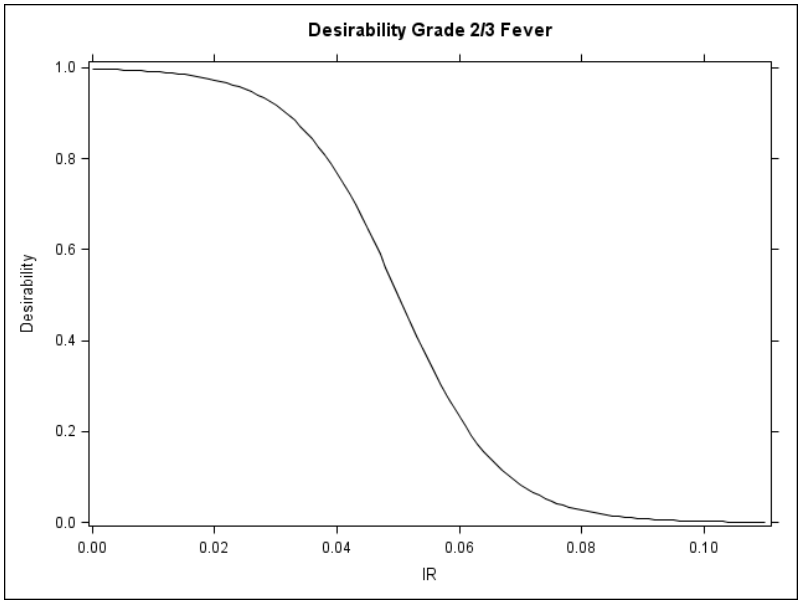


For Grade 2/3 fever, the incidence rate estimate (IR) will be transformed in a [0,1] desirability index using the following function:

$$DR2 = \frac{1}{1 + \exp(-120 * (0.05 - IR))}$$

where IR is the incidence rate estimated by the model. As illustrated in Figure 4, the function will allocate desirability values of 1, 0.5 and 0 to incidence rate equal to 0, 0.05 and 0.1 respectively.

Figure 4 Desirability function for the incidence rate of Grade 2/3 fever - for each investigational RSV vaccine formulation



Finally, the reactogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DR = \sqrt{DR1 * DR2}$$

Immunogenicity

A response-surface model will be fitted on the log-transformed titre for each immune response (neutralising anti-RSV-A and PCA), including all RSV formulations.

As formulations inducing a high immune response will be considered suitable, the lower limit (LL) of the estimated GMT/C adjusted for pre-vaccination titres will be the statistical criterion considered for decision making.

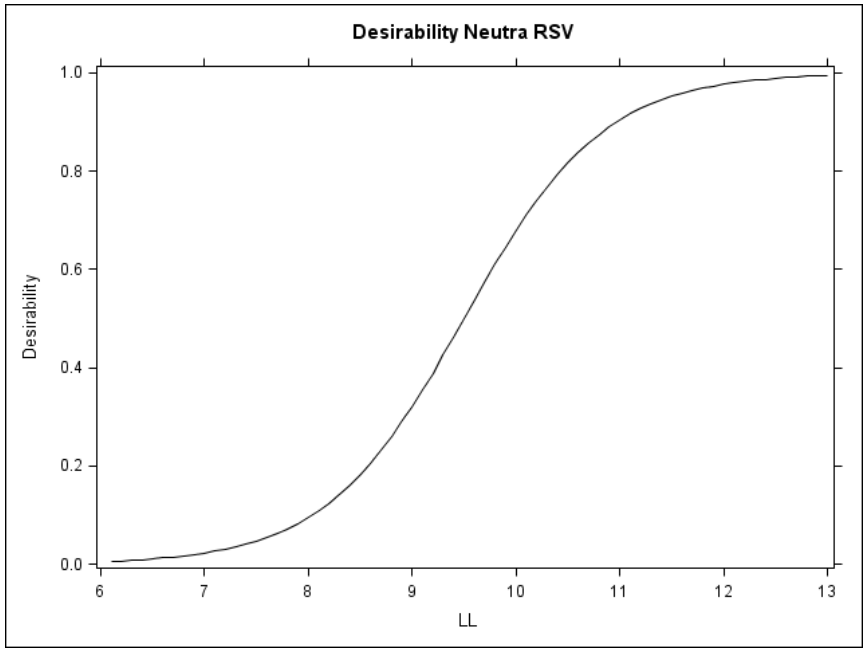
Neutralising anti-RSV-A titres

The LL of the GMT estimate will be transformed into a [0,1] desirability index using the function:

$$DI1 = \frac{1}{1 + \exp(1.5 * (9.5 - LL))}$$

where LL is the lower limit of the 95% confidence interval of the GMT adjusted for pre-vaccination titres in log base 2. The function was chosen to have a desirability of 0 at LL value ≤ 6 log2 (=128), and a desirability of 1 at LL value ≥ 13 log2. This function is illustrated in Figure 5.

Figure 5 Desirability function for neutralising anti-RSV-A GMTs - for each investigational RSV vaccine formulation



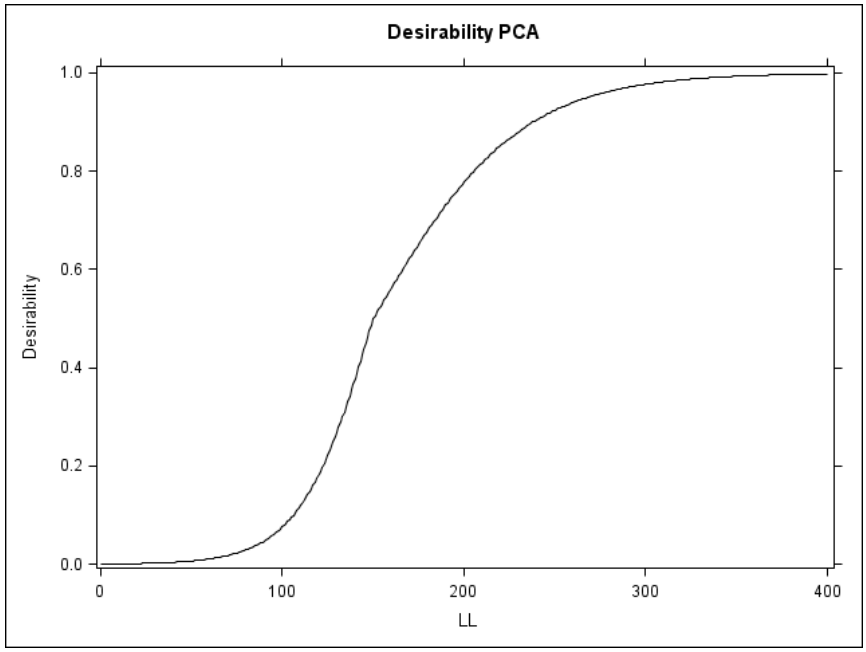
PCA concentrations

The LL of the GMC adjusted for pre-vaccination titres estimate will be transformed using the following function:

$$\mathrm{DI2} = \begin{cases} \dfrac{1}{1+\exp(0.05*(150-\mathrm{LL}))}, & \mathrm{if LL} \leq 150 \\ \dfrac{1}{1+\exp(0.025*(150-\mathrm{LL}))}, & \mathrm{if LL} \geq 150 \end{cases}$$

As illustrated in Figure 6, a PCA response of 25, 150 and 400 µg/mL will have a desirability value of 0, 0.5 and 1 respectively.

Figure 6 Desirability function for PCA concentrations - for each investigational RSV vaccine formulation



Finally, the immunogenicity index will be computed by taking the geometric mean of the 2 indexes:

$$DI = \sqrt{DI1 * DI2}$$

Overall desirability index

The overall desirability index will be obtained by computing the following weighted geometric mean: $D = DR^{0.4} * DI^{0.6}$

Finally, to address the robustness of the ranking, an evaluation of the uncertainty will be performed using a bootstrap approach.

- **SAMPLE SIZE EVALUATION THROUGH SIMULATION**

Two scenarios were envisaged with regards to immune response induced by the three RSV formulations (Table 24).

Table 24 Immunogenicity scenarios used for the desirability index simulations

Endpoint included in the desirability index	Formulation	Scenario 1	Scenario 2
RSV-A	30 PreF	10 log2	10 log2
	60 PreF	11 log2	10.5 log2
	120 PreF	12 log2	11 log2
PCA	30 PreF	100	100
	60 PreF	150	125
	120 PreF	200	150

Scenario 1 is assuming a higher increase of the immune response with the increased dose compared to scenario 2.

Two scenarios were also envisaged with regards to adverse event reactions induced by the three RSV formulations (Table 25).

Table 25 Reactogenicity scenarios used for the desirability index simulations

Endpoint included in the desirability index	Formulation	Scenario 1	Scenario 2
Grade 2/3 general AEs	30 PreF	25%	25%
	60 PreF	27.5%	35%
	120 PreF	30%	50%
Grade 2/3 fever	30 PreF	2%	4%
	60 PreF	3%	6%
	120 PreF	4%	10%

Scenario 2 is assuming a higher increase of the incidence of AEs with the increased dose compared to scenario 1.

These 4 combinations of scenarios were simulated 10000 times with a sample size of 95 evaluable subjects per group. The percentages for ranking each formulation at first place and for selecting the best one were computed and are described in the table below.

Table 26 Result of the ranking of the formulations following simulations of the different scenarios with a sample size of 95 subjects per group

Immuno scenario	Ranking #1 for immuno	Reacto scenario	Ranking#1 for reacto	Ranking #1 overall
1	120 PreF in 85.2% of simulations	1	30 PreF or 60 PreF in 90.2% of simulations	60 PreF or 120 PreF in 96.9% of simulations
		2	30 PreF in 91.2% of simulations	30 PreF or 60 PreF in 95.2% of simulations (4.8% for 120 PreF)
2	60 PreF or 120 PreF in 94% of simulations	1	30 PreF or 60 PreF in 90.2% of simulations	60 PreF or 120 PreF in 82.4% of simulations
		2	30 PreF in 91.6% of simulations	30 PreF or 60 PreF in 98.7% of simulations (1.3% for 120 PreF)

APPENDIX F AMENDMENTS TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccine Value & Health Science (VVHS) **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	204812 (RSV F-021)
IND number	15487
EudraCT number	2016-001135-12
Amendment number:	Amendment 1
Amendment date:	21 August 2017
Co-ordinating author:	PPD (XPE Pharma & Science for GSK Biologicals) PPD, Senior Science Writer
Rationale/background for changes: The following minor changes have been made: • The kit used for multiplex respiratory viral panel testing has been changed. • Changes to the study personnel have been included on the protocol cover page.	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Throughout the document, the following changes have been made:

On **the protocol cover page**, the following changes have been made:

Co-ordinating author(s)

(Amended 31 July 2017)

- PPD (XPE Pharma & Science for GSK Biologicals)
- PPD ***, Senior Science Writer***

Contributing authors

(Amended 31 July 2017)

- PPD and PPD, Clinical & Epidemiology Project Lead
- PPD, PPD, and PPD, Clinical Research & Development Leads
- PPD, Lead Statistician
- PPD, Project Statistician
- PPD, PPD, and PPD, Study Delivery Leads
- PPD ***(Aixial for GSK Biologicals)***

PPD (CVO-Europe for GSK Biologicals), Vaccine Supply Coordinator

- PPD, Clinical Read-Out Team Leader

In Section Trademarks, the following changes have been made:

Trademarks not owned by the ~~GlaxoSmithKline~~ GSK group of companies	Generic description
Synagis™ (MedImmune LLC.)	Recombinant humanized monoclonal anti-RSV antibody
Allplex (Seegene)	***Respiratory panel assay***

In Section 5.7.3 Laboratory assays, the following changes have been made.

The following laboratory assay is planned:

Table 9 Molecular biology (PCR tests)

System	Component	Method	Unit	Laboratory
Nasal swab*	~~RSV~~ ~~Influenza A, including subtypes H1 and H3~~ ~~Influenza A H1N1 2009~~ ~~Influenza B~~ ~~Parainfluenza virus type 1, 2, 3, and 4~~ ~~Human Metapneumovirus~~ ~~Enterovirus/Rhinovirus~~ ~~Adenovirus~~ ~~Bocavirus~~ ~~Coronavirus - 229E, OC43, NL63, HKU1~~ ***Influenza A virus (Flu A)*** ***Influenza B virus (Flu B)*** ***Human respiratory syncytial virus A (RSV A)*** ***Human respiratory syncytial virus B (RSV B)*** ***Human influenza A virus subtype H1 (Flu A- H1)*** ***Human influenza A virus subtype H3 (Flu A-H3)*** ***Human influenza A virus subtype H1pdm09 (Flu A-H1pdm09)*** ***Human adenovirus (AdV)*** ***Human metapneumovirus (MPV)*** ***Human enterovirus (HEV)*** ***Human parainfluenza virus 1 (PIV1)***	Multiplex PCR (PCRMTX) ~~(Luminex)~~** ***(Allplex Respiratory Panel or equivalent)*****	Qualitative assay (positive/negative)	GSK Biologicals*** ***or designated laboratory***

	Human parainfluenza virus 2 (PIV2) ***Human parainfluenza virus 3 (PIV3)*** ***Human parainfluenza virus 4 (PIV4)*** ***Human bocavirus 1/2/3/4 (HBoV)*** ***Human rhinovirus A/B/C (HRV)*** ***Human coronavirus 229E (229E)*** ***Human coronavirus NL63 (NL63)*** ***Human coronavirus OC43 (OC43)***			
Nasal swab*	RSV-A/B RNA	Quantitative ***Reverse Transcription*** ~~real-time~~ PCR (QRTPCR) ****	Copies/ml	GSK Biologicals***

Respiratory Viruses Panel (Multiplex PCR) will be performed on all specimens. ***Refer to APPENDIX B for the laboratory addresses.*

****Additional testing with RSV-A/B RNA quantitative ~~real-time~~ ***reverse transcription*** PCR may be performed.

Table 12 Molecular biology tests

Nasal swab sampling timepoint		**Group**	**No. Subjects**	**Component**
Type of contact (timepoint)	**Sampling timepoint**			
Unscheduled visit for MA-RTI*	Unscheduled	All subjects	All subjects with a nasal swab sample*	***Influenza A virus (Flu A)*** ***Influenza B virus (Flu B)*** ***Human respiratory syncytial virus A (RSV A)*** ***Human respiratory syncytial virus B (RSV B)*** ***Human influenza A virus subtype H1 (Flu A- H1)*** ***Human influenza A virus subtype H3 (Flu A-H3)*** ***Human influenza A virus subtype H1pdm09 (Flu A-H1pdm09)*** ***Human adenovirus (AdV)*** ***Human metapneumovirus (MPV)*** ***Human enterovirus (HEV)*** ***Human parainfluenza virus 1 (PIV1)*** ***Human parainfluenza virus 2 (PIV2)*** ***Human parainfluenza virus 3 (PIV3)*** ***Human parainfluenza virus 4 (PIV4)*** ***Human bocavirus 1/2/3/4 (HBoV)*** ***Human rhinovirus A/B/C (HRV)*** ***Human coronavirus 229E (229E)*** ***Human coronavirus NL63 (NL63)*** ***Human coronavirus OC43 (OC43)*** ~~RSV~~ ~~Influenza A, including subtypes H1 and H3~~ ~~Influenza A H1N1 2009~~ ~~Influenza B~~ ~~Parainfluenza virus type 1, 2, 3, and 4~~ ~~Human Metapneumovirus~~

				~~Enterovirus/Rhinovirus~~ ~~Adenovirus~~ ~~Bocavirus~~ ~~Coronavirus - 229E, OC43, NL63, HKU1~~
				RSV-A/B RNA**

Additional testing with RSV-A/B RNA quantitative ***reverse transcription* ~~real-time~~ PCR may be performed.

In Appendix B Detailed Description of the Assays Performed in the Study, the following changes have been made:

PCR

Quantitative PCR able to discriminate RSV-A and RSV-B subtypes

Briefly, RSV A and RSV B RNA extraction from the nasal/throat swabs are detected in a duplex PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process involves nucleic acids extractions, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real-time PCR reaction using a calibration curve (absolute quantiation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

Qualitative multiplex PCR for detection of a panel of viruses:

A qualitative PCR multiplex assay is used for the detection and identification of multiple respiratory virus nucleic acid in nasal/throat swab from subjects with an assessment visit for MA-RTI. The following virus types and subtypes can be indentified in the assay

- **Influenza A virus (Flu A)**
- **Influenza B virus (Flu B)**
- **Human respiratory syncytial virus A (RSV A)**
- **Human respiratory syncytial virus B (RSV B)**
- **Human Influenza A virus subtype H1 (Flu-A-H1)**
- **Human Influenza A virus subtype H3 (Flu-A-H3)**
- **Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09)**
- **Human adenovirus (AdV)**
- **Human metapneumovirus (MPV)**
- **Human entrovirus (HEV)**
- **Human parainfluenza virus 1 (PIV1)**
- **Human parainfluenza virus 2 (PIV2)**

- **Human parainfluenza virus 3 (PIV3)**
- **Human parainfluenza virus 4 (PIV4)**
- **Human bocavirus 1/2/3/4 (HBoV)**
- **Human rhinovirus A/B/C (HRV)**
- **Human coronavirus 229E (229E)**
- **Human coronavirus NL63 (NL63)**
- **Human coronavirus OC43 (OC43)**

Following total nucleic acids extraction, viruses are detected by multiplex real-time RT-PCR assays targeting the avove mentioned viruses. A comparative analysis of the fluorescence intensities of each target is preformed to detect the viruses present in the sample.

~~**RSV-A/B Quantitative PCR**~~

~~Quantitative PCR able to discriminate RSV-A and RSV-B subtypes: RSV-A and RSV-B RNAs, extracted from the nasal swab are detected in a duplex format using specific amplification primers and fluorescent TaqMan™ probes. The process involves viral RNA extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real- time PCR reaction using a calibration curve (absolute quantification).~~

~~**Multiplex Viral Qualitative PCR**~~

~~Qualitative multiplex PCR for detection of a panel of 17 viruses: xTAG™ RVP FAST assay: xTAG™ RVP FAST assay is a qualitative nucleic acid multiplex tests intended for the simultaneous detection and identification of multiple respiratory virus nucleic acids in nasal/nasopharyngeal swabs from individuals suspected of respiratory tract infections. After nucleic acid extraction, a multiplexed PCR reaction is performed to amplify the regions of interest in the targeted infectious agent genes. The PCR reaction product is then subjected to a hybridization/detection step and attached to an xTAG universal tag sequence. The 5' universal tag sequence is hybridized to the complementary anti-tag sequence coupled to a particular bead set. The hybridized beads are detected and results are analyzed by the data analysis software.~~

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204812 (RSV F-021)
IND number	15487
EudraCT number	2016-001135-12
Date of protocol amendment	Amendment **1** Final 21 August 2017
Detailed Title	A Phase II, randomised, observer-blind, controlled, multi-country study to rank different formulations of OSK Biologicals' investigational RSV vaccine (GSK3003891A), based on immunogenicity, reactogenicity and safety, when administered to healthy women, aged 18 - 45 years.
Sponsor signatory	***Alexander Schmidt*** Clinical & Epidemiology Project Lead
Signature	
Date	09/06/2017

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