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

Primary study vaccine and number	• GlaxoSmithKline (GSK) Biologicals' respiratory syncytial virus (RSV) vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A)
Other study vaccines	• GSK's multicomponent meningococcal B vaccine (recombinant, adsorbed) (*Bexsero*) • Pfizer's meningococcal group A, C, W-135 and Y conjugate vaccine (*Nimenrix*) • GSK's pneumococcal polysaccharide conjugate vaccine *(Synflorix)* • GSK's meningococcal group A, C, W-135 and Y conjugate vaccine (*Menveo*) • Placebo (Formulation buffer S9b)
eTrack study number and abbreviated title	204894 (RSV PED-011)
Investigational New Drug (IND) number	16999
EudraCT number	2018-000431-27
Date of protocol	Final Version 1: 08 February 2018
Date of protocol amendment	Amendment 1 Final: 16 July 2018 Amendment 2 Final: 24 January 2019 Amendment 3 Final: 21 March 2019 Amendment 4 Final: 01 August 2019
Title	A study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' RSV investigational vaccine based on viral proteins encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A) in infants.
Detailed title	A Phase 1/2, randomized, observer-blind, controlled, multi-center study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' respiratory syncytial virus (RSV) investigational vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A), when administered intramuscularly ***as*** a single dose or as two doses according to a 0, 1-month schedule**,** to infants aged 6 and 7 months.

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Co-ordinating authors	• PPD (Scientific Writer) • PPD (Scientific Writer) • PPD (Scientific Writer, Keyrus Biopharma contractor for GSK Biologicals) • PPD (Expert Scientific Writer)
Contributing authors **(Amended 1 August 2019)**	• PPD (Clinical Research and Development Lead) • PPD (Clinical Research and Development Lead) • PPD (Lead Statistician) • PPD ***(Project Statistician)*** • PPD *(Project Statistician)* • PPD (Study Delivery Lead) • PPD (Study Delivery Lead) • PPD (Study Delivery Lead) • PPD (Study Delivery Lead) • PPD (Clinical Trial Supply Manager) • PPD (Clinical Read-out Team Leader) • PPD (Clinical Read-out Team Leader) • PPD (Clinical Laboratory Sciences [CLS] Study Manager, Business & Decision Life Sciences contractor for GSK Biologicals)

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Contributing authors	• PPD (Central Safety Physician) • PPD (Central Safety Scientist) • PPD (Oversight Data Manager, Keyrus Biopharma contractor for GSK Biologicals) • PPD (Global Regulatory Representative) • PPD (Global Patent Representative) • PPD (Clinical and Epidemiology Research and Development Project Lead) • PPD (Clinical and Epidemiology Research and Development Project Lead)

GSK Biologicals' Protocol DS v 15.0

Protocol Amendment 4 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204894 (RSV PED-011)
IND number	16999
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Date of protocol amendment	Amendment 4 Final: 01 August 2019
Detailed Title	A Phase 1/2, randomized, observer-blind, controlled, multi-center study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' respiratory syncytial virus (RSV) investigational vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A), when administered intramuscularly as a single dose or as two doses according to a 0, 1-month schedule**,** to infants aged 6 and 7 months.
Sponsor signatory	Antonio Gonzalez Lopez (Clinical and Epidemiology Research & Development Project Lead)
Signature	
Date	

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Protocol Amendment 4 Rationale

Amendment number:	Amendment 4
Rationale/background for changes:	

- The per protocol set definition in the synopsis was updated.
- Clarification was added on recruiting sufficient subjects with negative RSV exposure status.
- Clarification was added to RTI and LRTI episode definitions.
- Table 24 was updated to clarify the visit window intervals.
- Additional wording was added to indicate that for countries where it is not acceptable to provide copies of medical records to the sponsors, the investigator will transcribe the required information in a manner that respects the subject's anonymization.
- In addition, some typographical errors have been corrected throughout the protocol.

Protocol Amendment 4 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' study 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 vaccines, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

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Investigator name	_____
Signature	_____
Date	_____

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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 9.4.2.

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 9.8.

SYNOPSIS

Detailed title

A Phase 1/2, randomized, observer-blind, controlled, multi-center study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' respiratory syncytial virus (RSV) investigational vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A), when administered intramuscularly as a single dose or as two doses according to a 0, 1-month schedule, to infants aged 6 and 7 months.

Indication

Active immunization of infants for the prevention of any lower respiratory tract infections (LRTI; bronchiolitis and [broncho]pneumonia) associated with respiratory syncytial virus (RSV).

Rationale for the study and study design

- **Rationale for the study**

GSK Biologicals is developing the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) to protect infants from RSV diseases.

The purpose of this study is to provide critical information on the safety, reactogenicity and immunogenicity profile of the ChAd155-RSV vaccine in infants likely to be unexposed to RSV before moving to a proof-of-concept trial in infants. An important aspect of this phase I/II study will be to compare a single lower dose of $1.5x10^{10}$ viral particles (vp) and two higher doses of $5x10^{10}$ vp according to a 0, 1 month schedule administered to infants aged 6 and 7 months likely to be unexposed to RSV, which is powered to statistically exclude a level of risk of 'vaccine-induced enhanced RSV disease', associated with historic FI-RSV vaccine trials.

- **Rationale for the study design**

Study population: The immunogenicity, safety and reactogenicity of the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) has been evaluated in healthy adults aged 18 to 45 years (study 201974 [RSV PED-001; NCT02491463]). A clinical study is currently being conducted in RSV-seropositive infants aged 12 to 23 months (study 204838 [RSV PED-002]). The safety profile of the ChAd155-RSV vaccine in adults (study 201974 [RSV PED-001; NCT02491463]) has been evaluated and determined to be satisfactory by an Independent Data Monitoring Committee (IDMC). Should there be a satisfactory safety profile of the ChAd155-RSV vaccine in RSV-seropositive infants, as evaluated by an IDMC on Day 60 data (i.e., 30 days post-Dose 2 of the highest dose level) of the study RSV PED-002, the present study will be performed. This study will

be conducted in infants aged 6 and 7 months, (having a low chance of natural exposure to RSV before inclusion in the study). Although potentially both RSV-exposed and RSV-unexposed subjects will be enrolled, the primary analysis for incidence of LRTI will be conducted in infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing). This study will support the decision to age de-escalate to the targeted population (infants as from 6 weeks of age) in the subsequent study.

C*ontrol vaccines:** Active comparators are included as a control for the reactogenicity, safety and immunogenicity assessments. The choice of one of four control vaccines, as active comparators has been driven by the fact that, in most countries at least one of these vaccines meet the criteria of being of medical benefit, and where possible licensed for infants and used with a similar dose and schedule as the investigational RSV vaccine, while not being part of a national immunization program. The choice of which active control comparator vaccine ***to be used will be done at the country level and will be used according to its approved label.

A placebo group was added to accommodate a request from countries that were not able to identify a suitable active comparator.

Study blinding: Given the different appearance and storage conditions of the investigational RSV vaccine and active control comparator vaccines, double blinding is not possible and the study will be conducted in an observer-blind manner.

When all data up to Day 61 are available, a statistical analysis will be performed. This analysis may lead to the unblinding of some subjects. As a consequence, after Day 61, the study cannot be considered as observer-blind, but will be conducted in a single blind manner, with subjects' parent(s)/ legally acceptable representative(s) (LAR[s]) remaining blinded up to the last study visit (end of the second RSV transmission season), while the investigator will still not have access to the individual subject treatment allocation up to the last study visit (end of the second RSV transmission season), except in case of emergency unblinding.

- **Regimen, dose and route of administration:**

This study will evaluate two regimens of the ChAd155-RSV vaccine; either one lower dose of $1.5x10^{10}$ vp or two doses of $5x10^{10}$ vp will be administered. For the two dose schedule, an interval of approximately one month between dosing will be used. A single dose arm was added in this 6-7 month-old

study population before going to target population in subsequent studies.

The dose levels to be evaluated in this study have previously been administered to RSV-seropositive infants aged 12 to 23 months (study RSV PED-002 [204838]) and will have been shown to have a satisfactory safety profile and reviewed by the IDMC. These doses might be modified following review by the IDMC of the safety data from study RSV PED-002 (204838). However, if no significant safety concerns are identified with the highest ChAd155-RSV vaccine dose of $5x10^{10}$ vp administered in the RSV PED-002 study, that dose will be the highest does level evaluated in this study.

In the bovine RSV challenge model in seronegative, colostrum-restricted newborn calves, both a single and two dose regimen of $5x10^{10}$ vp ChAd155-RSV have been evaluated. The two dose regimen was given at an interval of four weeks apart. Both regimens showed a similar level of protection against challenge with bovine RSV, but the two dose regimen showed higher immunogenicity. Neither regimen was associated with pulmonary pathology.

In this study, infants aged 6 and 7 months will be administered the first dose of the ChAd155-RSV vaccine before the RSV season to increase the probability of enrolling infants unexposed to RSV, and then followed up through the RSV season. The second dose will be given one month after the first dose.

Objectives

Primary

- To evaluate the safety and reactogenicity of the RSV investigational vaccine when administered IM as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses according to a 0, 1-month schedule, up to 60 days after Dose 1 (i.e., Day 61) in infants aged 6 and 7 months.

Secondary

- To evaluate the occurrence of RSV respiratory tract infections of any severity from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season, in infants aged 6 and 7 months.
- To evaluate the safety of the RSV investigational vaccine when administered IM as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses according to a 0, 1-month schedule**,** from study start (Day 1) up to the end of the second RSV transmission season in infants aged 6 and 7 months.

- To evaluate the occurrence of RSV respiratory tract infections from Visit 1 (Day 1, after Dose 1) up to the end of the second RSV transmission season, in infants aged 6 and 7 months.
- To evaluate the occurrence of very severe RSV-LRTI from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season in RSV infected infants aged 6 and 7 months with a negative RSV exposure status (at screening based on in-stream baseline serological testing).
- To evaluate the humoral immunogenicity induced by the RSV investigational vaccine when administered IM as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses according to a 0, 1-month schedule, from study start (Day 1) up to the end of the first RSV transmission season, in infants aged 6 and 7 months.

Tertiary

- If deemed necessary, to further characterize the immune response of the RSV investigational vaccine when one ($1.5x10^{10}$ vp) dose or two ($5x10^{10}$ vp) doses are administered IM according to a 0, 1-month schedule to infants aged 6 and 7 months.

Study design

- Experimental design: Phase I/II, observer-blind, randomized, controlled, multi-centric study with three parallel groups.
- Duration of the study: approximately 24 months.
  - Epoch 001: Screening Visit starting up to 30 days before first vaccination and ending on Day -1.
  - Epoch 002: primary starting at Visit 1 (Day 1) and ending at Visit 5 (Day 61).
  - Epoch 003: follow-up starting after Visit 5 (Day 61)* and ending at Visit 7 (end of the first RSV transmission season).
  - Epoch 004: follow-up starting after Visit 7 (end of the first RSV transmission season)* and ending at Visit 8 (end of the second RSV transmission season).

  *Any safety, immunogenicity and disease surveillance data collected beyond Visit 5 (Day 61) will be collected in Epoch 003. Any safety, immunogenicity and disease surveillance data collected beyond Visit 7 (end of the first RSV transmission season) will be collected in Epoch 004.

- Primary Completion Date (PCD): Visit 5 (Day 61).
- End of Study (EoS): Last testing results released of samples collected at Visit 8 (end of the second RSV transmission season) related to primary and secondary endpoints.*

  * Up to Visit 8 (end of the second RSV season), there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season ***or*** if following active or a passive surveillance contacts, a subject presents symptoms of respiratory tract infection (RTI), a nasal swab will be collected.
- Study population: healthy infants, born at term, aged 6 and 7 months (from the day they complete 6 months of life for a period of 2 months; for example a child born 01-Jan-2019 is eligible for the period 01-Jul-2019 through to 31-Aug-2019).
- Study groups:

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Target Numbers of subjects	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
1D RSV + Bexsero	50	6 – 7 months	N/A	x	x	x
1D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
1D RSV + Synflorix		6 – 7 months	N/A	x	x	x
1D RSV + Menveo		6 – 7 months	N/A	x	x	x
1D RSV + Placebo		6 – 7 months	N/A	x	x	x
2D RSV + Bexsero	50	6 – 7 months	N/A	x	x	x
2D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
2D RSV + Synflorix		6 – 7 months	N/A	x	x	x
2D RSV + Menveo		6 – 7 months	N/A	x	x	x
2D RSV + Placebo		6– 7 months	N/A	x	x	x
Bexsero	50	6 – 7 months	N/A	x	x	x
Nimenrix		6 – 7 months	N/A	x	x	x
Synflorix		6 – 7 months	N/A	x	x	x
Menveo		6 – 7 months	N/A	x	x	x
Placebo		6 – 7 months	N/A	x	x	x

1D*:* 1 Dose ($1.5x10^{10}$ vp/dose)***;*** **RSV**: ChAd155-RSV vaccine; **2D*:*** 2 Dose ($5x10^{10}$ vp/dose)***;*** **N/A*:*** Not Applicable.

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	1D RSV ChAd	2D RSV ChAd	Bexsero	Nimenrix	Synflorix	Menveo	FB
Vaccine/ Product name	1D ChAd155-RSV 1.5X10^{10} vp/dose	2D ChAd155-RSV 5X10^{10} vp/dose	Bexsero	Nimenrix	Synflorix	Menveo	FB
Study Groups							
1D RSV + Bexsero	x		x				x
1D RSV + Nimenrix	x			x			x
1D RSV + Synflorix	x				x		x
1D RSV + Menveo	x					x	x
1D RSV + Placebo	x						x
2D RSV + Bexsero		x	x				
2D RSV + Nimenrix		x		x			
2D RSV + Synflorix		x			x		
2D RSV + Menveo		x				x	
2D RSV + Placebo		x					
Bexsero			x				x
Nimenrix				x			x
Synflorix					x		x
Menveo						x	x
Placebo							x

ChAd155-RSV: Chimpanzee Adenovirus Type 155 RSV vaccine; **FB**: Formulation buffer S9b; **RSV ChAd**: ChAd155-RSV vaccine; **1D*:*** 1 Dose (1.5x10^{10} vp/dose)***; 2D:*** 2 Dose (5x10^{10} vp/dose).

– Controls: active comparator vaccines (Bexsero, or Nimenrix, or *Synflorix,* or *Menveo*, or Placebo (Formulation buffer [FB])*

* The choice of active comparator vaccine or Placebo is done at the country level.

- Vaccination schedules:

  RSV investigational vaccine:

  – In the 1 Dose (1D) groups, a single lower dose of 1.5x10^{10} vp will be administered IM at Day 1 (Visit 1). Formulation buffer will be administered in the 1D groups at Day 31 (Visit 3). In the 2 Dose (2D) groups, two doses of 5x10^{10} vp will be administered IM according to a 0, 1-month schedule, (i.e., at Day 1 [Visit 1] and Day 31 [Visit 3]) (see Synopsis Table 3). Dose 1 will be administered before the first RSV season and the second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the Study Procedures Manual [SPM]. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be

applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable.

Comparator or Placebo:

- In countries where Bexsero or Nimenrix is used as a control, two doses will be administered IM with at least a 2 month interval between these primary doses. A booster dose will be administered IM in the second year of life at Visit 7, with an interval of at least 2 months between the primary series and booster dose. The first Bexsero or Nimenrix dose will be administered at Day 1 (Visit 1) (in the groups receiving only Bexsero or Nimenrix, respectively). In the groups receiving only Bexsero or Nimenrix, the second dose will be at Day 61 (Visit 5). The first Bexsero or Nimenrix dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of Bexsero or Nimenrix in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5th vaccination visits (see Synopsis Table 3).
- In countries where *Synflorix* is used as a control, two doses will be administered IM with at least a 1 month interval between these primary doses. A booster dose will be administered IM in the second year of life at Visit 7. The first *Synflorix* dose will be administered at Day 31 (Visit 3) (in the group receiving only *Synflorix*). In the group receiving only *Synflorix,* the second dose will be at Day 61 (Visit 5). The first *Synflorix* dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of *Synflorix* in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Synopsis Table 3).
- In countries where Menveo is used as a control, two doses will be administered IM at least 3 months apart with the second dose in the second year of life at Visit 7. The first Menveo dose will be administered at Day 31 (Visit 3) (in the group receiving only Menveo). The first Menveo dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5),

following the 1 or 2 RSV vaccine doses, respectively. Since the second Menveo dose has to be administered in the second year of life at Visit 7, no administration will be performed at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 4 vaccination visits (see Synopsis Table 3).

- In countries where Placebo is used as a control, one dose will be administered IM at Day 31 (Visit 3) in the 1D RSV + Placebo group and two IM doses will be
- administered IM according to a 0, 1-month schedule at Day 1 (Visit 1) and Day 31 (Visit 3) in the Placebo group (see Synopsis Table 3).

Synopsis Table 3 Vaccines administered and vaccination schedules

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	**7-8 / (V3, D31)**	**8-9 / (V5, D61)**	**10-11 / (V6, D121)****	**14-18 / V7**
1D RSV + *Bexsero*	1D RSV ChAd	FB	*Bexsero*	*Bexsero*	*Bexsero*
2D RSV + *Bexsero*	2D RSV ChAd	2D RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	FB	*Bexsero*	FB	*Bexsero*
1D RSV + *Nimenrix*	*1D RSV ChAd*	*FB*	*Nimenrix*	*Nimenrix*	*Nimenrix*
2D RSV + *Nimenrix*	*2D* RSV ChAd	*2D* RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	*FB*	*Nimenrix*	FB	*Nimenrix*
1D RSV + *Synflorix*	*1D RSV ChAd*	*FB*	*Synflorix*	*Synflorix*	*Synflorix*
2D RSV + *Synflorix*	*2D* RSV ChAd	*2D* RSV ChAd	*Synflorix*	*Synflorix*	*Synflorix*
Synflorix	*FB*	*Synflorix*	*Synflorix*	FB	*Synflorix*
1D RSV + *Menveo*	*1D RSV ChAd*	*FB*	*Menveo*		*Menveo*
2D RSV + *Menveo*	*2D RSV ChAd*	*2D RSV ChAd*	*Menveo*		*Menveo*
Menveo	*FB*	*Menveo*	FB		*Menveo*
1D RSV + Placebo	1D RSV ChAd	FB			
2D RSV + Placebo	2D RSV ChAd	2D RSV ChAd			
Placebo	FB	FB			

V: Visit; **D:** Day; **1D:** 1 Dose ($1.5x10^{10}$ vp/dose); **2D:** 2 Dose ($5x10^{10}$ vp/dose); **RSV ChAd**: ChAd155-RSV vaccine**;** **FB:** Formulation buffer S9b.

* Assumes enrolled at 6 and 7 months of age for the vaccine Dose 1 to be administered before the first RSV season (RSV seasons will be determined for each country based on local epidemiological data).

** In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7.

- Treatment allocation: infants will be randomized using a centralized randomization system on internet (SBIR) before first vaccination and after assessment of eligibility (i.e., after screening conclusion). The randomization algorithm will use a minimization procedure accounting for country as a minimization factor and the grouping comparator/placebo as a stratification factor.

- Blinding: not applicable for Epoch 001 (Screening Visit), observer-blind in Epoch 002 and single-blind in Epoch 003 and Epoch 004.

Synopsis Table 4 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	N/A
Epoch 002	observer-blind
Epoch 003	single-blind
Epoch 004	single-blind

N/A: Not applicable.

- Sampling schedule:
  - Blood samples for **hematology/biochemistry** will be taken from all infants at Screening (up to 30 days before first vaccination to Day -1). Blood samples for **hematology/biochemistry** may be taken from infants at any timepoints, if deemed necessary by the investigator.
  - Blood samples for **humoral immunogenicity** will be taken from all subjects at Screening and on Day 31, Day 61, and at the visit occurring at the end of the first RSV transmission season.
  - Blood sample for **assessment of mechanism of illness (potential enhanced RSV disease [ERD])** will be taken from subjects hospitalized for LRTI (required only for RSV-positive subjects using a locally available RSV test).
  - Nasal swab: there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season and if following active or a passive surveillance contacts, a subject presents symptoms of respiratory tract infection (RTI), a nasal swab will be collected (as well as a sample for local testing i.e., the type of sample to be determined locally [e.g., swab, etc.]).
- Study visits: Other than the screening visit and assessment visits for active/passive surveillance, there will be 8 study visits except in countries where *Menveo* or Placebo is used as a control where there will be 7 study visits.
  - In countries where *Menveo* is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and *Menveo* will be administered at the end of the first RSV season at Visit 7.
  - In countries where Placebo is used as a control, no vaccine administration will be performed after Visit 3

and therefore in those countries there will be no Visit 6. There will be a Visit 5 and Visit 7 for countries using Placebo and all other study procedures will occur at these visits except vaccination.

- Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.

For authorized sites only, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.

- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: internal safety review committee (iSRC) and IDMC.
- Surveillance for RSV-RTI, difficulty in breathing, and wheezing episodes.

  Surveillance period will be carried out from Visit 1 (after Dose 1) until the last study visit (end of the second RSV transmission season). In order to detect asymptomatic RSV-RTI, monthly nasal swabs for analysis at sponsor laboratory will be performed for all subjects during the RSV season. In order to timely detect RSV-RTI and to ensure cases are timely captured by the study sites, both active and passive surveillance will be conducted:

  - **Passive surveillance**: parent(s)/LAR(s) are instructed to contact the investigator/study staff as soon as the subject experiences new RTI symptoms (cough, runny nose or blocked nose) or worsening of RTI symptoms, or in case of difficulty in breathing or wheezing.
  - **Active surveillance**: parent(s)/LAR(s) of all the subjects will be contacted by the investigator/study staff on a regular basis (weekly during the RSV season and every month outside the RSV season) to identify any potential RSV-RTI and to remind the parent(s)/LAR(s) of the subjects to report any new occurrence of RTI symptoms (cough, runny nose, blocked nose), or in case of difficulty in breathing or wheezing as soon as possible.

- Surveillance for spontaneous or excessive bleeding.

  Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination (Visit 1 and Visit 3), in order to detect any thrombocytopenic petechiae or purpura. The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets.

Case definition

During the analysis of the study, all cases identified during the surveillance of RSV-RTI will be definitively classified as either RTI, LRTI, severe LRTI or very severe LRTI according to the standardized case definitions (see Synopsis Table ***5***) based on the available World Health Organization (WHO) case definitions.

Synopsis Table 5 Case definitions for data analysis

Case	*At sea level up to 2500 meters elevation*	*Above 2500 meters elevation*
RSV-RTI	Runny nose OR blocked nose OR cough AND Confirmed RSV infection [4]	***Same***
RSV-LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3] AND Confirmed RSV infection [4]	***Same but with SpO2 <92%***
severe *RSV*-LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93% [2], OR lower chest wall in-drawing	***Same but with SpO2 <90%***
very severe *RSV*-LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 90% [2], OR inability to feed, OR failure to respond / unconscious	***Same but with SpO2 <88%***
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]	***Same***
All-cause LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3]	***Same but with SpO2 <92%***

Definitions based on [Modjarrad, 2016]

LRTI = lower respiratory tract infections; **RR** = respiratory rate; **RTI** = respiratory tract infections; **SpO2** = Blood oxygen saturation by pulse oximetry.

[1] Based on history reported by parents.

[2] The lowest value during the course of illness will be used.

[3] RR increase defined as:

≥ 50/minute (2 to 11 months of age)

≥ 40/minute (12 months of age or above)

The highest value during the course of the illness will be used.

[4] RSV infection confirmed on nasal swab positive for RSV A or B by quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR).

[5] RSV sampling and testing is based on medical judgment of medical practitioner or driven by algorithm.

[6] Hospitalization is defined as a medical decision that the infant requires admission for observation or treatment.

Number of subjects

The target will be to enroll approximately 150 infants likely to be previously unexposed to RSV with about 50 infants for each of three randomization groups. If necessary, the sample size ***may*** be increased through additional recruitment in order to achieve ***a sufficient number of*** RSV infected infants, with a negative RSV exposure status (at screening based on in-stream baseline serological testing), in each RSV vaccine group. Dose 1 of the ChAd155-RSV vaccine should be administered before the first RSV season and second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the SPM. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable.) **(Amended 1 August 2019)**.

Endpoints

Primary

- Occurrence of adverse events (AEs) from first vaccination (Day 1) up to Day 61.
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after each vaccination (i.e., the day of vaccination and 6 subsequent days).
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days).
  - Occurrence of any serious adverse event (SAE) from Day 1 up to Day 61.
  - Occurrence of episode of spontaneous or excessive bleeding (AE of special interest), during a 30-day follow-up period after each vaccination.

Secondary

- Occurrence of RSV-RTI, RSV-LRTI, severe RSV-LRTI and very severe RSV-LRTI (according to standardized case definitions) as from first vaccination (Day 1) up to the end of the first RSV transmission season.
- Occurrence of RSV-RTI, RSV-LRTI, severe RSV-LRTI and very severe RSV-LRTI (according to standardized case definitions) as from first vaccination (Day 1) up to the end of the second RSV transmission season.

- Occurrence of SAEs from first vaccination (Day 1) up to the end of the second RSV transmission season.
- Occurrence of RSV-LRTI (AE of special interest) as from first vaccination (Day 1) up to the end of the first RSV transmission season, and up to the end of the second RSV transmission season.
- Occurrence of very severe RSV-LRTI (according to standardized case definitions) among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season.
- Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61 and at the end of the first RSV transmission season):
  - Neutralizing antibody titers against RSV-A.
  - RSV F antibody concentrations.

Tertiary

- Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61).
  - *Palivizumab*-competing antibody concentrations**.**
- Any further exploratory immunology to detect disease-related or vaccine-related immune responses, such as but not limited to:
  - Anti-vector immunity: neutralization.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF APPENDICES

PAGE

LIST OF ABBREVIATIONS

AE:	Adverse Event
AESI:	Adverse Events of Special Interest
CD (CD4, CD8):	Cluster of Differentiation (4, 8)
ChAd155:	Chimpanzee Adenovirus Type 155
ChAd155-RSV:	Investigational recombinant chimpanzee adenovirus Type 155-vectored RSV vaccine
CI:	Confidence Interval
CLS:	Clinical laboratory sciences
eCRF:	electronic case report form
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
ERD:	Enhanced RSV disease
ES:	Exposed Set
F:	RSV fusion protein
FB:	Formulation buffer (S9b)
FI-PIV:	Formalin-Inactivated Parainfluenza Virus vaccine
FI-RSV:	Formalin-Inactivated whole virus RSV vaccine
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titer
GSK:	Glaxosmithkline
HIV:	Human Immunodeficiency Virus
HR:	Heart Rate
HRP:	Horse-Radish Peroxidase
IB:	Investigator Brochure

ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
ICS:	Intracellular Staining
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IgG :	Immunoglobulin G
IM:	Intramuscular
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
IRB:	Institutional Review Board
iSRC:	Internal Safety Review Committee
LAR:	Legally Acceptable Representative
LRTI:	Lower Respiratory Tract Infection
LSLV:	Last subject last visit
M2-1:	RSV matrix protein
MedDRA:	Medical dictionary for regulatory activities
mm^3:	cubic millimeter
N:	RSV nucleocapsid protein
PCD	Primary Completion Date
PCR:	Polymerase Chain Reaction
PP*S*:	Per-Protocol Set
RNA:	Ribonucleic Acid
RR:	Respiratory Rate
RSV:	Respiratory Syncytial Virus
RSV-RTI:	Respiratory Tract Infection associated with RSV infection

RTI:	Respiratory Tract Infection
RVP:	Respiratory Viral Panel
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBIR:	Randomization system on internet
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SPM:	Study procedures manual
SpO2:	Blood oxygen saturation by pulse oximetry
TLR:	Toll-like receptor
UK:	United Kingdom
ULN:	Upper Limit Of Normal
vp:	Viral Particles
VSMB:	Vaccine Safety Monitoring Board
WHO:	World Health Organization

GLOSSARY OF TERMS

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 a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not. 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 6.3 for details on observer-blinded studies).
Child in care:	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
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, study completion 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. Study completion must be achieved no later than 8 months after LSLV.
Epoch:	An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Sections 7.6.2 and 11.5 for details on criteria for evaluability).
Exposed Set	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Grade 1 abnormality with potential clinical relevance	Grade 1 laboratory parameters which cannot be explained or which are judged by the investigator to be potentially clinically relevant (refer to APPENDIX C).
Grade 1 abnormality without clinical relevance	Grade 1 laboratory parameters which can be explained by a condition which is not related to vaccination and does not increase the risk for an adverse outcome of vaccination (refer to APPENDIX C).
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.
Infant:	As per US Food and Drug Administration's definition an infant is aged one month to two years.

Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization 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.
Legally acceptable representative **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Per Protocol Set	***Subset of subjects in the exposed set (ES) who have complied with eligibility criteria, study procedures up to the time point of analysis and who have availability of measurement(s) for the analysis variable(s) of interest*** **(Amended 1 August 2019)**.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	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.
Study vaccine/product	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/ product as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
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(s) 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) intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to 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.

TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademarks of the GSK group of companies	Generic description
Bexsero	Meningococcal group B vaccine (recombinant, adsorbed)
Menveo	Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine
Nimenrix (licensed to Pfizer)	Meningococcal group A, C, W-135 and Y conjugate vaccine
Synflorix	***Pneumococcal*** polysaccharide conjugate vaccine (adsorbed)

Trademarks not owned by the GSK group of companies	Generic description
Synagis (MedImmune)	Recombinant humanized monoclonal anti-RSV antibodies
Allplex (Seegene)	Respiratory panel assay
TrueBlue (SeraCare)	Peroxidase substrate

1. INTRODUCTION

1.1. Background

1.1.1. RSV disease burden

Respiratory syncytial virus (RSV) is a ribonucleic acid virus of which two antigenically distinct subgroups exist, referred to as RSV-A and RSV-B [Borchers, 2013]. RSV is a highly contagious human pathogen that causes respiratory tract infections (RTI) in people of all ages.

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 second birthday. The risk for severe RSV-associated lower respiratory tract infections (LRTI) is highest in infants below 6 months of age and is a leading cause of hospitalization. It is estimated that on average 31 per 1000 children below 6 months of age are hospitalized for RSV-associated LRTI [Boyce, 2000; Deshpande, 2003; Hall, 2009; Holman, 2004; Iwane, 2004; Paramore, 2004; Vicente, 2003]. 50-70% of these hospitalized children do not have additional risk factors like preterm birth or cardiopulmonary disease [Boyce, 2000; García, 2010; Hall, 2009; Rietveld, 2004]. For human immunodeficiency virus (HIV)-infected children, the incidence rate of hospitalization for RSV-associated LRTI was reported to be 2.5- to 5-fold greater than in HIV-uninfected children [Cohen, 2015; Madhi, 2006]. Although RSV hospitalization rates substantially decrease after 6 months of age, a considerable number of RSV infections in children of 6-15 months of age, still lead to bronchiolitis or (broncho)pneumonia requiring medical attention [Fisher, 1997].

Previous infection with RSV does not prevent subsequent infections. Therefore, 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 persons (e.g., immunocompromized subjects or elderly), re-infections can however also lead to severe disease [Graham, 2011].

1.1.2. Current management of RSV disease in infants

To date, no vaccine is available against RSV and treatment of RSV disease is largely symptomatic and supportive care [Murray, 2014].

The antiviral drug ribavirin is currently the only approved antiviral therapy for RSV treatment, but its use is restricted to severe hospitalized cases due to uncertainties regarding its efficacy, difficulty in administration (aerosol) and high cost [American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis, 2006].

RSV-specific monoclonal antibodies (palivizumab, *Synagis*) are indicated for use in infants at highest risk for severe RSV disease. *Synagis* is only effective as prophylaxis and is not indicated or recommended in the general, healthy infant population.

1.1.3. History of enhanced RSV disease with formalin-inactivated RSV vaccines

In the late sixties, following initial encouraging results in small clinical trials, field evaluation trials of a formalin inactivated vaccine targeting RSV, called FI-RSV, were initiated in the United States. FI-RSV was cultured on monkey kidney cells, harvested, inactivated with formalin and aluminum-precipitated (FI-RSV lot 100). Four clinical studies in different age groups were conducted in parallel in 1965-1967 [Chin, 1969; Fulginiti, 1969; Kapikian, 1969; Kim, 1969]. The study results indicated that the FI-RSV vaccine did not protect against infection with the respective virus. In addition, children who had been vaccinated with the FI-RSV vaccine developed more severe clinical symptoms upon subsequent natural infection with RSV compared to the children who had not been vaccinated with the FI-RSV vaccine (resulting in 2 deaths in the study in which the youngest children were vaccinated [Kim, 1969]). This observation is referred to as "FI-RSV enhanced RSV disease" (ERD) in this document.

1.1.3.1. Clinical symptoms of FI-RSV enhanced RSV disease

The key clinical observations from the FI-RSV trials are summarized below. These need to be taken into consideration when defining potential safety signals during the clinical development of new RSV vaccine candidates.

Age at the time of FI-RSV vaccination

The four studies included children aged between 2 months and 9 years. When comparing the different age strata at which children were vaccinated in these studies (Young infants [0-5 months]; Older infants [6-11 months]; Toddlers [12-23 months]; Children [≥24 months]), the most prominent increase in RSV-associated LRTI and hospitalization following FI-RSV vaccination was observed in children vaccinated at younger age. In the study where the youngest subjects were vaccinated [Kim, 1969], 2 of the vaccinated children died, one at the age of 14 months, the other at the age of 16 months. Each had received three vaccine doses, the first one beginning at the age of 2 months, the other one at the age of 5 months.

Table 1 Overview of impact of FI-RSV vaccination on age-related RSV disease

Condition	Source	Def	0-5m*		6-11m*		12-23m*		≥24m*	
			FI-RSV	Cont	FI-RSV	Cont	FI-RSV	Cont	FI-RSV	Cont
Severe RSV-LRTI	[Kim, 1969] season 1	Hospitali-sation	20% (4/20)	0% (0/20)						
	[Kim, 1969] season 2 †	Hospitali-sation	51% (16/31)	2.5% (1/40)						
	[Fulginiti, 1969]/	Hospitali-sation			13.7% (7/54)	1.5% (1/65)	5% (3/60)	0.92% (1/108)	0.28% (1/353)	0% (0/364)
	[Kapikian, 1969]	Hospitali-sation			FI-RSV: 33% (5/15) Cont: 0% (0/48)				0% (0/22)	0% (0/61)
All RSV-LRTI	[Chin, 1969]	MAARI			30.2% (13/43)	11.6% (5/43)	FI-RSV: 1.3% (2/148) Control: 2.6% (4/151)			
	[Kapikian, 1969]	LRTI (crepitation)			100% (2/2)	14.3% (1/7)	53.8% (7/13)	7.3% (3/41)	18%§ (4/22)	11.4% (7/61)

m: months; **MAARI :** medically-attended acute respiratory infection (Emergency room)

* Age at time of vaccination – Age at time of disease can be several months later.

† During season 2, average age of the subjects was 12 months

§ All cases in subjects <36 months old.

Specific/ defining clinical symptoms

In the four studies an attempt was made to identify specific/ defining clinical symptoms of the "FI-RSV enhanced RSV disease" by comparing the clinical picture of these patients with unvaccinated matched control subjects diagnosed with severe RSV disease or with patients suffering from RSV-associated LRTI in the control group. However, apart from the unexpected severity, none of the observed symptoms were unique in FI-RSV vaccinated patients. Therefore, no specific/ defining symptom can be monitored as a safety signal in order to detect a similar adverse effect of new RSV vaccine candidates during clinical development. Finally, no increased incidence of RSV-associated respiratory disease of the *upper* and/or *large* airways was observed.

Definition of "FI-RSV enhanced RSV disease"

Based on the original publications, it can be summarised that "FI-RSV enhanced RSV disease" was:

1. Caused by vaccination with at least one dose of FI-RSV lot 100 (and not by similar vaccines [e.g., FI-PIV]) below 2 years of age.
2. More severe if the vaccine was administered at a younger age.
3. Initiated by RSV infection (and not by similar pathogens [e.g., PIV]).
4. Associated with high viral replication and shedding of RSV.
5. Defined by increased severity and potentially duration of typical symptoms of RSV-associated LRTI (but not upper RTI): bronchiolitis/(broncho)pneumonia.

Key characteristics of vaccinees

- **RSV priming status**: risk very low in subjects that are primed for RSV (*i.e.,* who have been naturally infected with RSV before) as vaccination of primed subjects is expected to amplify the (non-pathogenic) immune response induced by natural RSV infection.
- **Age at vaccination:** risk very low in children vaccinated at 2 years or older and progressively increasing with younger age (highest risk in infants < 6 months of age, who have a more immature immune system).
- **Age at first exposure to RSV after vaccination**: risk for severe RSV disease upon natural infection being higher in younger infants, who have smaller airways and a more immature immune system.

1.1.3.2. Serum immune responses to the FI-RSV vaccine and to subsequent RSV infection

During the trials with the FI-RSV vaccine, serological assays were performed to monitor 1) the immune response to vaccination 2) the immune response to natural infection post-vaccination. In general, vaccinees developed high levels of total serum antibodies in response to vaccination (as measured by complement fixation). When the sera of these infants and children were later compared with those of infants and children with natural RSV infection, it could be observed that FI-RSV vaccination induced high total IgG antibody titers, but a relatively low level of neutralising antibody titers [Murphy, 1986].

1.1.3.3. Pathological observations of RSV disease in FI-RSV vaccinated children

Post-mortem examinations of the 2 FI-RSV vaccinated children who died (aged 14 and 16 months at time of death, vaccinated at 2 and 5 months of age, respectively) showed extensive bronchopneumonia in both children with patchy atelectasis, emphysema and pneumothorax in one of them [Kim, 1969]. Microscopically, there was an intense inflammatory infiltrate, with a predominance of neutrophils and macrophages in the lungs accompanied by the occasional presence of eosinophils in smaller bronchioles; a pathological picture consistent with primary RSV infection. Since eosinophils were also detected in the blood of some of the vaccinees, this finding gained a lot of attention in later investigations. Large quantities (10^4 plaque-forming units [pfu] per gram) of RSV were recovered from the lungs and bacteria could be cultured from the lungs of both children (*Klebsiella* from one and *E. coli* from the other).

Re-examination of the original autopsy report and of new histological preparations from the same tissues confirmed the observations, and re-emphasised the relatively small contribution of eosinophils (1-2%) compared to neutrophils. Gram stain did not detect bacteria in the lungs, suggesting that the positive cultures may have been due to small numbers of bacteria only (and making it less likely that the primary cause of the disease process could have been bacterial) [Prince, 2001]. During a second re-examination of the lung samples, evidence of immune complex deposition (arthus-like reaction) was detected in the small airways [Polack, 2007].

In summary, the pathological observations indicate that 1) RSV viral replication was abundant, 2) the overall pathology was consistent with severe viral bronchopneumonia and 3) immune complexes were formed in the small airways.

1.1.3.4. Animal models for "FI-RSV enhanced RSV disease"

In order to better understand the pathophysiology of "FI-RSV enhanced RSV disease", several animal models have been developed to mimic this phenomenon. In general, animal models suggest that the immunopathology seen with the FI-RSV vaccine was a result of a poor functional antibody response [Graham, 2011; Openshaw, 2002] An unbalanced cellular immune response skewed towards Th2 (disturbed Th1/Th2 balance) could also ***be*** observed in mouse models [Connors, 1992; Connors, 1994; Waris, 1996], but is not consistently supported by data from other model animals [Antonis, 2003; Castilow, 2008; Phipps, 2007]. Note that the results of animal models of FI-RSV enhanced RSV disease should however be interpreted with caution due to the inherent differences between the animal model and humans per se and different replicative potential of RSV in the different species in particular.

1.1.3.5. Pathophysiology of "FI-RSV enhanced RSV disease"

Based on the clinical and pathological observations in the vaccinated children in combination with a large body of data from animal models, two (non-mutually exclusive) *hypotheses* on the immunological factors that contributed to FI-RSV enhanced RSV disease have been proposed:

- **Induction of low-quality, non-neutralising antibodies**. Murphy *et al* observed that upon natural RSV infection, the FI-RSV vaccinated subjects produced high amounts of poorly neutralising antibodies, indicating that natural infection boosted the low-quality antibody response induced by the FI-RSV vaccine [Murphy, 1986]. These antibodies did not neutralise RSV replication and contributed to the formation of immune complexes that may have contributed to the severe clinical symptoms and potentially immunopathology [Polack, 2002].

  Two (non-mutually exclusive) culprits for this poorly neutralising antibody response have been proposed 1) Formalin-induced disruption of *neutralising epitopes* on the inactivated virus vaccine, leading to an unusually large proportion of antibodies directed against non-protective epitopes [Murphy, 1986; Murphy, 1988; Moghaddam, 2006]. 2) Formalin-induced disruption of the Toll-like receptor (TLR)-4 agonist activity of the F-protein (a major surface protein of RSV). F-protein in its native form is known to bind and stimulate TLR-4, which leads to antibody affinity maturation and high avidity antibodies. If this binding is disrupted, affinity maturation may not (sufficiently) occur and antibodies remain of low affinity and neutralising capacity [Delgado, 2009].

- **An unbalanced cellular immune response**. Another potential explanation is the induction of an unbalanced cellular immune response skewed towards Th2 (disturbed Th1/Th2 balance) [Connors, 1992; Connors, 1994; Waris, 1996]. This latter hypothesis is however mainly based on preclinical data in mouse models and is not consistently supported by data from other model animals [Antonis, 2003;

Castilow, 2008; Phipps, 2007] and more likely a cytokine storm (irrespective of Th balance) has been contributing to FI-RSV enhanced RSV disease [Boukhvalova, 2006].

1.1.4. Rationale for a viral vector-based RSV vaccine

Immunity induced by natural RSV infection is not able to fully prevent RSV re-infection, allowing re-infections to occur commonly throughout life. Both arms of the immune system are involved in protection from severe disease.

The humoral immune response is capable of neutralizing the virus and inhibiting viral replication, thereby playing a major role in protection against lower RSV infection and severe disease [Piedra, 2003]. Indeed, passive immunization with RSV-specific monoclonal antibodies (*Synagis*), when given prophylactically, has been shown to reduce RSV disease in premature infants and newborns with bronchopulmonary dysplasia or underlying cardiopulmonary disease [Cardenas, 2005].

T-cells are also involved in the control of RSV disease. Lethal RSV infections have been described in patients with low CD8 T-cells counts as in the case of severe combined immunodeficiency, bone marrow and lung transplant recipients [Hertz, 1989]. The histopathology of fatal cases of RSV infection of newborns shows that there is a relative paucity of CD8 T-cells in the lung infiltrate [Welliver, 2007]. Moreover, the presence of CD8 T-cells producing interferon gamma (IFN-γ) has been associated with diminished both Th2 responses and eosinophilia in animal models of RSV [Castilow, 2008; Stevens, 2009].

A vaccine based on recombinant viral vectors carrying relevant RSV antigens, mobilizing both humoral and cellular arms of the immune response, is considered as an adequate solution to induce a balanced and more effective immune response against the RSV virus in a naïve population. Adenoviral vector-based vaccines have been shown to be potent inducers of CD8 T-cells producing IFN-γ and antibodies against expressed antigens [Liniger, 2007; Barnes, 2012].

Potent immunogenicity and lack of prolonged transgene expression have made replication incompetent adenoviruses attractive viral vectors for vaccine development. They possess a stable virion, allowing inserts of foreign genes not to be deleted and they can infect many different cell types; the transferred information remains epichromosomal thus avoiding the risk of insertional mutagenesis.

Chimpanzee-derived adenoviruses exhibit sequence homology to human adenoviruses within the hexon protein in particular, which is a major capsid protein used for subgroup classification of adenoviruses [Roy, 2011; Colloca, 2012]. They are not known to cause pathological illness in humans and antibodies against chimpanzee adenoviruses have low or no seroprevalence ranging from 0-4% in Europe and in the United States, up to 20% in the developing countries, which is far less than the most common human adenovirus serotype 5 (Ad5), with seroprevalence rates of 40–45% in the United States and up to 90% in sub-Saharan Africa [Capone, 2013].

In conclusion, the chimpanzee-derived adenovectors have the following important features:

- Weak neutralization by human sera.
- Potent immunogenicity, mainly Th1-directed.
- Track record of good tolerability in human clinical trials.

1.1.5. Antigens selected for the vaccine

The investigational vaccine is a recombinant viral vector manufactured using a synthetic deoxyribonucleic acid fragment that encodes three RSV proteins:

- The fusion (F) protein deleted from the transmembrane and cytoplasmic regions (F0ΔTM). The F protein is a major surface antigen of the RSV virus that is well conserved among RSV-A and RSV-B subgroups. In addition, it is the main target of the neutralizing antibody response to RSV, which is considered essential for protection against RSV-associated severe disease [Magro, 2012].
- The nucleocapsid (N) protein is an internal (non-exposed) antigen, highly conserved between RSV strains and known to be a source of many T-cell epitopes [Anderson, 2010; Townsend, 1984]. The N protein is essential for the replication and transcription of the RSV genome. Its primary function is to encapsidate the virus genome protecting it from ribonucleases.
- The matrix (M2-1) protein is a transcription anti-termination factor that is important for the efficient synthesis of full-length messenger ribonucleic acid (RNA) as well as for the synthesis of polycistronic readthrough messenger RNA, which are characteristic of non-segmented negative-strand RNA viruses. M2-1 is an internal (non-exposed) antigen, highly conserved between RSV strains and known to be a source of many T-cell epitopes [Anderson, 2010; Townsend, 1984].

The N and M2-1 antigens were therefore included in the vaccine construct as source of T-cell epitopes for the induction of cell-mediated immunity (CMI).

Please refer to the current Investigator Brochure (IB) for additional information.

1.1.6. Pre-clinical experience

The candidate vaccine is based on the RSV viral proteins F, N and M2-1 encoded by a chimpanzee-derived adenovector (ChAd155-RSV). A number of pre-clinical studies were conducted to demonstrate immunogenicity, efficacy and safety of intramuscular (IM) injection of the ChAd155-RSV vaccine. Several animal models have been selected for such studies: mice, cotton rats and newborn calves. Importantly, vaccination has not induced hallmarks of enhanced pathology in these models.

Please refer to the current IB for information regarding the pre-clinical studies of GSK Biologicals' investigational ChAd155-RSV vaccine.

1.1.7. Clinical experience

The immunogenicity, safety and reactogenicity of the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) have been evaluated in healthy adults aged 18 to 45 years (study 201974 [RSV PED-001; NCT02491463]) There were no significant safety concerns identified up to Day 60 in study RSV PED-001. Overall, the ChAd155-RSV vaccine high dose ($5x10^{10}$ ***viral particles [***vp***]***) seems to be more reactogenic (local and general) than the ChAd155-RSV vaccine low dose ($5x10^{9}$ vp), however, the reactogenicity profile was less than that observed in the *Bexsero* group. No safety signal from the assessed hematology parameters (hemoglobin, platelet count, prothrombin time and APTT) was observed in subjects receiving the ChAd155-RSV vaccine. No significant reductions in platelet count or clinically significant changes in coagulation parameters were observed up to 30 days post Dose 2. An approximately 2.4-fold increase in RSV-A neutralizing antibody titers (geometric mean titer [GMT] from baseline) was observed in both RSV low dose and RSV high dose after Dose 1. No booster effect was evident after Dose 2. An anti-F IgA and IgG antibody secreting B-cells response and an RSV F, N and M2-1 specific IFN-γ secreting T-cells response in RSV high dose group after the first dose were observed with ELISpot. There was no booster response after the second vaccination. There was no specific vaccine-induced CD4 T-cellular response observed with intracellular staining (ICS). For CD8 T-cells only a weak CD8 IFN-γ response to N was shown with ICS for some subjects.

Please refer to the current IB for information regarding the clinical studies of GlaxoSmithKline (GSK) Biologicals' investigational ChAd155-RSV vaccine.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

GSK Biologicals is developing the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) to protect infants from RSV diseases.

The purpose of this study is to provide critical information on the safety, reactogenicity and immunogenicity profile of the ChAd155-RSV vaccine in infants likely to be unexposed to RSV before moving to a proof-of-concept trial in infants. An important aspect of this phase I/II study will be to compare a single lower dose of $1.5x10^{10}$ viral particles (vp) and two higher doses of $5x10^{10}$ vp according to a 0, 1 month schedule administered to infants aged 6 and 7 months likely to be unexposed to RSV, which is powered to statistically exclude a level of risk of 'vaccine-induced enhanced RSV disease', associated with historic FI-RSV vaccine trials [Kim, 1969].

This study is the first of a careful de-risking sequence of studies in a clinical development plan that will progressively exclude ERD as a potential risk prior to Phase III.

1.2.2. Rationale for the choice of study population

1.2.2.1. Study population

The immunogenicity, safety and reactogenicity of the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) has been evaluated in healthy adults aged 18 to 45 years (study 201974 [RSV PED-001; NCT02491463]). A clinical study is currently being conducted in RSV-seropositive infants aged 12 to 23 months (study 204838 [RSV PED-002]). The safety profile of the ChAd155-RSV vaccine in adults (study 201974 [RSV PED-001; NCT02491463]) has been deemed satisfactory by GSK and an Independent Data Monitoring Committee (IDMC). Should there be a satisfactory safety profile of the ChAd155-RSV vaccine in RSV-seropositive infants, as evaluated by an IDMC on Day 60 data (i.e., 30 days post-Dose 2 of the highest dose level) of the study RSV PED-002, the present study will be performed. This study will be conducted on infants aged 6 and 7 months (having a low chance of natural exposure to RSV before inclusion in the study). Although potentially both RSV-exposed and RSV-unexposed subjects will be enrolled, the primary analysis for incidence of LRTI will be conducted in infants with a negative RSV exposure status (at screening based on in-stream serological testing). This study will support the decision to age de-escalate to the targeted population (infants as from 6 weeks of age).

1.2.2.2. Choice of study population

Infants aged 6 and 7 months were selected to be vaccinated in this study because:

- Infants of this age are more likely to be unexposed to RSV compared to older infants [Dunn, 2013].
- The natural course of RSV disease is generally less severe at this age. Their airways are relatively larger and they are therefore less at risk of serious RSV-RTI than younger infants.
- Risk of adverse outcome of natural infection following FI-RSV vaccination was more pronounced when the vaccine was administered to younger infants.

For safety reasons, the population will have no predisposing risk factors for severe outcome following RSV disease (e.g., premature birth, past or current chronic lung disease, or cardiovascular disease).

1.2.2.3. In-stream serological testing of baseline samples to determine exposure status (Amended 1 August 2019)

Subjects will not be screened for serostatus as criterion for enrolment in the study, due to the potential presence and detection of residual maternal antibodies (Refer to Section 6.7.3 for more details on the determination of a negative RSV exposure status). The assumption is that the majority of infants are previously unexposed (see Section 1.2.2.2). Serological testing of baseline samples to determine exposure status will be performed in-stream to ensure at least 50% of infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) and the sample size may be adjusted as needed through additional recruitment (Section 11.4).

1.2.3. Rationale for regimen, dose and route of administration

This study will evaluate two regimens of the ChAd155-RSV vaccine; either one dose of $1.5x10^{10}$ vp or two doses of $5x10^{10}$ vp will be administered. For the two dose schedule an interval of approximately one month between dosing will be used. A single dose arm was added in this 6-7 month-old study population before going to target population in subsequent studies.

The dose levels to be evaluated in this study have previously been administered to RSV-seropositive infants aged 12 to 23 months (study RSV PED-002 [204838]) and will have been shown to have a satisfactory safety profile and reviewed by the IDMC. These doses might be modified following review by the IDMC of the safety data from study RSV PED-002 (204838). However if no significant safety concerns are identified with the highest ChAd155-RSV vaccine dose of $5x10^{10}$ vp administered in the RSV PED-002 study, that dose will be the highest does level evaluated in this study.

In the bovine RSV challenge model in which seronegative, colostrum-restricted newborn calves, both a single and two dose regimen of $5x10^{10}$ vp ChAd155-RSV have been evaluated. The two dose regimen was given at an interval of four weeks apart. Both regimens showed a similar level of protection against challenge with bovine RSV, but the two dose regimen showed higher immunogenicity. Neither regimen was associated with pulmonary pathology. Low or potentially suboptimal dosing could be associated with lack of efficacy but is not likely to be associated with ERD. This is supported by animal data evaluating protection against a delayed challenge after a period of waning immunity. Non-clinical calf data showed that a challenge 4 months after the second dose or a challenge after a single dose did not induce any sign of ERD and demonstrated similar efficacy against LRTI. Despite waning immunity after 4 months, animals were fully protected upon challenge.

Similarly, the selected one dose level of $1.5x10^{10}$ vp is the same as the mid-dose administered to RSV-seropositive infants in the RSV PED-002 study that will have been shown to have a satisfactory safety profile and reviewed by the IDMC. The rationale for using the mid-dose level is to collect safety and immunogenicity data on a lower dose and on the one-dose regimen in 6-7 months RSV-naïve infants before progressing to the target population i.e. infants as of 6 weeks of age.

If tolerated, both candidate regimens would be evaluated in the target population to determine immune response and evaluate efficacy.

In this study, infants aged 6 to 7 months will be administered with the first dose of the ChAd155-RSV vaccine before the RSV season to increase the probability of enrolling infants unexposed to RSV, and then followed up through the RSV season. The second dose will be given one month after the first dose. RSV seasons will be determined for each country based on local epidemiological data (The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. Refer to the Study Procedures Manual [SPM] for RSV seasons per country).

Please refer to the current IB for information regarding the pre-clinical, clinical and toxicology studies of GSK Biologicals' investigational ChAd155-RSV vaccine.

Refer to Section 1.2.6 for the rationale for the use of active controls.

1.2.4. Rationale for safety monitoring plan

During this study, safety evaluations will be performed by an internal safety review committee (iSRC) (refer to Section 9.10.2) and an independent data monitoring committee (IDMC) (refer to Section 9.10.3), with specific holding rules. Data of LRTI associated with RSV infection will be received by the IDMC within 48 hours upon GSK becoming aware (refer to Section 9.10.3 for more detailed information). Any holding rules met during the study will be escalated to the Vaccine Safety Monitoring Board (VSMB; refer to Sections 9.10.4 and 9.10.5).

1.2.4.1. Rationale for RSV disease surveillance

ChAd155-RSV vaccine has been successfully tested in several preclinical models assessing the risk of vaccine-related ERD and it was associated with a profile that did not suggest disease enhancement. ChAd155-RSV vaccine induced an immune response associated to inhibition of viral replication in the lungs in all animal models tested and reduction of bovine RSV-LRTI signs in young calves. The ChAd155-RSV vaccine has been tested in young seronegative calves, which is a model that mimics natural RSV infection. Bovine RSV causes respiratory disease in young calves that is very similar to that observed in human infants. In addition, bovine RSV is genetically and antigenically close to human RSV. Exacerbation of respiratory disease has been reproduced in calves vaccinated with FI-bovine RSV vaccine [Antonis, 2003]. The similarities of FI-RSV vaccine-induced ERD and the observed clinical signs make the newborn calve/bovine RSV model a relevant animal model for evaluation of safety of human RSV vaccines. In this model, vaccination with ChAd155-RSV vaccine was immunogenic, protected initially seronegative calves from bovine RSV infection and pulmonary pathology and did not induce ERD.

Although the risk of ERD is thought to be very low with an adenovirus-based vaccine, a cautious approach is taken and this is the first of a series of trials in potentially naïve infants. In this first step the minimum number of subjects is exposed to allow detection of a serious signal of ERD of the magnitude that occurred in association with the RSV-FI trials. For details of the sample size and assumptions refer to Section 11.4. Rates of RSV infection are highly variable by season and therefore a conservative rate of infection of 20% in the first season is taken.

All subjects will be closely monitored for the occurrence of RSV-RTI and the early detection of ERD by IDMC and sponsor will comprise three complementary approaches: the detailed review of individual cases of RSV-LRTI, the monitoring of the disease severity of cases of RSV infection occurring in vaccinees and the comparison of RSV-LRTI disease rates between vaccinees and control recipients.

All subjects with symptoms of RTI detected by active or passive surveillance contacts will be reviewed by the investigator as soon as possible and those based on any suspicion of difficulty in breathing, wheezing or parental concern seen within 24 hours (refer to Section 9.2). This will ensure prompt assessment of need for medical care.

All cases of RSV-LRTI will be considered as adverse events (AEs) of special interest (refer to Section 9.1.5) and will have to be reported within 24 hours to the sponsor, and notified to the IDMC (which is not blinded), together with full case details, within 48 hours upon sponsor becoming aware. In order to support this timely reporting, the investigator will make the diagnosis according to his/her medical judgment and locally-available diagnostic tests of RSV infections. Criteria for hospitalization are not protocol defined but based on the attending clinicians' judgment of medical need.

The IDMC will receive on a regular basis cumulative summary reports of the number of RSV infections (asymptomatic and symptomatic) and the proportion progressing to hospitalization in the vaccinees by group and the incidence of RSV-RTI, RSV-LRTI and severe RSV-LRTI according to standardized case definitions by group (refer to Section 4.1). The frequency will be initially monthly from the beginning of the RSV season and will be adapted based on the instruction of the IDMC (refer to Section 9.10.3). The objective of this intense monitoring of cumulative RSV-RTI data by the IDMC is to ensure that, if it occurs, ERD is detected early in the course of the study allowing enrolment to be stopped and thereby minimizing the number of infants exposed to the ChAd155-RSV vaccine.

The final analysis of the incidence of RSV-LRTI by group will be performed according to the standardized case definitions for clinical symptomatology and diagnostic test at sponsor's laboratory (refer to Table 6) ensuring consistency across sites.

1.2.4.2. Rationale for monitoring for spontaneous or excessive bleeding

During a study carried out in adult subjects (RSV001), a mild non-clinically significant drop in hemoglobin was noted following vaccination with another adenoviral vector (PanAd3-RSV) without clinical signs and with a reversal towards baseline values over time [RSV001 Interim Study Report, 2014]. In the repeat dose toxicology study in rabbits using the ChAd155-RSV vaccine, a transient non-clinically significant drop in platelets was noted post IM vaccination (maximal drop of platelet observed 24 hours after vaccination; refer to the current IB for further details). In light of these data, subjects' parent(s)/ legally acceptable representative(s) (LAR[s]) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination (Visit 1 and Visit 3), in order to detect any thrombocytopenic petechiae or purpura. The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets.

Note that a broad safety hematology and biochemistry evaluation was performed at each study visit in adults during study RSV PED-001 (201974; NCT02491463). In this study, blood samples for hematology/biochemistry were taken from all subjects at all study visits, i.e., at Screening, on the day of vaccination (Day 0 and Day 30), 1 day post vaccination (Day 1 and Day 31), 3 days post vaccination (Day 3 and 33), 7 days post vaccination (Day 7 and 37), 30 days post Dose 2 (Day 60), on Day 180 and on Day 360. The safety profile of the ChAd155-RSV vaccine was found to be satisfactory by an IDMC. No safety signal from the assessed hematology parameters (hemoglobin, platelet count, prothrombin time and APTT) was observed in subjects receiving the ChAd155-RSV vaccine. No significant reductions in platelet count or clinically significant changes in coagulation parameters were observed up to 30 days post Dose 2.

1.2.5. Rationale for study blinding

Given the different appearance and storage conditions of the investigational RSV vaccine and the active control comparator vaccines / Placebo, double blinding is not possible and the study will be conducted in an observer-blind manner.

When all data up to Day 61 are available, a statistical analysis will be performed. This analysis may lead to the unblinding of some subjects. As a consequence, after Day 61, the study cannot be considered as observer-blind, but will be conducted in a single blind manner, with subjects' parent(s)/ legally acceptable representative(s) (LAR[s]) remaining blinded up to the last study visit (end of the second RSV transmission season*), while the investigator will still not have access to the treatment allocation up to the last study visit (end of the second RSV transmission season), except in case of emergency unblinding (see Section 9.8).

*Refer to the SPM for RSV seasons per country.

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

1.2.6. Rationale for the use of controls

The comparator / Placebo groups are included as a control for the reactogenicity, safety and immunogenicity assessments. The choice of control between an active comparator or Placebo will be done at country level. Refer to the Informed Consent Form (ICF) for the local choice of comparator/Placebo.

Active comparators are included as a control for the reactogenicity, safety and immunogenicity assessments. The choice of one of four control vaccines, as active comparators has been driven by the fact that, in most countries at least one of these vaccines meet the criteria of being of medical benefit, and where possible licensed for infants and used with a similar dose and schedule as the investigational RSV vaccine, while not being part of a national immunization program. The choice of which active control comparator vaccine will be used will be done at the country level and will be used according to its approved label.

Since the immunization schedule for the active comparator vaccines for infants between 6 and 18 months of age is slightly different, infants in the active control group will be administered FB at the time of administration of the first dose of the investigational RSV vaccine (for either *Menveo or Synflorix*) or the second dose of the investigational RSV vaccine (for either *Bexsero* or *Nimenrix*). To accommodate the various vaccination schedules of the active comparator vaccines across countries, FB may also be offered once during the two to three additional vaccinations given to complete the comparator vaccine schedule in the study (see Figure 1 and Table 2).

1.2.7. Rationale for ChAd155 RSV vaccine recipients receiving *active comparator* vaccine

To provide potential benefit to all trial participants and to maintain the study blind until the end of follow up, the ChAd155-RSV vaccine recipients will also receive immunization with the selected active comparator vaccine**.**

1.3. Benefit : Risk Assessment

Approximately two thirds of the infants (100) in this study will be exposed to the ChAd155-RSV vaccine, whereas all infants will receive either an active control comparator vaccine (*Bexsero,* or *Nimenrix,* or *Synflorix***,** or *Menveo*), or Placebo (see Figure 1 and Table 2).

The choice of active comparator vaccine or Placebo is done at the country level.

Please refer to the current IB for the summary of potential risks and benefits of ChAd155-RSV vaccine.

Please refer to the local Prescribing Information for information regarding the summary of potential risks and benefits of *Bexsero*, *Nimenrix, Synflorix* and *Menveo*.

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. In order to be able to treat infants with an immediate systemic allergic reaction to vaccination, all infants across all groups will need to remain under observation (visual follow-up as well as measurement of vital signs) at the study site for at least 60 minutes after vaccination for Visit 1 and Visit 3 and 30 minutes for all remaining vaccination visits.

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

Although the ChAd155-RSV vaccine is not a FI-RSV vaccine and the risk of ERD is thought to be very low (refer to Section 1.2), this is the first time that this vaccine will be administered to subjects likely to be unexposed to RSV. Consequently, all subjects will be closely monitored by active and passive surveillance for detection of RSV-RTI and wheezing (refer to Section 9.2). All cases of LRTI associated with RSV will be considered as AEs of special interest (refer to Section 9.1.5) and will have to be reported as SAEs (within 24 hours).

IM vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include redness, swelling and tenderness.

Most systemic symptoms observed in a clinical trial with a similar product carried out in healthy adults (chimpanzee adenovirus-based vaccine with ChAd3 as vector for vaccination against hepatitis C) at doses to be used in this trial did not exceed mild severity [HCV001 Clinical Study Report, 2011]. Fatigue, headache and malaise were the most commonly reported systemic AEs overall.

In a Phase I clinical trial with a similar simian adenoviral vector-based RSV vaccine with the same insert (PanAd3-RSV) carried out in healthy adults, the most commonly reported AEs concerned injection site reactions. However, a mild non-clinically significant drop in hemoglobin was noted following vaccination without clinical signs and with a reversal towards baseline values over time [RSV001 Interim Study Report, 2014].

A transient non-clinically significant drop in platelets was noted post IM vaccination in a preclinical study with the ChAd155-vector (refer to the current IB for further details). Furthermore, in Ebola Phase I studies in adults investigating a similar adenoviral vectored vaccine (ChAd3-EBO-Z), transient non-clinically significant decreases in thrombocyte counts were also observed (refer to the current IB of recombinant chimpanzee adenovirus Type 3-vectored Ebola Zaire vaccine for further details). A broad safety hematology and biochemistry evaluation was performed at each study visit in adults during study RSV PED-001 (201974). In this study, no significant safety concerns were identified up to 30 days post Dose 2 in healthy adults aged 18 to 45 years (refer to Section 1.1.7 and to the current IB). Hematology and biochemistry parameters are also being intensively evaluated in RSV-seropositive infants aged 12 to 23 months during study RSV PED-002 (204838).

Risks linked to the active control comparator vaccines

Refer to the local Prescribing Information for potential risks and contraindications related to *Bexsero*, *Nimenrix, Synflorix* or *Menveo* vaccines.

1.3.2. Benefit Assessment

The infants receiving the investigational ChAd155-RSV vaccine may not directly benefit from vaccination since the efficacy of the investigational ChAd155-RSV vaccine has not been assessed yet and it is hence not known whether it is effective in protecting against RSV infection.

The choice of active comparator vaccine (*Bexsero*, *Nimenrix, Synflorix,* or *Menveo*) for each participating country ensures that the vaccine may be given according to the local label and provides potential medical benefit in the country that chose active comparator. Within a given participating country, all infants in both groups of this study will receive the full locally recommended vaccination course of active comparator vaccine where possible and may be immunized against either invasive meningococcal disease caused by *Neisseria meningitidis* (with the meningococcal vaccines *Bexsero*, *Nimenrix or Menveo*)*;* or against invasive pneumococcal disease, pneumonia**,** and acute otitis media caused by *Streptococcus pneumoniae* (with the pneumococcal vaccine *Synflorix)*

Subjects' parent(s)/ LAR(s) could gain medical advice about their infant's general health status through the medical evaluations/assessments associated with this study (i.e., physical examination, blood testing [hematology and biochemistry data], surveillance for RTI and LRTI).

1.3.3. Overall Benefit:Risk Conclusion

The investigational ChAd155-RSV vaccine is currently in Phase I/II stage of clinical development and no vaccine efficacy has been demonstrated. Taking into account the measures taken to minimize the risk to infants participating in this study, the potential risks to the subjects are justified by the potential benefits linked to the development of this pediatric RSV vaccine.

The four control vaccines administered to all participants in this study as active comparators, are licensed for infants in the particular country where possible, and therefore have demonstrated medical benefit in the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* (for the *meningococcal vaccines Bexsero, Nimenrix, Menveo);* or against invasive *pneumococcal* disease, pneumonia**,** and acute otitis media caused by *Streptococcus pneumoniae* (for the *pneumococcal* vaccine *Synflorix*

2. OBJECTIVES

2.1. Primary objective

- To evaluate the safety and reactogenicity of the RSV investigational vaccine when administered IM as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses according to a 0, 1-month schedule, up to 60 days after Dose 1 (i.e., Day 61) in infants aged 6 and 7 months.

Refer to Section 11.1 for the definition of the primary endpoints.

2.2. Secondary objectives

- To evaluate the occurrence of RSV respiratory tract infections ***of any severity*** from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season, in infants aged 6 and 7 months.
- To evaluate the safety of the RSV investigational vaccine when administered IM as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses according to a 0, 1-month schedule, from study start (Day 1) up to the end of the second RSV transmission season in infants aged 6 and 7 months.
- To evaluate the occurrence of RSV respiratory tract infections from Visit 1 (Day 1, after Dose 1) up to the end of the second RSV transmission season, in infants aged 6 and 7 months.
- To evaluate the occurrence of very severe RSV-LRTI from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season in RSV infected infants aged 6 and 7 months with a negative RSV exposure status (at screening based on in-stream baseline serological testing).
- To evaluate the humoral immunogenicity induced by the RSV investigational vaccine when administered IM as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses according to a 0, 1-month schedule, from study start (Day 1) up to the end of the first RSV transmission season, in infants aged 6 and 7 months.

Refer to Section 11.2 for the definition of the secondary endpoints.

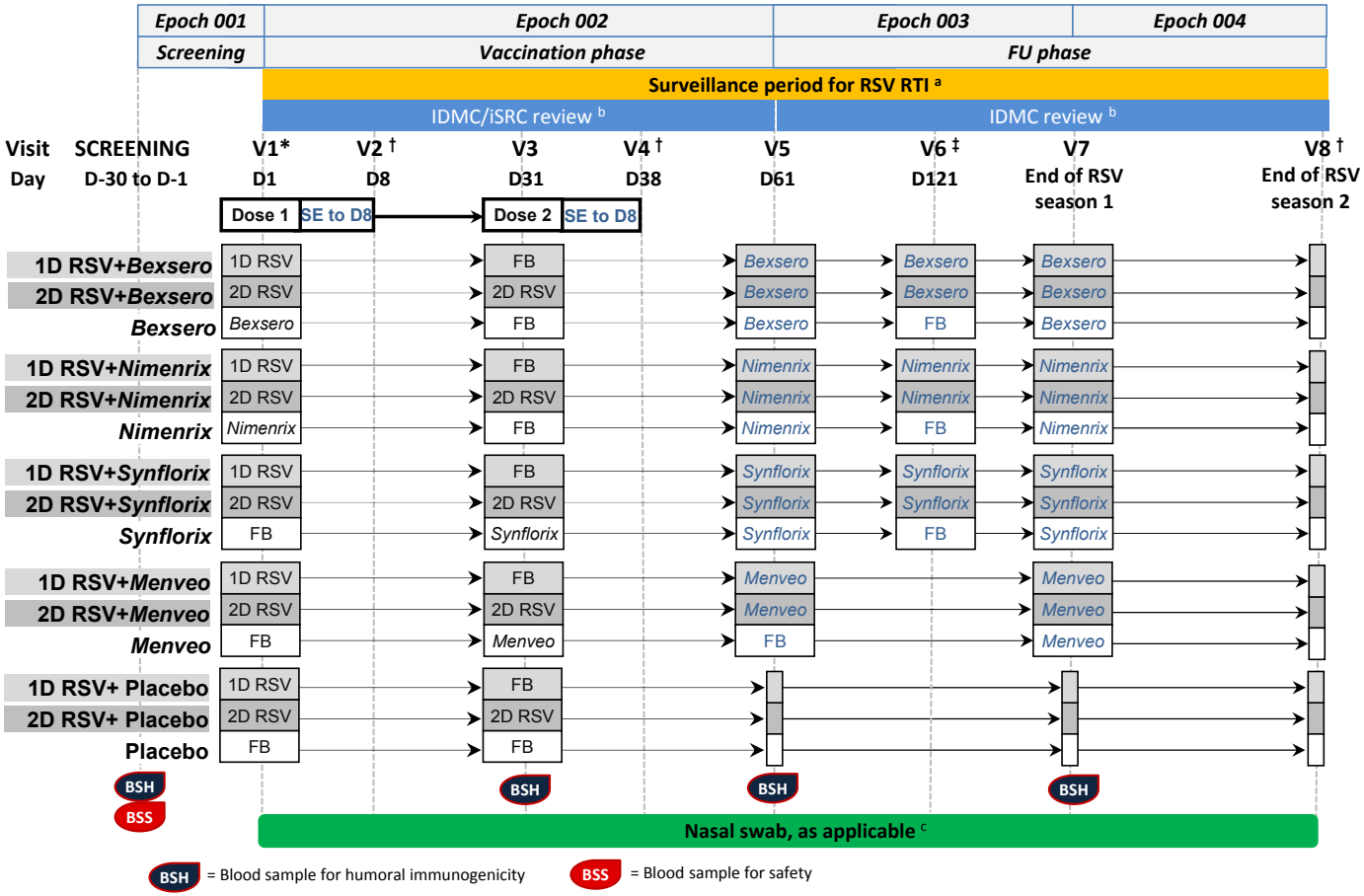
2.3. Tertiary objectives

- If deemed necessary, to further characterize the immune response of the RSV investigational vaccine when one ($1.5x10^{10}$ vp) dose or two ($5x10^{10}$ vp) doses are administered IM according to a 0, 1-month schedule to infants aged 6 and 7 months.

Refer to Section 11.3 for the definition of the tertiary endpoints and to Section 11.12.1 for the reporting of tertiary endpoint results.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design



D: Day; **FU**: follow-up; **IDMC**: Independent Data Monitoring Committee; **iSRC***:* internal Safety Review Committee; **RSV**: respiratory syncytial virus; **RTI:** respiratory tract infection; **SE**: solicited events; **V**: Visit **1D***:* 1 Dose ($1.5x10^{10}$ vp/dose)*;* **2D***:* 2 Dose ($5x10^{10}$ vp/dose)*;* **FB***:* Formulation buffer S9b.

* Vaccine Dose 1 at Day 1 will be administered before the first RSV season (refer to Section 5.1 for definition of RSV season).

† Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator. *For authorized sites only, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.*

‡ In countries where *Menveo or Placebo* is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

[a] Surveillance for RSV-RTI comprises monthly nasal swab collected to detect asymptomatic RSV infections during RSV season and active and passive surveillance contacts for RSV symptomatic RTI. Of note the swab may be omitted if a nasal swab has been taken at a symptomatic visit in the same month (see Section 9.2). Data about RSV–RTI incidence will be reviewed monthly by an IDMC.

[b] An iSRC will review all accumulating safety data monthly until the IDMC reviews has reviewed all safety data up to 30 days after administration of Dose 2 (i.e., Day 61). The IDMC will review all accumulating safety data monthly throughout the period of vaccination and accumulating SAEs until the end of the second RSV transmission season. Refer to Sections 9.10.2 and 9.10.3.

[c] Refer to Section 6.6.12.3.

Table 2 Vaccines administered and vaccination schedules

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	7-8 / (V3, D31)	8-9 / (V5, D61)	10-11 / (V6, D121)**	14-18 / (V7)
1D RSV + *Bexsero*	1D RSV ChAd	FB	*Bexsero*	*Bexsero*	*Bexsero*
2D RSV + *Bexsero*	2D RSV ChAd	2D RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	FB	*Bexsero*	FB	*Bexsero*
1D RSV + *Nimenrix*	1D RSV ChAd	FB	*Nimenrix*	*Nimenrix*	*Nimenrix*
2D RSV + *Nimenrix*	2D RSV ChAd	2D RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	FB	*Nimenrix*	FB	*Nimenrix*
1D RSV + *Synflorix*	1D RSV ChAd	FB	*Synflorix*	*Synflorix*	*Synflorix*
2D RSV + *Synflorix*	2D RSV ChAd	2D RSV ChAd	*Synflorix*	*Synflorix*	*Synflorix*
Synflorix	FB	*Synflorix*	*Synflorix*	FB	*Synflorix*
1D RSV + *Menveo*	1D RSV ChAd	FB	*Menveo*		*Menveo*
2D RSV + *Menveo*	2D RSV ChAd	2D RSV ChAd	*Menveo*		*Menveo*
Menveo	FB	*Menveo*	FB		*Menveo*
1D RSV + Placebo	1D RSV ChAd	FB			
2D RSV + Placebo	2D RSV ChAd	2D RSV ChAd			
Placebo	FB	FB			

V: Visit; **D:** Day; **1D:** 1 Dose ($1.5x10^{10}$ vp/dose**); 2D**: 2 Dose ($5x10^{10}$ vp/dose)**; RSV ChAd**: ChAd155-RSV vaccine**; FB:** Formulation buffer S9b.

* Assumes enrolled at 6 and 7 months of age for the vaccine Dose 1 to be administered before the first RSV season; the second dose will be given one month after the first dose. (RSV seasons will be determined for each country based on local epidemiological data [The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. Refer to the SPM for RSV seasons per *country*.])

** In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7.

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 6.5), are essential and required for study conduct.

- Experimental design: Phase I/II, observer-blind, randomized, controlled, multi-centric study with three parallel groups.
- Duration of the study: approximately 24 months.
  - Epoch 001: Screening Visit starting up to 30 days before first vaccination and ending on Day -1).
  - Epoch 002: primary starting at Visit 1 (Day 1) and ending at Visit 5 (Day 61).
  - Epoch 003: follow-up starting after Visit 5 (Day 61)* and ending at Visit 7 (end of the first RSV transmission season).
  - Epoch 004: follow-up starting after Visit 7 (end of the first RSV transmission season)* and ending at Visit 8 (end of the second RSV transmission season).

*Any safety, immunogenicity and disease surveillance data collected beyond Visit 5 (Day 61) will be collected in Epoch 003. Any safety, immunogenicity and disease surveillance data collected beyond Visit 7 (end of the first RSV transmission season) will be collected in Epoch 004. Refer to the SPM for RSV transmission seasons per country.

- Primary Completion Date (PCD): Visit 5 (Day 61).

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit 8 (end of the second RSV transmission season) related to primary and secondary endpoints.*

  * Up to Visit 8 (end of the second RSV season), there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season ***or*** if following active or a passive surveillance contacts, a subject presents symptoms of respiratory tract infection (RTI), a nasal swab will be collected.

Refer to the glossary of terms for the definition of EoS.

Study groups:

Table 3 Study groups and epochs foreseen in the study

Study groups	*Target* Number of subjects	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
1D RSV + Bexsero	50	6 – 7 months	N/A	x	x	x
1D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
1D RSV + Synflorix		6 – 7 months	N/A	x	x	x
1D RSV + Menveo		6 – 7 months	N/A	x	x	x
1D RSV + Placebo		6 – 7 months	N/A	x	x	x
2D RSV + Bexsero	50	6 – 7 months	N/A	x	x	x
2D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
2D RSV + Synflorix		6 – 7 months	N/A	x	x	x
2D RSV + Menveo		6 – 7 months	N/A	x	x	x
2D RSV + Placebo		6– 7 months	N/A	x	x	x
Bexsero	50	6 – 7 months	N/A	x	x	x
Nimenrix		6 – 7 months	N/A	x	x	x
Synflorix		6 – 7 months	N/A	x	x	x
Menveo		6 – 7 months	N/A	x	x	x
Placebo		6 – 7 months	N/A	x	x	x

1D: 1 Dose (1.5x10^{10} vp/dose); **RSV**: ChAd155-RSV vaccine; ***2D: 2 Dose (5x10^{10} vp/dose); N/A: Not Applicable***.

Table 4 Study groups and treatment foreseen in the study

Treatment name	***1D RSV ChAd***	***2D RSV ChAd***	***Bexsero***	***Nimenrix***	***Synflorix***	***Menveo***	***FB***
Vaccine/ Product name	***1D ChAd155-RSV 1.5X10[10] vp/dose***	***2D ChAd155-RSV 5X10[10] vp/dose***	***Bexsero***	***Nimenrix***	***Synflorix***	***Menveo***	***FB***
Study Groups							
1D RSV + Bexsero	***x***		***x***				***x***
1D RSV + Nimenrix	***x***			***x***			***x***
1D RSV + Synflorix	***x***				***x***		***x***
1D RSV + Menveo	***x***					***x***	***x***
1D RSV + Placebo	***x***						***x***
2D RSV + Bexsero		***x***	***x***				
2D RSV + Nimenrix		***x***		***x***			
2D RSV + Synflorix		***x***			***x***		
2D RSV + Menveo		***x***				***x***	
2D RSV + Placebo		***x***					
Bexsero			***x***				***x***
Nimenrix				***x***			***x***
Synflorix					***x***		***x***
Menveo						***x***	***x***
Placebo							***x***

ChAd155-RSV: Chimpanzee Adenovirus Type 155 RSV vaccine; **FB**: Formulation buffer S9b; **RSV ChAd**: ChAd155-RSV vaccine; ***1D:*** 1 Dose (1.5x10[10] vp/dose)***; 2D:*** 2 Dose (5x10[10] vp/dose).

- Controls: active comparator vaccines (Bexsero, or Nimenrix, or *Synflorix,* or *Menveo*, or Placebo (FB)*.

  * The choice of active comparator vaccine (*Bexsero*, *Nimenrix, Synflorix,* or *Menveo*) or Placebo is done at the country level. Refer to the ICF for the local choice of comparator/Placebo.

- Vaccination schedules:

  RSV investigational vaccine:

  – In the 1 Dose (1D) groups, a single lower dose of 1.5x10[10] vp will be administered IM at Day 1 (Visit 1). Formulation buffer will be administered in the 1D groups at Day 31 (Visit 3). In the 2 Dose (2D) groups, two doses of 5x10***[10]*** vp will be administered IM according to a 0, 1-month schedule, (i.e., at Day 1 [Visit 1] and Day 31 [Visit 3]) (see Figure 1 and Table 2). Dose 1 will be administered before the first RSV season and the second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the Study Procedures Manual [SPM]. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable..

Comparator or Placebo:

- In countries where *Bexsero or Nimenrix* is used as a control, two doses will be administered IM with at least a 2 month interval between these primary doses. A booster dose will be administered IM in the second year of life at Visit 7, with an interval of at least 2 months between the primary series and booster dose. The first *Bexsero or Nimenrix* dose will be administered at Day 1 (Visit 1) (in the groups receiving only *Bexsero* or *Nimenrix*, respectively). In the groups receiving only *Bexsero* or *Nimenrix,* the second dose will be at Day 61 (Visit 5). The first *Bexsero* or *Nimenrix* dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of *Bexsero* or *Nimenrix* in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Figure 1 and Table 2).
- In countries where *Synflorix* is used as a control, two doses will be administered IM with at least a 1 month interval between these primary doses. A booster dose will be administered IM in the second year of life at Visit 7. The first *Synflorix* dose will be administered at Day 31 (Visit 3) (in the group receiving only *Synflorix).* In the group receiving only *Synflorix*, the second dose will be at Day 61 (Visit 5). The first *Synflorix* dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of *Synflorix* in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Figure 1 and Table 2).
- In countries where *Menveo* is used as a control, two doses will be administered IM at least 3 months apart with the second dose in the second year of life *at* Visit 7. The first *Menveo* dose will be administered at Day 31 (Visit 3) (in the group receiving only Menveo). The first *Menveo* dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. Since the second Menveo dose has to be administered in the second year of life at Visit 7, no administration will be performed at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine or comparator is scheduled, at the 4 vaccination visits (see Figure 1 and Table 2).
- In countries where Placebo is used as a control, one dose will be administered IM at Day 31 (Visit 3) in the 1D RSV + Placebo group and two IM doses will be administered IM according to a 0, 1-month schedule at Day 1 (Visit 1) and Day 31 (Visit 3) in the Placebo group (see Figure 1 and Table 2).

- Treatment allocation: infants will be randomized using a centralized randomization system on internet (SBIR) before first vaccination and after assessment of eligibility (i.e., after screening conclusion) (refer to Section 6.2.2 for details about randomization of treatment). The randomization algorithm will use a minimization procedure accounting for country as a minimization factor and the grouping comparator/placebo as a stratification factor.

- Blinding: not applicable for Epoch 001 (Screening Visit), observer-blind in Epoch 002 and single-blind in Epoch 003 and Epoch 004. Refer to Section 6.3 for details of blinding procedure.

Table 5 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	N/A
Epoch 002	observer-blind
Epoch 003	single-blind
Epoch 004	single-blind

N/A: Not applicable.

- Sampling schedule:
  - Blood samples for **hematology/biochemistry** will be taken from all infants at Screening (up to 30 days before first vaccination to Day -1). Blood samples for **hematology/biochemistry** may be taken from infants at any timepoints, if deemed necessary by the investigator. Refer to Table 12 for the list of parameters to be tested.

    Refer to Section 6.6.12.2 and Figure 2 for information about the re-testing of samples in case of any Grade 1 abnormality with potential clinical relevance (according to investigators judgment) or any ≥ Grade 2 abnormality.
  - Blood samples for **humoral immunogenicity** will be taken from all subjects at Screening and on Day 31, Day 61, and at the visit occurring at the end of the first RSV transmission season.
  - Blood sample for **assessment of mechanism of illness (potential ERD)** will be taken from subjects hospitalized for LRTI (only for RSV-positive subjects using a locally available RSV test).
  - Nasal swab: there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season and if following active or a passive surveillance contacts, a subject presents symptoms of RTI, a nasal swab will be collected (as well as a sample for local testing i.e., the type of sample to be determined locally [e.g., swab, etc.]) (Refer to the SPM).
- Study visits: Other than the screening visit and assessment visits for active/passive surveillance, there will be 8 study visits except in countries where *Menveo* or Placebo is used as a control where there will be 7 study visits.
  - In countries where *Menveo* is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).
  - In countries where Placebo is used as a control, no vaccine administration will be performed after Visit 3 and therefore in those countries there will be no Visit 6. There will be a Visit 5 and Visit 7 for countries using Placebo and all other study procedures will occur at these visits except vaccination.

  - Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.
    - For authorized sites only, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.

- Type of study: self-contained.
- Data collection: electronic Case Report Form (eCRF).
- Safety monitoring: internal safety review committee (iSRC) and IDMC (refer to Section 9.10).
- Surveillance for RSV-RTI, difficulty in breathing, and wheezing episodes.

  Surveillance period will be carried out from Visit 1 (after Dose 1) until the last study visit (end of the second RSV transmission season). In order to detect asymptomatic RSV-RTI, monthly nasal swabs for analysis at sponsor laboratory will be performed for all subjects during the RSV season. In order to timely detect RSV-RTI and to ensure cases are timely captured by the study sites, both active and passive surveillance will be conducted:

  - **Passive surveillance**: parent(s)/LAR(s) are instructed to contact the investigator/study staff as soon as the subject experiences new RTI symptoms (cough, runny nose or blocked nose) or worsening of RTI symptoms, or in case of difficulty in breathing or wheezing.
  - **Active surveillance**: parent(s)/LAR(s) of all the subjects will be contacted by the investigator/study staff on a regular basis (weekly during the RSV season and every month outside the RSV season) to identify any potential RSV-RTI and to remind the parent(s)/LAR(s) of the subjects to report any new occurrence of RTI symptoms (cough, runny nose or blocked nose), or in case of difficulty in breathing or wheezing as soon as possible.

Refer to Section 9.2 for more information about active and passive surveillance.

- Surveillance for spontaneous or excessive bleeding.

Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination (Visit 1 and Visit 3), in order to detect any thrombocytopenic petechiae or purpura. The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets.

4. CASE DEFINITION

It should be noted that for the reporting of safety (unsolicited AEs, AEs of special interest and SAEs), the investigator will use all available information and his/her medical judgment to make diagnoses. The case definitions presented below will be used for a safety analysis complementary to standard safety tabulations of events according to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

4.1. RTI case definitions

During the analysis of the study, all cases identified during the surveillance of RSV-RTI will be definitively classified as either RTI, LRTI, severe LRTI or very severe LRTI according to the standardized case definitions (see Table 6) based on the available World Health Organization (WHO) case definitions [Modjarrad, 2016].

Table 6 Case definitions for data analysis

Case	*At sea level up to 2500 meters elevation*	*Above 2500 meters elevation*
RSV-RTI	Runny nose OR blocked nose OR cough AND Confirmed RSV infection [4]	***Same***
RSV-LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3] AND Confirmed RSV infection [4]	***Same but with SpO2 <92%***
severe *RSV*-LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 93% [2], OR lower chest wall in-drawing	***Same but with SpO2 <90%***
very severe *RSV*-LRTI	Meeting the case definition of RSV-LRTI AND SpO_2 < 90% [2], OR inability to feed, OR failure to respond / unconscious	***Same but with SpO2 <88%***
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]	***Same***
All-cause LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3]	***Same but with SpO2 <92%***

LRTI = lower respiratory tract infections; **RR** = respiratory rate; **RTI** = respiratory tract infections; **SpO2** = blood oxygen saturation.

Based on [Modjarrad, 2016]

[1] Based on history reported by parents.

[2] The lowest value during the course of illness will be used.

[3] RR increase defined as:

≥ 50/minute (2 to 11 months of age)

≥ 40/minute (12 months of age or above)

The highest value during the course of the illness will be used.

[4] RSV infection confirmed on nasal swab positive for RSV A or B by quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR).

[5] RSV sampling and testing is based on medical judgment of medical practitioner or driven by algorithm.

[6] Hospitalization is defined as a medical decision that the infant requires admission for observation or treatment.

5. STUDY COHORT

5.1. Number of subjects

The target will be to enroll approximately 150 infants likely to be previously unexposed to RSV with about 50 infants for each of three randomization groups. If necessary, the sample size ***may*** be increased through additional recruitment in order to achieve ***a sufficient number of*** RSV infected infants, with a negative RSV exposure status (at screening based on in-stream serological testing), in each RSV vaccine group. Dose 1 administration should be completed before the first RSV season and second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the SPM). The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. Refer to the SPM for RSV seasons per country. Refer to Section 11.4 for the determination of sample size **(Amended 1 August 2019**).

Overview of the screening plan:

Upon completion of all screening procedures (refer to Table 7), the investigator will review the inclusion/exclusion criteria for each infant. Infants meeting all eligibility criteria will be enrolled in the study. Their screening information will be recorded on the appropriate screen of eCRF.

If the investigator believes there is a reasonable reason to do so, screening procedures may be repeated once only. All screening procedures may be repeated except the blood sampling for humoral response (neutralizing antibody titers against RSV-A, RSV-F protein antibody concentrations and palivizumab-competing antibody concentrations).

5.2. Inclusion criteria for enrolment

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

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

- Subjects' parent(s)/LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
- A male or female between and including 6 and 7 months of age (from the day the infant becomes 6 months of age until the day before the infant achieves 8 months of age) at the time of the first vaccination.

- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born full-term (i.e., after a gestation period of 37 to less than 42 completed weeks) with a minimum birth weight of 2.5 kg.
- Subjects' parent(s)/LAR(s) need to have access to a consistent mean of telephone contact (e.g., land line or mobile) or computer.

5.3. Exclusion criteria for enrolment

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

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

- Child in care

  Please refer to the glossary of terms for the definition of child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day (for pediatric subjects), or equivalent. Topical steroids are allowed.
- Administration of long-acting immune-modifying drugs (e.g., infliximab) or planned administration at any time during the study period.
- Administration of immunoglobulins and/or any blood products during the period starting three months before the first dose of study vaccine or planned administration during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of vaccine administration, with the exception of scheduled routine pediatric vaccines. (For details of permitted concomitant vaccines refer to Section 7.6). Scheduled routine pediatric vaccines may be administered ≥ 7 days before a dose of study vaccine or ≥ 7 days following a dose of study vaccine, with the exception of live viral vaccines which may be administered ≥ 14 days before a dose or ≥ 7 days after a dose.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- A history of, or on-going confirmed RSV disease or highly compatible clinical picture (e.g., bronchiolitis).

- Serious chronic illness.
- Major congenital defects.
- History of any neurological disorders or seizures.
- History of or current autoimmune disease.
- History of recurrent wheezing. ("Recurrent wheezing" is defined as ≥ 2 episodes of wheezing in the subject´s lifetime). Wheezing should have been verified on auscultation by doctor.
- History of chronic cough (4 weeks or more duration).
- Previous hospitalization for lower respiratory illnesses.
- Previous, current or planned administration of *Synagis* (palivizumab).
- Neurological complications following any prior vaccination.
- Born to a mother known or suspected to be HIV-positive (no laboratory testing required).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- Previous vaccination with a recombinant simian or human adenoviral vaccine.
- History of any reaction or hypersensitivity to any component of the vaccine***s*** (investigational or control) or placebo used in this study or any contraindication to them.
- Hypersensitivity to latex.
- Current severe eczema.
- Acute disease and/or fever at the time of enrolment (Visit 1).
  - Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the rectum for subjects < 12 months of age.
  - Clinically significant upper respiratory tract infection.
  - Subjects with a minor illness (such as mild diarrhea) without fever may be enrolled at the discretion of the investigator.
- Any clinically significant Grade 1 or any ≥ Grade 2* hematological or biochemical laboratory abnormality detected at the last screening blood sampling.

  * Refer to APPENDIX C. For Grade 1 laboratory abnormalities, the investigator should use his/her clinical judgment to decide which ones are clinically relevant. Infants with hematological/biochemical values out of normal range which are expected to be temporary, may be re-screened at a later date.
- Any medical condition that in the judgment of the investigator would make IM injection unsafe.

- Any other conditions that the investigator judges may interfere with study procedures (e.g., drawing blood), findings (e.g., immune response).
- Any conditions that could constitute a risk for the subjects while participating to this study.
- Weight below the fifth percentile according to the World Health Organization (WHO) weight-for-age tables (https://www.who.int/childgrowth/standards/weight_for_age/en/).
- Participating in another clinical study, at any time during the study period, in which the subject or mother (if breastfeeding) has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device)
- Planned move to a location that will prohibit participating in the trial until study end.
- For Thailand only, subjects who have received Synflorix prior to enrolment.

6. CONDUCT OF THE STUDY

6.1. 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 GCP, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonized Tripartite Guideline for clinical investigation of medicinal products in the pediatric population (ICH E11) and all other applicable ethical guidelines.

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's parent(s)/LAR(s) 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's parent(s)/LAR(s), prior to participation in the study.

GSK Biologicals will prepare a model 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.

6.2. Subject identification and randomization

6.2.1. 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 center.

6.2.2. Randomization of treatment

6.2.2.1. Randomization of supplies

The randomization 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 centers /warehouse(s).

6.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by components**.**

6.2.2.2.1. Study group and treatment number allocation

The target will be to enroll approximately 150 infants. Approximately 50 infants likely to be previously unexposed to RSV will be randomly assigned to receive 2 doses at 0, 1 month schedule of 0.5 mL of the ChAd155-RSV vaccine ($5x10^{10}$ vp) [the 2D RSV + comparator group], approximately 50 infants likely to be previously unexposed to RSV will be randomly assigned to receive a single dose of 0.5 mL of ChAd155-RSV vaccine ($1.5x10^{10}$ vp) [the 1D RSV + comparator group], and approximately 50 infants likely to be previously unexposed to RSV will be randomly assigned to receive 0.5 mL of the comparator/Placebo control vaccine [the comparator/Placebo control alone group].

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR) operated at the study level.

The randomization algorithm will assign each subject to the 2 doses of RSV vaccine + comparator group, the single dose of RSV vaccine + comparator group, or its corresponding active control comparator group with the aim of keeping the ratio between the pooled 2 dose RSV + comparator group, the pooled single dose RSV + comparator group and the pooled comparator group at 1:1:1 in the entire study (see Table 25 for a description of pooled groups).

Countries will be grouped into five levels according to the choice of comparator vaccine or Placebo, the randomization algorithm will use a minimization procedure accounting for country as a minimization factor and the grouping comparator/placebo as a stratification factor to attempt to maintain a 1:1:1 ratio as well within each level in the assignment of RSV + comparator vaccine versus comparator/Placebo control vaccine alone.

The actual randomization assignment the subject received (to one of five 2 dose of RSV + comparator vaccine groups, to one of five single dose of RSV + comparator vaccine groups, or to one of five comparator/Placebo control alone groups) will be able to be identified in SBIR.

After obtaining the signed and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, the delegated study staff will access SBIR. Upon providing the subject identification number and the age, the randomization 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 SPM for specific instructions.

6.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the delegated study staff will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

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

6.3. Method of blinding

Data will be collected in an observer-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, reactogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorized medical personnel who will not participate in any of the study clinical evaluation assays.

When all data up to Day 61 are available, a statistical analysis will be performed. This analysis may lead to the unblinding of some subjects. As a consequence, after Day 61, the study cannot be considered as observer-blind, but will be conducted in a single blind manner, with subjects' parent(s)/ LAR(s) remaining blinded up to the last study visit (end of the second RSV transmission season), while the investigator will still not have access to the treatment allocation up to the last study visit (end of the second RSV transmission season), except in case of emergency unblinding (see Section 9.8).

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.

6.4. 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.

In the same investigational center, infants will be vaccinated sequentially, separated by a minimum interval of 60 minutes.

Refer to Section 9.10 for information about limited vaccination, holding rules, safety monitoring and safety evaluation by iSRC and IDMC.

6.5. Outline of study procedures

Table 7 List of study procedures

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	*E*nd of the 1st RSV season [d]	*E*nd of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Informed consent	●												
Check inclusion/exclusion criteria	●	O											
Collect demographic data	● [i]												
Medical history [j]	●												
Physical examination [k]	●	O	O	O	O	O		O	O	O		O	●
Growth monitoring [l]	●			●		●		●	●				
Check contraindications and warnings and precautions		O		O		O	O	O					
*(*Pre-vaccination*)* body temperature		●		●		●	●	●					
Randomization		O											
Vaccine administration [m]		●		●		●	● [c]	●					
Recording of administered treatment number		●		●		●	●	●					
60 minutes post-vaccination observation [n]		O		O									
30 minutes post-vaccination observation for additional comparator/FB vaccinations						O	O	O					

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	*E*nd of the 1st RSV season [d]	*E*nd of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Blood sampling for assessment of mechanisms of illness (potential ERD; ~2.5 mL)													● [o]
Blood sampling for hematology and biochemistry (~2.3 mL)	● [p]									● [q]			
Blood sampling for humoral response (~2.5 mL)	● *[r]*			● *[s]*		●		●					
Surveillance for RSV-RTI, difficulty in breathing and wheezing		O	O	O	O	O	O	O	O		O	O	
Documentation of symptoms and signs of RTI *[t]*													●
Nasal swab for central testing (RSV and RVP)												● *[u]*	● *[v]*
Specimen for local testings (RSV and RVP)													● *[w]*
Distribution of RTI episode card *[x]*		O	O	O	O	O	O	O					
Collection of RTI episode card *[x]*			O	O	O	O	O	O	O	O		O	O
Transcription of RTI episode card			●	●	●	●	●	●	●	O		●	●
Record any concomitant medications/vaccinations		●	●	●	●	●	●	●	●	●		●	●
Distribution of the subject card	O												
Distribution of diary card		O	O	O	O								

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	*E*nd of the 1st RSV season [d]	*E*nd of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Return of diary card			O	O	O	O							
Diary card transcription by investigator			●	●	●	●							
Recording of solicited AEs (Day 1–7)		●	●	●	●					● *y*			
Recording of unsolicited AEs (Day 1-30)		●	●	●	●	●				● *y*			
Recording of AE leading to study withdrawal		●	●	●	●	●	●	●	●	●	●	●	●
Recording of AESI (RSV-LRTI)		●	●	●	●	●	●	●	●	●	●	●	●
Recording of AESI (spontaneous or excessive bleeding) [z]		●	●	●	●	●				●			
Reporting of easy bruising, or rash/petechiae monitored by parent(s)/LAR(s) [z]		O	O	O	O	O							
Recording of SAEs		●	●	●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	●	●
Screening conclusion	●												
Study conclusion									●				

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	*E*nd of the 1st RSV season [d]	*E*nd of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Signing of investigator signature form by investigator after Screening and before each analysis	●					●		●	●				

AE: adverse event; AESI: Adverse Events of Special Interest; FB: Formulation buffer S9b; LRTI: lower respiratory tract infection; RSV: respiratory syncytial virus; RTI: respiratory tract infection, RVP: respiratory viral panel SAE: serious adverse event.

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

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

Note: the double-bordered lines following Visit 5 (Day 61), Visit 7 (end of the first RSV transmission season) and Visit 8 (end of the second RSV transmission season) indicate the statistical analyses which will be performed. After Visit 5 (Day 61) the study will be conducted in a single blind manner, with patients remaining blinded up to the last study visit (end of the second RSV transmission season). The investigator will not have access to the treatment allocation up to the last study visit (end of the second RSV transmission season), except in case of emergency unblinding.

[a] For vaccination done on the same day as screening, it must be ensured that screening procedures only begin after signing consent and that all the screening procedures confirming eligibility, including the laboratory results, are made available prior to vaccination (see Section 6.6.2).

[b] Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator. For authorized sites only; screening, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator [redacted]

[c] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Figure 1 and Table 2).

[d] Refer to the SPM for RSV seasons per country.

[e] This visit is applicable for infants with hematological/biochemical values out of normal range or for further evaluation of clinical suspicion of low platelet count.

[f] Active contacts for surveillance of RSV-RTI will take place weekly during each RSV season and every month outside the RSV season. Passive phone contacts from the carers to the investigator will take place when symptoms occur.

[g] In order to detect asymptomatic RSV infection, monthly visits will be performed during the RSV season.

[h] This visit is only applicable for infants with potential RSV-RTI.

[i] Recording of demographic data includes date of birth, sex, race, ethnicity and comparator group.

[j] Medical history is collected by interview and/or review of the subject's medical records and includes recording the subject's weight at birth and gestation in weeks at birth as well as any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF.

[k] At screening, perform a complete physical examination, including assessment of vital signs (body temperature, heart rate [HR], and RR). At subsequent study visits, perform a physical examination only if the subject's parent(s)/LAR(s) indicate(s) during questioning that there might be some underlying pathology(ies) or if deemed necessary.

[l] Growth monitoring includes weight and length (for infants < 24 months of age) or height (for subjects ≥ 24 months of age).

[m] Refer to Table 2 and to the SPM for the comparator vaccine selection for each country.

[n] Infants will need to remain under observation (visual follow-up as well as measurement of resting vital signs) at the study site for at least 60 minutes after vaccination. Vital signs are body temperature, HR and RR. Vital signs are measured preferably when the infant is calm.

[o] Blood sample collected for subjects hospitalized for LRTI (only for RSV-positive subjects using a locally available RSV test). Refer to Section 6.7.3.

[p] At Screening, for infants with hematological/biochemical values out of normal range which are expected to be temporary, a re-screening visit may be scheduled during which blood sample collection for hematology/biochemistry will be repeated (maximum one re-screening visit per infant is allowed).

[q] If any Grade 1 abnormality with potential clinical relevance (according to investigator judgment) or any ≥ Grade 2 abnormality is detected, or for further evaluation of clinical suspicion of low platelet count, refer to Section 6.6.12.2 and Figure 2 for re-test.

[r] If no blood sample was collected for humoral immunogenicity at the screening visit, an additional blood sample will be taken at Visit 1 that must be taken before vaccination.

[s] Samples ***must*** be taken before vaccination.

[t] Signs and symptoms to be recorded in the eCRF are listed in the SPM.

[u] Nasal swab collected at the monthly surveillance for asymptomatic RSV-RTI will be tested by quantitative RT-PCR. This swab may be omitted upon investigator discretion if a swab has been taken for a symptomatic episode in the previous 4 weeks (see Section 6.6.12.3).

[v] If during passive or active surveillance contact, the investigator/study staff assesses that an infant presents a potential RSV-RTI (refer to Table 6 for definition), the potential RSV infection will be assessed by quantitative RT-PCR.

[w] At a local routine laboratory

[x] Subject's parent(s)/LAR(s) will be instructed to record on the RTI episode card symptoms the start date and the end date of the following symptoms (cough, runny nose, blocked nose, difficulty in breathing, or wheezing) and to return it to the investigator at the next visit or by mail (e-mail or postal mail).

[y] Only when the unscheduled visit occurs within the AE reporting time frame, i.e., from Day 1 to Day 7 for solicited AEs and from Day 1 to Day 30 for unsolicited AEs.

[z] Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination, in order to detect any thrombocytopenic petechiae or purpura ***(see*** Table 19***)***.

Whenever possible, the investigator should arrange study visits within the interval described in Table 8.

Table 8 Target intervals between study visits

Interval	Length of interval
Screening → Visit 1 (Day 1)	30 days [1]
Visit 1 (Day 1) → Visit 2 (Day 8)	7 days
Visit 1 (Day 1) → Visit 3 (Day 31)	30 days
Visit 1 (Day 1) → Visit 5 (Day 61)	60 days
Visit 3 (Day 31) → Visit 4 (Day 38)	7 days
Visit 3 (Day 31) → Visit 5 (Day 61)	30 days
Visit 5 (Day 61) → Visit 6 (Day 121) [2]	60 days
Visit 7 (end of the first RSV transmission season)	From vaccination to the defined end of the first RSV transmission season
Visit 8 (end of the second RSV transmission season)	From vaccination to the defined end of the second RSV transmission season

[1] Visit 1 should take place no longer than 30 days after the Screening visit. When applicable, a re-screening visit may be scheduled at any time (but only once to assess eligibility). All screening procedures need to be performed within 30 days of Visit 1.

[2] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and if applicable it will be administered at the end of the first RSV season at Visit 7 (refer to Figure 1 and Table 2).

Refer to Table 24 for intervals between study visits that determine subjects' eligibility for inclusion in the per-protocol (PP) analysis.

6.6. Detailed description of study procedures

6.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. Refer to Section 6.1 for the requirements on how to obtain informed consent.

6.6.2. Screening visit

Following the signing of the informed consent, the screening procedures must be done within 30 days prior to vaccination.

For vaccination done on the same day as screening, all the screening procedures confirming eligibility including the laboratory results must be made available prior to vaccination.

6.6.3. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 5.2 and 5.3 before enrolment.

6.6.4. Collect demographic data

Record demographic data such as date of birth (day, month and year), sex, race, ethnicity and comparator group in the subject's eCRF.

6.6.5. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record weight at birth and gestation in weeks at birth as well as any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF. For World Health Organization (WHO) weight percentile standards for girls and boys, refer to the following link: https://www.who.int/childgrowth/standards/weight_for_age/en/.

6.6.6. Physical examination

At screening, perform a physical examination of the subject, including assessment of vital signs preferably when the infant is calm. Vital signs are body temperature, heart rate (HR) and RR. Collected information needs to be recorded in the eCRF.

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

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

6.6.7. Growth monitoring

Growth monitoring includes weight and length (for infants < 24 months of age) or height (for subjects ≥ 24 months of age; [United Nations, 1986]). Collected information needs to be recorded in the eCRF.

6.6.8. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 7.5 for more details.

6.6.9. Assess pre-vaccination body temperature

The rectal (preferred route) body temperature of each subject needs to be measured prior to any study vaccines administration. If the subject has fever (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 8).

6.6.10. Randomization

Study group and treatment number allocation will be performed as described in Section 6.2.2. The number of each administered treatment must be recorded in the eCRF.

6.6.11. Study vaccines administration

- In the same investigational center, infants will be vaccinated sequentially, separated by a minimum interval of 60 minutes (Refer to Section 9.10.1).
- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered via IM injection in the anterolateral thigh. Refer to Section 7.3 for detailed description of the vaccines administration procedure. If the investigator or delegate determines that the infant's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 8).
- The subjects will be observed closely (visual follow-up as well as measurement of resting vital signs) for at least 60 minutes following the administration of the vaccines at Visit 1 and Visit 3, with appropriate medical treatment readily available in case of anaphylaxis. Vital signs are body temperature, HR and RR. Vital signs are preferably measured when the infant is calm. After administration of comparator vaccines or FB at Visit 5, Visit 6 and Visit 7, the subjects will be observed closely (visual follow-up as well as measurement of resting vital signs) for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

6.6.12. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

To minimize any development of needle aversion, pain relief by means of a topical local anesthetic may be offered to infants prior to any blood sampling requested by the protocol at the discretion of the investigator and in line with prescribing information.

6.6.12.1. Blood sampling for humoral immunity

Blood samples will be taken during certain study visits as specified in Section 6.5 List of Study Procedures.

- A volume of 2.5 mL of whole blood (to provide at least 800 µL of serum) should be drawn from all infants for analysis of humoral response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.
  - Blood sampling for humoral response will not be repeated in case of insufficient volume, at any timepoint except if no blood sample for humoral immunogenicity was collected at the screening visit. In that case an additional blood sample will be taken at Visit 1 that must be taken before vaccination.

6.6.12.2. Blood sampling for hematology and biochemistry

- A volume of maximum 2.3 mL of whole blood should be drawn from all infants for analysis of the hematology and biochemistry parameters (refer to Table 12) at each pre-defined timepoint.

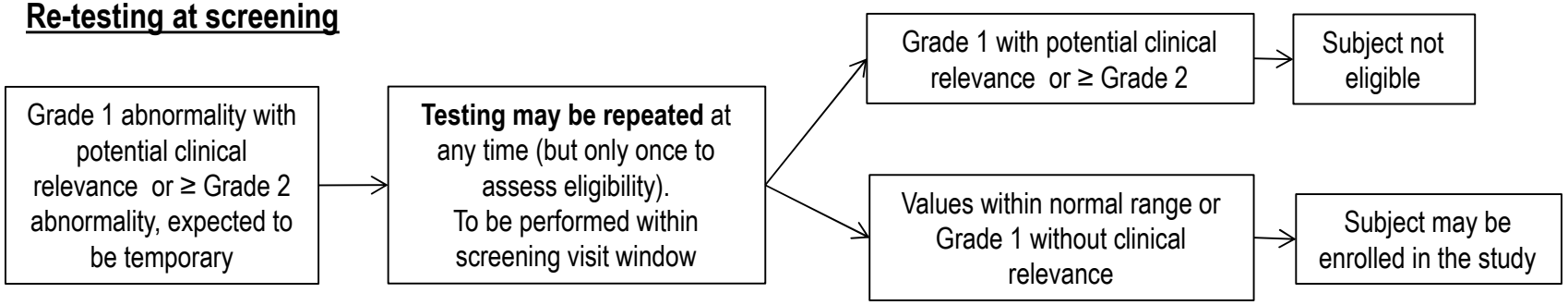
  Hematology and biochemistry parameters measurement will be performed according to laboratory practices.

  If any Grade 1 abnormality with potential clinical relevance (according to investigators judgment, refer to the glossary of terms) or any ≥ Grade 2 abnormality is detected (refer to Figure 2 and APPENDIX C):

  – at **Screening**, for infants with hematological/biochemical values out of normal range which are expected to be temporary, a re-screening visit may be scheduled during which blood sample collection for hematology/biochemistry will be repeated (maximum one re-screening visit per infant is allowed within the interval planned in Table 8; blood for humoral response will not be re-sampled at the re-screening visit).

Note: Blood may be re-sampled for hematology and biochemistry assessment during a re-screening visit (as described above) or during an Unscheduled Visit where there is clinical indication for additional testing.

Figure 2 Schematic overview of required additional hematology and biochemistry testing during the study



Note: Blood can be re-sampled for hematology and biochemistry assessment where there is clinical indication for additional testing.

6.6.12.3. Nasal swab *or* other specimen for PCR assay

Nasal swab *or* other specimen for PCR assay collected during assessment visit

Real time assessment of potential RSV-LRTI cases is important for the timely monitoring of safety.

If during passive or active surveillance contact, the investigator/study staff assesses that an infant presents a potential RSV-RTI (refer to Section 9.2), a nasal swab ***or*** another specimen for assay will be collected during an assessment visit:

- The nasal swab will allow assessing the potential RSV infection by quantitative RT-PCR and respiratory viral panel (RVP) at sponsor laboratory.
- The specimen for local assay will allow assessing the potential RSV infection and RVP at a local routine laboratory, where available. The specimen type will depend on the assay run locally.

Nasal swab collected *for PCR assay* to detect asymptomatic RSV infections

During RSV season, there will be monthly nasal swabs to detect asymptomatic RSV infections. These nasal swabs will allow assessing the potential RSV infection by quantitative RT-PCR performed centrally at the sponsor laboratory. This swab may be omitted upon investigator discretion if a swab has been taken for a symptomatic episode in the previous 4 weeks.

Refer to the SPM for more details about nasal swab.

6.6.13. Surveillance for RSV-RTI and wheezing

Surveillance period for RSV-RTI and wheezing will start at Visit 1 (after Dose 1) until the final visit (Visit 8 [end of the second RSV transmission season]). In order to timely detect RSV-RTI and to ensure cases are timely captured by the study sites, both active and passive surveillance will be conducted as described in Section 9.2. Contacts for active and passive surveillance will be recorded in the eCRF.

If an assessment visit is performed (refer to Section 9.2.4), this visit will be recorded in the eCRF, as well as signs and symptoms. Signs and symptoms to be recorded in the eCRF are listed in the SPM.

At the first vaccination visit (Visit 1 [Day 1]), RTI episode cards will be provided to the subject's parent(s)/LAR(s). At subsequent study visits, new RTI episode card(s) will be distributed as needed. The subject's parent(s)/LAR(s) will record the start date and the end date of the following symptoms: cough, runny nose, blocked nose, difficulty in breathing, or wheezing. The subject's parent(s)/LAR(s) will be instructed to return the completed RTI episode card to the investigator at the next visit or by mail (e-mail or postal mail). The investigator will transcribe the collected information into the eCRF. Any unreturned RTI episode cards will be sought from the subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.

6.6.14. Check and record concomitant medication/vaccination

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 7.6.

6.6.15. Recording of AEs, AEs of special interest and SAEs

- Refer to Section 9.3 for procedures for the investigator to record AEs, AEs of special interest (RSV-LRTI) and SAEs. Refer to Section 9.4 for guidelines and how to report AEs of special interest and SAE reports to GSK Biologicals.
- The subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.
- Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination (Visit 1 and Visit 3), in order to detect any thrombocytopenic petechiae or purpura after each vaccination from Visit 1 [Day 1] to Visit 5 Day 61.
- At each vaccination visit of the RSV investigational vaccine (Visit 1 [Day 1] and Visit 3 [Day 31]), a diary card will be provided to the subject's parent(s)/LAR(s). The subject's parent(s)/LAR(s) will be instructed to measure and record the rectal body temperature (preferred route), any solicited local/general AEs, any unsolicited AEs, and concomitant medications/products/vaccinations on the day of vaccination and 6 subsequent days. The subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at Visit 2 (Day 8) and Visit 4 (Day 38).

  The subject's parent(s)/LAR(s) will record on the same diary card any unsolicited AEs and concomitant medications/products/vaccinations from 7 to 29 days after each vaccination. The subject's parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at Visit 3 (Day 31) and Visit 5 (Day 61).

  The investigator will collect and verify completed diary cards during discussion with the subject's parent(s)/LAR(s) on Visit 2 (Day 8), Visit 3 (Day 31), Visit 4 (Day 38), and Visit 5 (Day 61). The investigator will transcribe the collected information into the eCRF in English.

  Any unreturned diary cards will be sought from the subject's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.

6.6.16. Screening conclusion

At the end of the screening visit, the investigator will:

- Review data collected.
- Complete the Screening Conclusion screen in the eCRF.

6.6.17. Signing of investigator signature form by investigator

At the end of the screening visit, Visit 5 (Day 61), Visit 7 (end of the first RSV transmission season) and Visit 8 (end of the second RSV transmission season), the investigator will sign the investigator signature form in the eCRF.

6.6.18. Study conclusion

At the last visit (Visit 8 [end of the second RSV transmission season]), the investigator will:

- Review data collected to ensure accuracy and completeness.
- Complete the Study Conclusion screen in the eCRF.

6.7. 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's parent(s)/LAR(s).

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 6.7.4 may be changed.

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

6.7.1. 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 per-protocol analysis (See Section 11.5 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.

6.7.2. Biological samples

Table 9 Biological samples

Sample	Timepoint	Type of sample†	Subject	Number of subjects	Quantity
Blood	Screening	Blood sample for hematology and biochemistry	All infants	≥ 150	2.3 mL
		Blood sample for humoral response #	All infants	≥ 150	2.5 mL
		Total volume of blood collected for each subject			**4.8 mL**
	Visit 3 (Day 31)	Blood sample for humoral response	All infants	~150	2.5 mL
	Visit 5 (Day 61)	Blood sample for humoral response	All infants	~150	2.5 mL
	Total volume of blood collected for each subject from Screening to Visit 5 (Day 61)*				**9.8 mL**
	Visit 7 (end of the first RSV transmission season)	Blood sample for humoral response	All infants	~150	2.5 mL
	Assessment of potential RSV-RTI	Blood sampling for assessment of mechanisms of illness (potential ERD)	Hospitalization for RSV-LRTI (only for RSV-positive subjects using a locally available RSV test)	Hospitalization for RSV-LRTI (only for RSV-positive subjects using a locally available RSV test)	2.5 mL
	Unscheduled visit for safety	Blood sample for hematology and biochemistry	Event-driven	Event-driven	2.3 mL
	Total volume of blood collected for each subject from Screening to Visit 8 (end of the second RSV transmission season)*				**12.3 mL**
Nasal swab	Assessment of potential RSV-RTI	Nasal swab**	Event-driven	Event-driven	-
	Surveillance for asymptomatic RSV-RTI	Nasal swab***	All infants	~150	-

† The priority ranking in blood sampling is hematology > biochemistry > humoral response.
Venipuncture will not be repeated for humoral response in case of insufficient volume, at any timepoint except if no blood sample for humoral immunogenicity was collected at the screening visit. In that case an additional blood sample will be taken at Visit 1 that must be taken before vaccination.

* Total quantity of blood for each subject excludes any optional or unscheduled hematology and biochemistry blood sampling or blood sample for assessment of mechanism of illness collected if a subject has been hospitalized for RSV-LRTI.

** If during passive or active surveillance contact, the investigator/study staff assesses that an infant presents a potential RSV-RTI (refer to Table 6 for definition), the potential RSV infection will be assessed by quantitative RT-PCR of nasal swab specimens taken at an assessment visit.

*** During RSV season, there will be monthly nasal swabs to detect asymptomatic RSV infections. These swabs will be tested by quantitative RT-PCR at sponsor laboratory.

These assays will be performed only on enrolled infants and samples from non-enrolled subjects will be discarded.

6.7.3. Laboratory assays

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

Determination of a negative RSV exposure status in infants at 6 to 7 months of age will be based on RSV A and/or B neutralizing antibody titers present in serum at screening (before vaccination with the RSV vaccine) based on in-stream baseline serological testing. At birth, newborns do show positive for neutralizing antibodies due to maternal transfer during gestation. The titer of these antibodies declines over time. At the age of 6 to 7 months a cut-off can be defined below which infants are considered to have a negative RSV exposure status. Infants that show neutralizing antibody titers above this cut-off are suspected to have experienced a recent RSV infection. This cut-off will thus allow the discrimination between a negative RSV exposure status versus RSV infected infants before start of vaccination.

The following laboratory assays are planned:

- Functional (neutralizing) antibody titers against RSV-A will be measured by a neutralization assay on serum samples (Table 10).
- RTI will be assessed by:
  - Quantitative RT-PCR that is able to discriminate RSV-A and RSV-B subtypes (Table 11).
  - Qualitative multiplex PCR for detection of a panel of viruses (Table 11).
  - Local RSV assay, and***/or*** local RVP where available (Table 11) **(Amended 1 August 2019)**.

Final confirmation of RSV presence will be obtained through the definitive results from the central test.

These assays will be performed at the investigator's laboratory, at GSK Biologicals' laboratory or at laboratory designated by GSK Biologicals (refer to Table 10 and Table 11).

Table 10 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off*	Laboratory**
SERUM	Respiratory Syncytial Virus A Ab	NEUTRALIZATION	In-house	ED60	18 ED60	GSK Biologicals[1]
SERUM	Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	ELISA	In-house	EU/ml	To be defined	NÉOMED-LABS[1]

Ab: antibody; **ELISA**: enzyme-linked immunosorbent assay; **IgG**: immunoglobulin G; **RSV**: respiratory syncytial virus

* Assay cut-off and unit might be subject to change (e.g., in case of requalification, revalidation or standardization). In this case, this will be documented in the clinical report.

**Refer to APPENDIX B for the laboratory addresses.

[1] GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium.

Table 11 Molecular Biology (PCR tests)

System	Component	Kit / Manufacturer	Method	Unit	Laboratory*
Nasal swab	RSV A RNA RSV B RNA	In-house	Quantitative RT-PCR	Copies/ml	GSK Biologicals[1]
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) [2]	*Allplex* Respiratory Panel (Seegene) or equivalent [2]	Multiplex PCR (Luminex)	Qualitative assay (positive/ negative)	GSK Biologicals[1]
Other specimen	RSV	Not applicable	Locally available RSV assay	Not applicable	Routine local laboratory
Other specimen	RVP	Not applicable	Locally available RVP assay	Not applicable	Routine local laboratory

PCR: polymerase chain reaction; **PIV**: parainfluenza virus; **RSV**: respiratory syncytial virus; **RT**: Reverse Transcription; **RVP**: respiratory viral panel.

*Refer to APPENDIX B for the laboratory addresses.

[1] GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium.

[2] The list of components might be subject to change in case equivalent kit is used for multiplex RVP testing.

Additional exploratory testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These assays may not be represented in the objectives/endpoints of the study protocol

Additional viral diagnosis testing on the nasal swabs, such as (but not limited to) multiplex PCR and/or high-throughput sequencing, may be done, if deemed necessary, provided specific assays become available at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals.

Additional testing may include, but is not limited to, the following:

- Anti-vector immunity: neutralization.
- RSV F protein antibody concentrations and *palivizumab*-competing antibody concentrations will be determined by in-house ELISA on serum sample.

For subjects hospitalized for LRTI and RSV-positive using a locally available RSV test, an additional blood sample will be collected (refer to Section 9.2.5). The corresponding serum sample will be stored at GSK Biologicals' laboratory to further characterize the mechanisms of illness (potential ERD), if deemed necessary. In this event, the serum samples could be tested by RSV neutralization assay and also by ELISA (or alternative method) for measurement of protein F antibodies and cytokines.

Hematology and biochemistry assessments will be performed in the investigator's laboratory as per local practice using standardized and validated procedures (Table 12).

Table 12 Hematology and biochemistry tests

System	Discipline	Component	Timepoint	Method	Scale	Laboratory
Whole blood	Hematology	Hemoglobin	Screening	As per local practice	Quantitative	Local laboratory
		Leukocytes (White Blood Cells)				
		Lymphocytes				
		Neutrophils				
		Platelets				
Serum	Biochemistry	Alanine Aminotransferase	Screening	As per local practice	Quantitative	
		Aspartate Aminotransferase				
		Creatinine				

At screening repeat testing may be performed once according to Figure 2. At any time during the trial additional hematology and/or biochemistry testing may be performed for the further investigation of a potential AE.

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.

6.7.4. Biological samples evaluation

6.7.4.1. Immunological read-outs

Table 13 Immunological read-outs

Blood sampling timepoint			No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint	System			
Screening (Day -30 to Day -1)	Pre-Vaccination	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2
Visit 3 (Day 31)	Post-Vaccination 1	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2
Visit 5 (Day 61)	Post-Vaccination 2	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2
Visit 7 (end of the first RSV transmission season)	Post-Vaccination 2	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2

Ab: Antibody; **IgG**: immunoglobulin G; **RSV**: respiratory syncytial virus.

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 13.

The RVP (Multiplex PCR) on specimens from all RSV-A/B positive and confirmed LRTI cases, according to case definition presented in Table 6 (Figure 3), will qualitatively assess the potential co-infections occurring in these subjects. The panel of viruses profiled is presented in Table 14.

Table 14 Molecular biology for nasal swab and specimen analysis

Sampling timepoint			No. subjects	Component	Components priority rank
Type of contact and timepoint	**Sampling timepoint**	**System**			
Surveillance for asymptomatic RSV-RTI	Monthly contact during the RSV season	Nasal swab	~ ***15***0	Quantitative RT-PCR (RSV A RNA and RSV B RNA)	Not applicable
Assessment of potential RSV-RTI	All subjects attending assessment visit	Nasal swab	Event-driven	Quantitative RT-PCR (RSV A RNA and RSV B RNA)	Not applicable
Assessment of potential RSV-RTI	All subjects attending assessment visit with positive Quantitative RSV A/B RT-PCR results	Nasal swab	Event-driven	Qualitative multiplex PCR (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)	Not applicable
Assessment of potential RSV-RTI	All subjects presenting confirmed LRTI* (with negative Quantitative RSV A and B RT-PCR results)	Nasal swab	Event-driven	Qualitative multiplex PCR (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)	Not applicable

Sampling timepoint			No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint	System			
				Human rhinovirus A/B/C (HRV) Human coronavirus 229E (229E) Human coronavirus NL63 (NL63) Human coronavirus OC43 (OC43)	
Assessment of potential RSV-RTI	All subjects attending assessment visit	Other specimen	Event-driven	Locally available RSV assay	Not applicable
Assessment of potential RSV-RTI	All subjects attending assessment visit	Other specimen	Event-driven	Locally available RVP assay	Not applicable

* Refer to Table 6 for the case definitions.

[2] The list of components might be subject to change in case equivalent kit is used for multiplex RVP testing.

PCR: polymerase chain reaction; **RSV**: respiratory syncytial virus; **RTI**: respiratory tract infection; **RVP**: respiratory viral panel.

6.7.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been established so far for the antigens used in the candidate ChAd155-RSV vaccine.

7. STUDY VACCINES AND ADMINISTRATION

7.1. Description of study vaccines

The investigational ChAd155-RSV vaccine has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine 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.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 15 Study vaccines

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
1D RSV ChAd	***1D* ChAd155-RSV**	**ChAd155-RSV=3*10^{10}vp/mL**	***Liquid in monodose vial*** †	**0.5 ml**	*1*
2D RSV ChAd	2D ChAd155-RSV	ChAd155-RSV=1*10^{11}vp/mL	Liquid in monodose vial †	0.5 ml	2
Formulation buffer (FB)	Formulation buffer S9b	Na_2HPO_4=1.3mg; KH_2PO_4=186µg; NaCl=3.85mg; KCl=100µg; $MgCl_2$=50µg	Clear liquid	0.5 ml	0***, 1*** or 2 ‡
Placebo	Formulation buffer S9b	Na_2HPO_4=1.3mg; KH_2PO_4=186µg; NaCl=3.85mg; KCl=100µg; $MgCl_2$=50µg	***Clear liquid***	***0.5 ml***	***2***
Bexsero	*Bexsero*	Recombinant Neisseria meningitidis group B NHBA fusion protein=50µg; Recombinant Neisseria meningitidis group B NadA protein=50µg; Recombinant Neisseria meningitidis group B fHbp fusion protein=50µg; Outer membrane vesicles (OMV) from Neisseria meningitidis group B strain NZ98/254=25µg; $Al(OH)_3$=500µg Al3+	White opalescent liquid suspension for injection in pre-filled syringe	0.5 ml	3
Nimenrix	*Nimenrix* § MenACWY-TT	PSA=5µg TT; PSC=5µg TT; PSW_{135}=5µg TT; PsY=5µg TT; TT~=44µg	White powder or cake in a single dose glass vial	0.5 ml	3
	Nimenrix § NaCl	NaCl=150mM	Sodium chloride as a clear liquid for suspension		
Menveo	*Menveo* ¥ MenA lyo	MenA=10µg,CRM197=16.7-33.3µg; KH_2PO_4=5mM; Sucrose=12.5mg	Lyophilized component in a vial	0.5 ml	2
	Menveo ¥ MenCWY liquid	MenC=5µg,CRM197=7.1-12.5µg; MenW=5µg,CRM197=3.3-8.3µg; MenY=5µg,CRM197=5.6-10µg; NaCl=4.5mg; Na3PO4=10mM; NaH2PO4=2.5mM; Na_2HPO_4=7.5mM; water=0.5ml	Liquid component in a vial		
Synflorix	***Synflorix 10Pn-PD-DiT***	***PS1=1µg PD; PS4=3µg PD; PS5=1µg PD; PS6B=1µg PD; PS7F=1µg PD; PS9V=1µg PD; PS14=1µg PD; PS18C=3µg TT; PS19F=3µg DT; PS23F=1µg PD; PD=9-16µg; DT=3-6µg; TT=5-10µg; $AlPO_4$=500µg Al3+***	***Turbid white suspension***	***0.5 ml***	***3***

† Clear, colorless solution free from visible particles.

‡ The number of Formulation buffer doses depends on the study arm and study country (see Table 2).

§ MenACWY-TT, a white powder or cake, is resuspended with a NaCl solution, to make Nimenrix.

¥ MenA lyo, a lyophilized component, is resuspended with MenCWY liquid, to make Menveo.

* Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the vaccination visits (see Figure 1, Table 2 and Table 16).

7.2. 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. 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.

For the Placebo [Saline] (Formulation buffer S9b) and for the active control comparator vaccines (*Bexsero*, *Nimenrix, Synflorix* and *Menveo*) any temperature excursion outside the range of 2.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) and for the ChAd155-RSV vaccine any temperature excursion above -60°C (for ≤ -60°C/≤ -76°F label storage condition) must be reported in the appropriate (electronic) temperature excursion decision form. The impacted investigational medicinal products (IMPs) must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

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.

Refer to the SPM for more details on aspects vaccine handling including disposal of waste and management of accidental spills.

7.3. Dosage and administration of study vaccines

The first IM dose of ChAd155-RSV vaccine must be administered before the first RSV season while the second dose (when applicable) will be given one month after the first dose. The volume to be administered for each IM vaccination will be 0.5 mL in the anterolateral thigh. The preferable side for administration is the left side. If for some reason the left side cannot be used, please ensure the subsequent doses are administered on the same side as the first dose. In the second year of life at Visit 7 if the muscle size is adequate, the site of administration can be the deltoid on the left side.

Table 16 Dosage and administration

Type of contact and timepoint	Study group	Treatment name[1]	Volume to be administered *(0.5 mL)*	Route[2] (*IM*)	Site	
					Location (*Anterolateral Thigh*) [3]	Laterality [4] (Left)
Visit 1 (Day 1)	***1D RSV + Bexsero***	***1D RSV ChAd***	0.5 mL	IM	Anterolateral Thigh	Left
	1D RSV + Nimenrix	***1D RSV ChAd***				
	1D RSV + Synflorix	***1D RSV ChAd***				
	1D RSV + Menveo	***1D RSV ChAd***				
	1D RSV + Placebo	***1D RSV ChAd***				
	2D RSV + *Bexsero*	***2D*** RSV ChAd				
	2D RSV + *Nimenrix*	***2D*** RSV ChAd				
	2D RSV + Synflorix	***2D*** RSV ChAd				
	2D RSV + Menveo	***2D RSV ChAd***				
	2D RSV + Placebo	***2D*** RSV ChAd				
	Bexsero	*Bexsero*				
	Nimenrix	*Nimenrix*				
	Synflorix	***FB***				
	Menveo	***FB***				
	Placebo	***FB***				
Visit 3 (Day 31)	***1D RSV + Bexsero***	***FB***				
	1D RSV + Nimenrix	***FB***				
	1D RSV + Synflorix	***FB***				
	1D RSV + Menveo	***FB***				
	1D RSV + Placebo	***FB***				
	2D RSV + *Bexsero*	***2D*** RSV ChAd				
	2D RSV + *Nimenrix*	***2D*** RSV ChAd				
	2D RSV + Synflorix	***2D*** RSV ChAd				
	2D RSV + Menveo	***2D*** RSV ChAd				
	2D RSV + Placebo	***2D*** RSV ChAd				
	Bexsero	***FB***				
	Nimenrix	***FB***				
	Synflorix	***Synflorix***				
	Menveo	***Menveo***				
	Placebo	***FB***				
Visit 5 (Day 61)	***1D RSV + Bexsero***	***Bexsero***				
	1D RSV + Nimenrix	***Nimenrix***				
	1D RSV + Synflorix	***Synflorix***				
	1D RSV + Menveo	***Menveo***				
	2D RSV + *Bexsero*	*Bexsero*				
	2D RSV + *Nimenrix*	*Nimenrix*				
	2D RSV + Synflorix	***Synflorix***				
	2D RSV + Menveo	*Menveo*				
	Bexsero	*Bexsero*				
	Nimenrix	*Nimenrix*				
	Synflorix	***Synflorix***				
	Menveo	***FB***				

Type of contact and timepoint	Study group	Treatment name[1]	Volume to be administered *(0.5 mL)*	Route[2] (*IM*)	Site	
					Location (*Anterolateral Thigh*) [3]	Laterality [4] (Left)
Visit 6 (Day 121) [5]	***1D RSV + Bexsero***	***Bexsero***	0.5 mL	IM	Anterolateral Thigh	Left
	1D RSV + Nimenrix	***Nimenrix***				
	1D RSV + Synflorix	***Synflorix***				
	2D RSV + Bexsero	*Bexsero*				
	2D RSV + Nimenrix	*Nimenrix*				
	2D RSV + Synflorix	***Synflorix***				
	Bexsero	**FB**				
	Nimenrix	**FB**				
	Synflorix	**FB**				
Visit 7 (end of the first RSV transmission season)	***1D RSV + Bexsero***	***Bexsero***				
	1D RSV + Nimenrix	***Nimenrix***				
	1D RSV + Synflorix	***Synflorix***				
	1D RSV + Menveo	***Menveo***				
	2D RSV + Bexsero	*Bexsero*				
	2D RSV + Nimenrix	*Nimenrix*				
	2D RSV + Synflorix	***Synflorix***				
	2D RSV + Menveo	*Menveo*				
	Bexsero	*Bexsero*				
	Nimenrix	*Nimenrix*				
	Synflorix	***Synflorix***				
	Menveo	*Menveo*				

1D: 1 Dose (1.5x10[10] vp/dose); 2D: 2 Dose (5x10[10] vp/dose); **RSV ChAd:** Chimpanzee Adenovirus Type 155 RSV vaccine; **NA**: not applicable**;** ***FB***: ***F***ormulation buffer S9b.

[1] The choice of active comparator vaccine or Placebo control is done at the country level (see Table 2).

[2] **IM:** Intramuscular.

[3] In the second year of lifeon Visit 7 if the muscle size is adequate, the site of administration can be the deltoid on the left side.

[4] The preferable side for administration is the left side. If for some reason the left side cannot be used, please ensure the subsequent doses are administered on the same side as the first dose.

[5] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Figure 1, Table 2 and Table 7).

7.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization 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 vial 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 randomization.

7.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of ChAd155-RSV. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 9.5).

- Anaphylaxis following the administration of vaccines.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.
- Any condition that in the judgment of the investigator would make IM injection unsafe.
- Current autoimmune disease.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory tests.
- Failure to thrive.

The following events constitute contraindications to administration of ChAd155-RSV at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 6.5), or the subject may be withdrawn at the discretion of the investigator (see Section 9.5).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the axilla for subjects ≥ 1 and < 5 years of age and the rectum for subjects < 12 months of age.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory tract infections) without fever can be administered all vaccines.
  - Receipt of a routine pediatric vaccine within the previous 7 days, with the exception of live viral vaccines, for which an interval of 14 days should be respected.

7.6. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator or delegate should question the subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject.

Scheduled routine pediatric vaccines may be administered ≥ 7 days before a dose of study vaccine or ≥ 7 days following a dose of study vaccine, with the exception of live viral vaccines which may be administered ≥ 14 days before a dose or ≥ 7 days after a dose. Vaccines needed for urgent individual medical need (e.g., rabies prophylaxis) may be administered at any time.

In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by the public health authorities, outside the routine immunization 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 Product Characteristics (SmPC) or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

7.6.1. 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 in the 30 day follow-up period after the administration of each dose of study vaccines (Day 1 to Day 30).
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccines and ending at the last study visit (Day -29 to end of the second RSV transmission season).
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination or blood sampling).
  - E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement). The preferred location for measuring temperature in this study will be the axilla for subjects ≥ 1 and < 5 years of age and the rectum for subjects < 12 months of age.
  - E.g. a topical local anesthetic used prior to a blood sampling is considered to be prophylactic.
- Any concomitant medications/products/vaccines listed in Section 7.6.2.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol or administered at any time 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 antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination need to be recorded on the specific page of the eCRF.

7.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 11.5 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) during the study period. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day (for pediatric subjects), or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g., infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose and ending 30 days after the last dose of vaccine*, with the exception of:
  - Scheduled routine pediatric vaccines which may be administered ≥ 7 days before a dose and ≥ 7 days after a dose of study vaccines, with the exception of live viral vaccines which may be administered ≥ 14 days before a dose or ≥ 7 days after a dose.
  - Vaccines needed for urgent individual medical need (e.g., rabies prophylaxis).

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization 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 Product Characteristics (SmPC) or 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 during the study period.

8. HEALTH ECONOMICS

Not applicable.

9. SAFETY

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

Each subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

9.1. Safety definitions

9.1.1. 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:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccines 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 study vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccines administration.
- 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 9.1.3. 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 first study vaccination. These events will be recorded in the medical history section of the eCRF.

9.1.2. 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 hospitalization or prolongation of existing hospitalization,

   Note: In general, hospitalization 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 hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity,

   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, diarrhea, 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.

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 hospitalization 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 hospitalization.

9.1.3. Solicited adverse events

9.1.3.1. Solicited local (injection-site) adverse events

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

Table 17 Solicited local adverse events

All age groups
Pain at injection site
Redness at injection site
Swelling at injection site

9.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 18 Solicited general adverse events

Infant
Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

Note: parent(s)/LAR(s) will be instructed to measure and record the rectal body temperature in the evening. Should additional temperature measurements be performed at other times of day, parent(s)/LAR(s) will be instructed to record the highest temperature in the diary card.

9.1.4. 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, hematology, urinalysis) or other abnormal assessments (e.g., physical examination) 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 9.1.1 and 9.1.2). 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.

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.

9.1.5. Adverse events of special interest

9.1.5.1. Spontaneous or excessive bleeding

Subjects' parent(s)/ legally acceptable representative(s) (LAR[s]) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination (Visit 1 and Visit 3), in order to detect any thrombocytopenic petechiae or purpura. The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets.

Any episode of spontaneous or excessive bleeding occurring within 30 days after each vaccination should be fully investigated with a full range of hematological tests to identify the underlying cause and reported as an AE of special interest.

9.1.5.2. RSV-LRTI

LRTI associated with RSV infection will be reported as an adverse event of special interest in an expedited manner. These will be detected through the surveillance for RSV-RTI (refer to Section 9.2).

To identify RSV-LRTI for the purpose of AE of special interest, the diagnosis should be based on the investigators' clinical judgment taking into account the clinical history, the examination, relevant medical investigations and within 24 hours of results of a locally-available diagnostic test for RSV. Of note the case definition presented in Table 6 is based on a limited set of symptoms and signs and is designed for protocol specified analyses pooled across sites at study conclusion and should not be used for the purpose of reporting RSV-LRTI as an AE of special interest during the trial conduct.

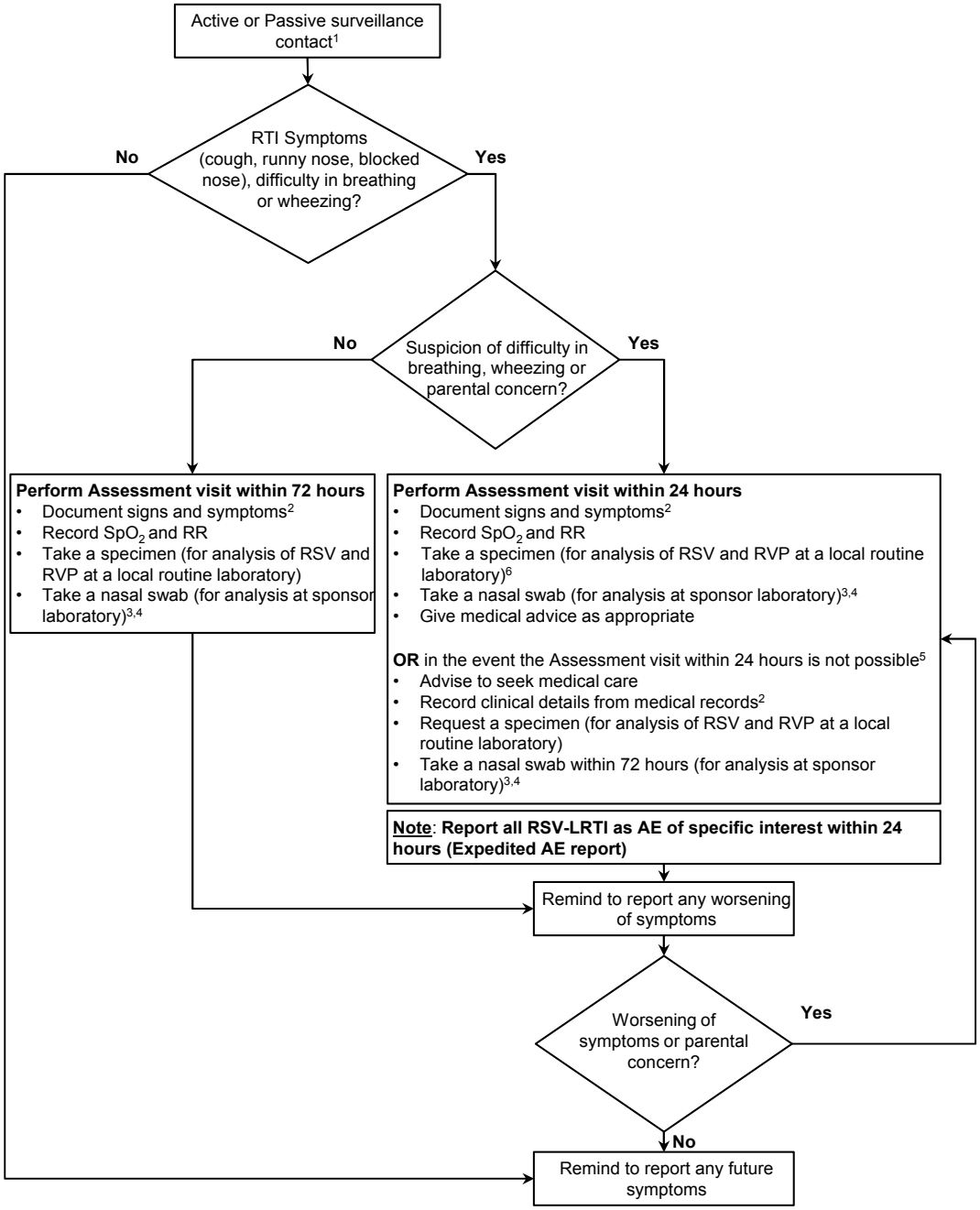
In addition to report these cases as AE of special interest, the investigator should investigate the case according to the procedures for the surveillance of RSV-RTI (refer to Section 9.2) and document it in the eCRF. Of note a nasal swab should be taken for confirmatory and quantitative testing of RSV infection by the sponsor.

9.2. Surveillance for RSV-RTI, difficulty in breathing and wheezing episodes

Each subject will be under surveillance for RSV-RTI, difficulty in breathing, and wheezing episodes from the administration of Dose 1 (Visit 1) and will continue until the final visit (Visit 8). Surveillance will be performed via phone or e-mail contacts and assessment visits (refer to Figure 3). The passive and active surveillance contacts can also be made by/with the person designated by the parent(s)/LAR(s) (e.g., grandparents, nanny) as long as the parent(s)/LAR(s) have given approval.

The safety of the infant is paramount and for any reported illness, the investigator/study staff should assess the need for any intervention and provide this as part of regular healthcare or instruct/advise the parent(s)/LAR(s) where to obtain this care.

Figure 3 Decision tree for passive and active surveillance contacts



[1] Active contacts will take place weekly during each RSV season and every month outside the RSV season. Passive phone contacts from the parents/LARs to the investigator will take place when symptoms occur.

[2] Refer to the SPM for signs and symptoms to be collected.

[3] RSV-A/B quantitative PCR on all specimens.

[4] RVP (Multiplex PCR) on all specimens RSV-A/B positive and on all cases of confirmed LRTI according to case definition presented in Table 6.

[5] For example, in the event that the subject requires urgent medical evaluation and care or has travelled to another location.

[6] In case of worsening of symptoms, optional sample if the previous specimen was RSV-positive, and mandatory if the previous sample was RSV-negative.

Refer to APPENDIX D for the symptoms and grading for assessment visits and worsening visits.

9.2.1. Passive surveillance

All subjects' parent(s)/LAR(s) will be instructed to contact investigator/study staff in case of any new or worsened RTI symptoms (cough, runny nose or blocked nose) or in case of any new difficulty in breathing or wheezing. They will be also reminded to record the start date and the end date of the RTI symptoms on the RTI episode card.

- **If there is** any new difficulty in breathing, wheezing or parental concern, the investigator/study staff will schedule an assessment visit as soon as possible (refer to Section 9.2.4), but no later than 24 hours after the phone contact to ensure prompt assessment of the need for medical care.
- **If there is no suspicion** of difficulty in breathing, nor wheezing, nor parental concern, but there are any new symptoms of an RTI (cough, runny nose or blocked nose), the investigator/study staff will schedule an assessment visit as soon as possible (refer to Section 9.2.4), but no later than 72 hours after the phone contact. Performing the visit as soon as possible is important to assess the need for medical care, to ensure that early symptoms are captured, and also to collect an optimal nasal swab for the detection of RSV.
- All passive surveillance contacts will be documented in the eCRF.
- In the event that it is not possible to schedule an assessment visit, which may arise if the family has travelled, then the assessment visit page of the eCRF should be filled in as completely as possible using available medical records.

9.2.2. Surveillance for asymptomatic RSV-RTI

- In order to detect asymptomatic RSV-RTI, monthly nasal swabs for analysis at sponsor laboratory will be performed for all subjects during the RSV season who are 'RTI symptom free' within an approximate 30 day period. Upon investigators discretion, the asymptomatic visit may be omitted if a nasal swab has been taken for a potential disease episode in the previous 4 weeks (please refer to the SPM for an example of when to schedule the visit). The asymptomatic nasal swab will be tested by quantitative PCR.
- These nasal swabs may be performed in the subject's home or the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.
- All surveillance visits for asymptomatic RSV-RTI will be documented in the eCRF.

9.2.3. Active surveillance

There will be contact between the investigator/study staff and subject's parent(s)/LAR(s) on a regular basis (weekly during the RSV season and every month outside the RSV season). If there has not been a contact through a clinic visit (i.e., Visits 1, 2, 3, 4, 5, 6*, 7, 8), a passive surveillance contact (refer to Section 9.2.1), an assessment visit (refer to Section 9.2.4) or a surveillance for asymptomatic RSV infection (refer to Section 9.2.2), then the investigator/study staff will contact the subject's parent(s)/LAR(s). The active surveillance will be performed by phone, mobile phone or e-mail.

* In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

During each active follow-up contact, the investigator/study staff will:

- Confirm with the subjects' parent(s)/LAR(s), if the subject has developed new RTI symptoms (cough, runny nose or blocked nose) and if he/she has developed any symptoms of difficulty in breathing or wheezing (during and between contacts).
  - **If there is** any new or on-going difficulty in breathing, wheezing or parental concern, the investigator/study staff will schedule an assessment visit as soon as possible (refer to Section 9.2.4), but no later than 24 hours after the contact to ensure prompt assessment of the need for medical care.
  - **If there is no suspicion** of difficulty in breathing, nor wheezing, nor parental concern, but any new symptoms of an RTI (cough, runny nose or blocked nose) are present, the investigator/study staff will schedule an assessment visit as soon as possible (refer to Section 9.2.4), but no later than 72 hours after the contact.
- Performing the visit as soon as possible is important to assess the need for medical care, to ensure that early symptoms are captured, and also to collect a nasal swab for the detection of RSV.
- The investigator/study staff will remind subjects' parent(s)/LAR(s) to record the start date and the end date of the RTI symptoms on the RTI episode card.
- All active surveillance contacts will be documented in the eCRF.
- In the event that it is not possible to schedule an assessment visit, which may arise if the family has travelled, then the assessment visit page of the eCRF should be filled in as completely as possible using available medical records.

9.2.4. Assessment visit

The purpose of the assessment visit is to objectively document signs and symptoms by an appropriately qualified person (i.e., medical or nursing), provide medical advice and to take a nasal swab for detection of RSV infection.

- Assessment visits may take place in the subject's home, the investigators clinical facility or a medical facility as appropriate to the circumstances in the judgment of the investigator.
- If the reported symptoms are already of a level of severity that urgent care is indicated, the parent(s)/LAR(s) should be redirected to the proper location to receive this care (e.g., Emergency Room) and an assessment visit could be scheduled to take place there at a suitable time.
- During the assessment visit, the investigator/study staff will evaluate the clinical signs and symptoms of the RTI. Signs and symptoms to be recorded in the eCRF are listed in the SPM.
- Oxygen saturation will be measured by pulse oximetry in room air using standardized equipment in preference.
- Specimen for testing of RSV and RVP at a local routine laboratory will be collected for all the subjects who have symptoms of an RTI.
- Nasal swabs for analysis at sponsor laboratory will be collected for all the subjects who have symptoms of an RTI. Note: all subjects experiencing an RSV-LRTI must be reported as an SAE in an expedited manner (refer to Section 9.4).
- Parent(s)/LAR(s) will be instructed to contact the study staff if the severity of the already existing symptoms increases or if the subject develops difficulty in breathing or wheezing and this may lead to a repeat assessment visit upon the judgment of the investigator.
- During subsequent surveillance contacts after an assessment visit, the status and evolution of the case will be followed until case resolution.
- Each assessment visit will be encoded in the eCRF.

9.2.5. Subject hospitalized for LRTI

Subjects admitted to hospital and treated for an LRTI will be documented fully as SAEs. In addition, to establish the severity of the illness, the eCRF screen corresponding to the assessment visit will be completed as fully as possible from medical records. Signs and symptoms to be recorded in the eCRF are listed in the SPM, and include where available oxygen saturation in air. Study staff will collect a nasal swab for all the subjects who have been hospitalized with a RTI for analysis at sponsor laboratory. All subjects with clinical suspicion of LRTI must be tested for RSV and RVP using locally available test.

Study staff will also collect a blood sample to be stored at sponsor's laboratory for future assessment of mechanism of illness (potential ERD). This will be required to be done only for RSV-positive subjects using a locally available RSV test.

9.3. Detecting and recording adverse events, adverse events of special interest and serious adverse events

9.3.1. Time period for detecting and recording adverse events, adverse events of special interest and serious adverse events

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

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at study conclusion. See Section 9.4 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 first receipt of study vaccine.

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

The time period for collecting AEs of special interest (RSV-LRTI) will begin at the first receipt of study vaccine and will end at study conclusion. The time period for collecting AEs of special interest (spontaneous or excessive bleeding) will begin at the first receipt of study vaccine and will end 30 days after the last vaccination on Day 61. See Section 9.4 for instructions on reporting of AEs of special interest.

An overview of the protocol-required reporting periods for AEs, AEs of special interest and SAEs is given in Table 19.

Table 19 Reporting periods for collecting safety information (Amended 1 August 2019)

Visit	SCR	V1		V2		V3		V4		V5	V6	V7	V8
Days	-30 to -1	1	7	8	30	31	37	38	60	61	121	end of the 1st RSV season	end of the 2nd RSV season
Solicited local and general AEs													
Unsolicited AEs													
AEs/SAEs leading to withdrawal from the study													
AE of special interest (RSV-LRTI)													
AE of special interest (spontaneous or excessive bleeding)*													
SAEs**													
SAEs related to study participation (start at signature of informed consent form) or concurrent GSK medication/ vaccine													

AE: Adverse Event; **RSV-LRTI:** Respiratory Syncytial Virus-Lower Respiratory Tract Infection; **SAE**: Serious Adverse Event; **SCR**: Screening**; V**: Visit.

* Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination, in order to detect any thrombocytopenic petechiae or purpura.

** Each subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

9.3.2. 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 19.

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 study vaccine the investigator will promptly notify the Study Contact for Reporting SAEs.

9.3.3. Evaluation of adverse events and serious adverse events

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

As a consistent method of collecting AEs, the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last 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. ***For countries where it is not acceptable to provide copies of medical records to the sponsor, the required information will be transcribed by the investigator and provided to GSK respecting the subject's anonymization*** **(Amended 1 August 2019)**.

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.

9.3.3.2. Assessment of adverse events

9.3.3.2.1. Assessment of intensity

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

Table 20 Intensity scales for solicited symptoms in infants

Infant		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
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/°F
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

* Fever is defined as temperature ≥ 38.0°C / 100.4° F by any route. The preferred location for measuring temperature in this study will be the axilla for subjects ≥ 1 and < 5 years of age and the rectum for subjects < 12 months of age.

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

0 : None
1 : < 5 mm
2 : 5 to 20 mm
3 : > 20 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

0 : < 38.0°C/100.4°F
1 : ≥ 38.0°C/100.4°F to ≤ 39.0°C/102.2°F
2 : > 39.0°C/102.2°F to ≤ 40.0°C/104.0°F
3 : > 40.0°C/104.0°F

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 school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice.

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 9.1.2.

9.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccines and the occurrence of each AE/SAE using clinical judgement.

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 study vaccines will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK 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.

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 study vaccine?

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

If an event meets the criteria to be determined as 'serious' (see Section 9.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

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

9.3.3.3. 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).

9.3.3.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalization, 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.

9.4. Reporting of serious adverse events and adverse events of special interest

9.4.1. Prompt reporting of serious adverse events and adverse events of special interest to GSK Biologicals

SAEs that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 21, once the investigator determines that the event meets the protocol definition of a SAE.

AEs of special interest (RSV-LRTI and spontaneous or excessive bleeding) that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 21.

Table 21 Timeframes for submitting serious adverse event and adverse events of special interest reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* †	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
AEs of special interest (RSV-LRTI)	24 hours*†	electronic Expedited Adverse Events Report	24 hours*‡	electronic Expedited Adverse Events Report
AE of special interest (spontaneous or excessive bleeding)	24 hours*†	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.

† The investigator will be required to confirm review of the SAE/ AE of special interest causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/ AE of special interest.

‡ In the timeframe of awareness for the local RSV test result.

9.4.2. Contact information for reporting serious adverse events and adverse events of special interest

Study Contact for Reporting SAEs and AEs of special interest
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs and AEs of special interest
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Worldwide except US & Canada sites: Fax: PPD or PPD Email address: PPD US sites only: Fax: PPD Canadian sites only: Fax: PPD

9.4.3. 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.

9.4.3.1. 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.

9.4.4. Reporting of adverse events of special interest to GSK Biologicals

9.4.4.1. RSV-LRTI

Note that ALL LRTI meeting the criteria of an SAE should be reported as SAEs with the timing of SAE reports.

In addition, once an investigator becomes aware that an episode of LRTI not meeting the criteria of an SAE, but which has been confirmed on local testing to be due to RSV 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. Later 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 causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AE of special interest.

Refer to Section 9.4.3.1 for back-up system in case the electronic reporting system does not work.

9.4.4.2. Spontaneous or excessive bleeding

Once an investigator becomes aware that an episode of spontaneous or excessive bleeding 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 the event of spontaneous or excessive bleeding 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 causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AE of special interest.

Refer to Section 9.4.3.1 for back-up system in case the electronic reporting system does not work.

9.4.5. Updating of serious adverse event and adverse event of special interest information after removal of write access to the subject's eCRF

When additional SAE or AE of special interest 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 21.

9.4.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 9.4.1. 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 both attributable to the study vaccines and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

9.5. Follow-up of adverse events, serious adverse events and adverse events of special interest

9.5.1. Follow-up during the study

After the initial AE, AE of special interest or 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 AEs of special interest and SAEs; refer to Table 21).

All AEs of special interest (RSV-LRTI) and 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 last visit of the subject.

All AE of special interest (spontaneous or excessive bleeding) 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.

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.

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

The investigator will follow subjects:

- with SAEs, with AEs of special interest 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.

9.6. 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 a SAE and AE of special interest should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.6).

9.7. 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 study 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 9.4.1).

9.8. 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: Worldwide except US/Canada: PPD (GSK Biologicals Central Safety Physician on-call) For US/Canada only: PPD (GSK Biologicals Central Safety Physician on-call)
GSK Biologicals' Central Safety Physician Back-up: Worldwide except US/Canada: PPD US/Canada only: PPD
Emergency Unblinding Documentation Form transmission: Worldwide except US & Canada: Fax: PPD or PPD US/Canada only: Fax: PPD

9.9. Subject card

Study subjects' parent(s)/LAR(s) 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's parent(s)/LAR(s). 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' parent(s)/LAR(s) must be instructed to keep subject cards in their possession at all times during the study duration.

9.10. Holding rules and safety monitoring

The investigational ChAd155-RSV vaccine has never been administered to RSV-potentially naïve infants. Safety precautions such as limited vaccination, safety evaluations by an iSRC and an IDMC, and study holding rules have therefore been defined.

9.10.1. Limited vaccination

In the same investigational center, all the infants should be vaccinated sequentially and at least 60 minutes apart to allow monitoring of any acute events (e.g., hypersensitivity reaction). All infants should be closely observed (visual follow-up as well as measurement of vital signs) for at least 60 minutes after vaccination. Vital signs are body temperature, HR and RR. Vital signs are preferably measured when the infant is calm.

9.10.2. Internal safety review committee (iSRC) oversight

This study will be overseen by an iSRC operating under a charter. An iSRC was already involved in study RSV PED-002 (204838). Core members of the iSRC will include a GSK Biologicals' safety physician, a CRDL, and a biostatistician who are not otherwise involved in the conduct of the project. The iSRC safety reviews will be conducted using unblinded data. The iSRC has access to the subject randomization and reviews unblinded data.

The iSRC will review all accumulating safety and reactogenicity data four weeks after the start of vaccination and then every 4 weeks until all dosing with ChAd155-RSV vaccine is complete on the study. The iSRC members will determine if a safety signal should be escalated to the VSMB. The iSRC members will determine whether any of the predefined holding rules are met (refer to Section 9.10.4) or if there is any other safety signal. In this case, vaccination in the study will be immediately put on hold (refer to Section 9.10.5).

The iSRC will receive the following safety data within 48 hours upon GSK becoming aware of:

- Fatal SAEs.
- Life-threatening SAEs.
- Related SAEs.
- SAEs occurring within 30 days of vaccination.
- LRTI associated with RSV infection (AE of special interest) occurring from Day 1 to the end of the second RSV transmission season.
- Spontaneous or excessive bleeding (AE of special interest) occurring within 30 days after each vaccination.

In addition, the iSRC will receive:

- Unblinded summary reports of accumulated solicited AEs and unsolicited AEs.
- New information that may adversely affect the safety of the subjects or the conduct of the study.
- All subsequent protocol amendments or administrative changes (for information).

9.10.3. Independent Data Monitoring Committee (IDMC) oversight

This study will be overseen by an IDMC operating under a charter. The IDMC involved in the present study was already involved in study RSV PED-002 (204838). Overall, the role of the IDMC includes the review and protection of data integrity and rights and safety of study participants throughout the study period. It will provide initial, regular, and closing advice to GSK Biologicals on medical, ethical, scientific and safety-related issues. Its advice will be based on the interpretation of study data with reference to the study protocol.

The IDMC will review the protocol and statistical analysis plan. Meetings will be documented and minutes of open sessions of the IDMC meetings made available to the sponsor. The IDMC may, if deemed necessary, convene a meeting with, or request further information from the principal investigators and GSK Biologicals' designated project representatives at any stage of the study.

The IDMC may recommend to the sponsor to suspend the enrolment to the study and/or vaccination based on their review of safety data arising in this study (refer to Section 9.10.4).

The IDMC safety reviews will be conducted using unblinded data. The IDMC will review all available safety data while taking into account any other findings that could have an impact on the safety of the subjects.

The IDMC members will determine whether any of the predefined study holding rules are met (refer to Section 9.10.4) or if there is any other safety signal. If this is the case, vaccination in the study will be immediately put on hold. If no safety signal is observed,

the favorable outcome of the safety evaluation authorizing the investigator to proceed with vaccination of infants as outlined in Figure 1 will be also documented and provided in writing.

- The IDMC will receive the following safety data within 48 hours upon GSK becoming aware of:
  - Fatal SAEs occurring from Day 1 to the end of the second RSV transmission season.
  - Life-threatening SAEs occurring from Day 1 to the end of the second RSV transmission season.
  - Related SAEs occurring from Day 1 to the end of the second RSV transmission season.
  - SAEs occurring within 30 days of vaccination.
  - LRTI associated with RSV infection (AE of special interest) occurring from Day 1 to the end of the second RSV transmission season.
  - Spontaneous or excessive bleeding (AE of special interest) occurring within 30 days after each vaccination.
- The IDMC will receive the following safety data monthly:
  - Summary reports of solicited and unsolicited AEs. (during the period of vaccination).
  - Cumulative reports of the incidence of RSV RTI, RSV-LRTI, severe RSV-LRTI, very severe RSV-LRTI and RSV-RTI leading to hospitalization based on Table 6 by using local test results until the quantitative PCR results are available.
  - Cumulative tables of incidence of all SAEs.

Additionally, an analysis on occurrence of the progression from infection to very severe RSV-LRTI from first vaccination (Day 1) up to the end of the first RSV transmission season will be conducted on all subjects who have completed Visit 7 (end of the first RSV transmission season) by independent Data Analysis Center if there are minimum of 5 infections among subjects with a negative RSV exposure status (at screening which will be assessed by in-stream serological testing of baseline samples) in each randomized group.

In addition, the IDMC will receive from GSK Biologicals:

- New information that may adversely affect the safety of the subjects or the conduct of the study.
- All subsequent protocol amendments, informed consent changes or revisions or other documents originally submitted for review.
- All subsequent protocol administrative changes (for information).

9.10.4. Holding rules

The safety holding rules which will be assessed by the investigator are defined in Table 22 and the safety holding rules which will be assessed by the iSRC or IDMC during the safety evaluation are defined in Table 23.

Table 22 Holding rules assessed by the investigator

Holding Rule	Event	Number of infants/group
1a	Death or any life-threatening serious adverse event (SAE) that can be causally related to vaccination, according to investigator's assessment.	≥ 1
1b	Any withdrawal from the study (by investigator or parent(s)/LAR(s) of the subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination.	≥ 1
1c	Any local or general solicited AE leading to hospitalization that cannot reasonably be attributed to a cause other than vaccination.	≥ 1
1d	Within 30 days post-vaccination (Visit 1 and Visit 3), Any spontaneous local or general bleeding AND Thrombocytopenia < 50000/mm^3	≥ 1

If an investigator detects one of the holding rules mentioned above, he/she will immediately put the enrolment or the vaccination on hold (refer to Section 9.10.4) and he/she will immediately inform the sponsor and enter the data in the eCRF. It is sponsor's responsibility to put the enrolment or the vaccination on hold at all sites.

Table 23 Holding rules during the planned iSRC or IDMC evaluation

Holding Rule	Event	Number of infants
2a	Any Grade 3 solicited local AE lasting 48 hours or more following administration of an investigational RSV vaccine, within the 7-day (Days 1-7) post-vaccination period.	≥ 25% & ≥ 2 infants in any of two pooled RSV vaccine groups
2b	Any Grade 3 solicited general AE lasting 48 hours or more following administration of an investigational RSV vaccine, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Days 1-7) post-vaccination period.	≥ 25% & ≥ 2 infants in any of two pooled RSV vaccine groups
2c	Any ≥ Grade 3 unsolicited AE following administration of an investigational RSV vaccine, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Days 1-7) post-vaccination period	≥ 25% & ≥ 2 infants in any of two pooled RSV vaccine groups
2d	Infants hospitalized for RSV-LRTI	≥ 6 (in the combination of two pooled RSV vaccine and the pooled comparator/Placebo groups)

Of note, no formal holding rules will be applied for other safety data collected. However, these data will also be reviewed by the iSRC and the IDMC in order to allow for an overall assessment of the benefit/risk ratio of vaccination.

Risk assessment

Figure 4 gives the probability of not meeting holding rule assessed by the investigator and the sponsor when 30 or 50 subjects are enrolled per study group.

Figure 4 **Evaluations based on 30 or 50 enrolled subjects - Risk assessment curve for one formulation based on the proposed safety holding rules assessed by the investigator and the sponsor**

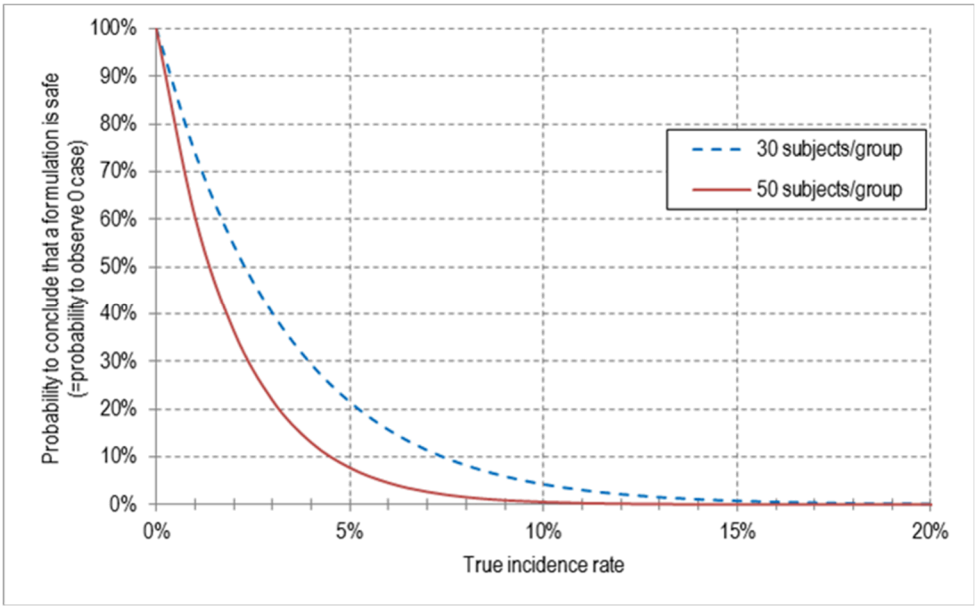
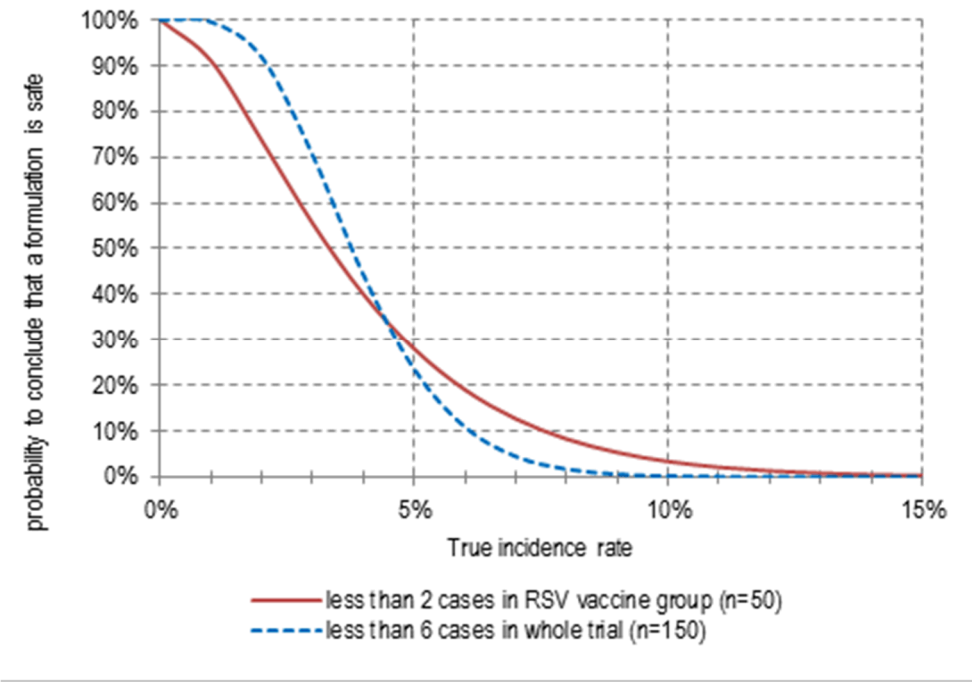


Figure 5 gives the probability of not meeting holding rule assessed during the planned IDMC evaluation when 50 subjects are enrolled per study group and 150 subjects in the whole trial.

Figure 5 **Evaluations based on 50 subjects per group - Risk assessment curve for one formulation based on the proposed safety holding rules during the planned IDMC evaluation**



9.10.5. Procedure if the trial is put on hold

If the trial is put on hold by the investigator ***or*** iSRC or IDMC because a pre-defined holding rule is met or because of a safety concern, then all enrolment in the study and all vaccination will cease immediately, but all other procedures relating to safety, immunology and disease monitoring will continue. The iSRC/IDMC will review all available safety information and may ask for additional information to be provided by the investigators or the study team. The iSRC/IDMC will make a recommendation to the study team whether the study should be stopped permanently, modified or continued unchanged.

The VSMB will review all data and iSRC/IDMC recommendation and will decide whether to stop permanently, modify or continue the conduct of the study. The decision of the VSMB regarding the further conduct of the study will be documented and provided in writing to the investigators.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

10.2. Subject withdrawal

Withdrawals will not be replaced.

10.2.1. Subject withdrawal from the study

From an analysis perspective, a ‘withdrawal’ from the study refers to any subject who did not come back for the concluding visit 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 an attempt (e.g., three telephone calls and a certified letter to the last known address) to contact those subjects who do not return for scheduled visits or follow-up.

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's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited 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 he/she/the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's parent(s)/LAR(s), 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 9.5.1.1).

10.2.2. Subject withdrawal from study vaccine

A 'withdrawal' from the study vaccine refers to any subject who does not receive the complete treatment, i.e., when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol. The investigator should make all efforts to ensure that the subjects remain in the study to ensure a proper safety follow-up and medical care if needed.

Information relative to premature discontinuation of the study vaccine will be documented on the Vaccine Administration page/screen of the /eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parent(s)/LAR(s) or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

10.3. Extension study

During the study conclusion visit, the investigator will ask each subject's parent(s)/LAR(s) if they are interested to allow the subject to participate in a booster study/long-term study. If subject's parent(s)/LAR(s) is/are not interested in participating in the booster study/long-term study the reason for refusal will be documented in the subject's eCRF.

10.4. Screen and baseline failures

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

The following information will be collected for screening failures:

- Informed consent.
- Inclusion/exclusion criteria.
- Demographic data.
- Medical history.
- Physical examination.
- Growth monitoring.
- Blood samples for hematology and biochemistry and humoral response.
- SAEs related to study participation, to concomitant use of GSK products or any fatal SAEs.
- Screening conclusion.

11. STATISTICAL METHODS

11.1. Primary endpoints

- Occurrence of adverse events (AEs) from first vaccination (Day 1) up to Day 61.
  - Occurrence of each solicited local and general AE, during a 7-day follow-up period after each vaccination (i.e., the day of vaccination and 6 subsequent days).
  - Occurrence of any unsolicited AE, during a 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days).
  - Occurrence of any serious adverse event (SAE) from Day 1 up to Day 61.
  - Occurrence of episode of spontaneous or excessive bleeding (AE of special interest), during a 30-day follow-up period after each vaccination.

11.2. Secondary endpoints

- Occurrence of RSV-RTI, RSV-LRTI, severe RSV-LRTI and very severe RSV-LRTI (according to standardized case definitions) as from first vaccination (Day 1) up to the end of the first RSV transmission season.
- Occurrence of RSV-RTI, RSV-LRTI, severe RSV-LRTI and very severe RSV-LRTI (according to standardized case definitions) as from first vaccination (Day 1) up to the end of the second RSV transmission season.
- Occurrence of SAEs from first vaccination (Day 1) up to the end of the second RSV transmission season.
- Occurrence of RSV-LRTI (AE of special interest) as from first vaccination (Day 1) up to the end of the first RSV transmission season, and up to the end of the second RSV transmission season.
- Occurrence of very severe RSV-LRTI (according to standardized case definitions) among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season.
- Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61 and at the end of the first RSV transmission season):
  - Neutralizing antibody titers against RSV-A.
  - RSV F antibody concentrations.

11.3. Tertiary endpoints

- Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61).
  - *Palivizumab*-competing antibody concentrations**.**
- Any further exploratory immunology to detect disease-related or vaccine-related immune responses, such as but not limited to:
  - Anti-vector immunity: neutralization.

11.4. Determination of sample size

The sample size determination is based on the minimum number of subjects needed to allow detection of a serious ERD signal having a magnitude similar to that of the historic FI-RSV vaccine trials [Kim, 1969]. A total of 150 infants will be enrolled and randomized with 1:1:1 ratio to receive either 1 dose of the $1.5x10^{10}$ vp/dose ChAd-155 RSV vaccine [the 1D RSV + comparator group], 2 doses of the $5x10^{10}$ vp/dose ChAd-155 RSV vaccine [the 2D RSV + comparator group], or no ChAd-155 RSV vaccine [the comparator/Placebo control alone group].

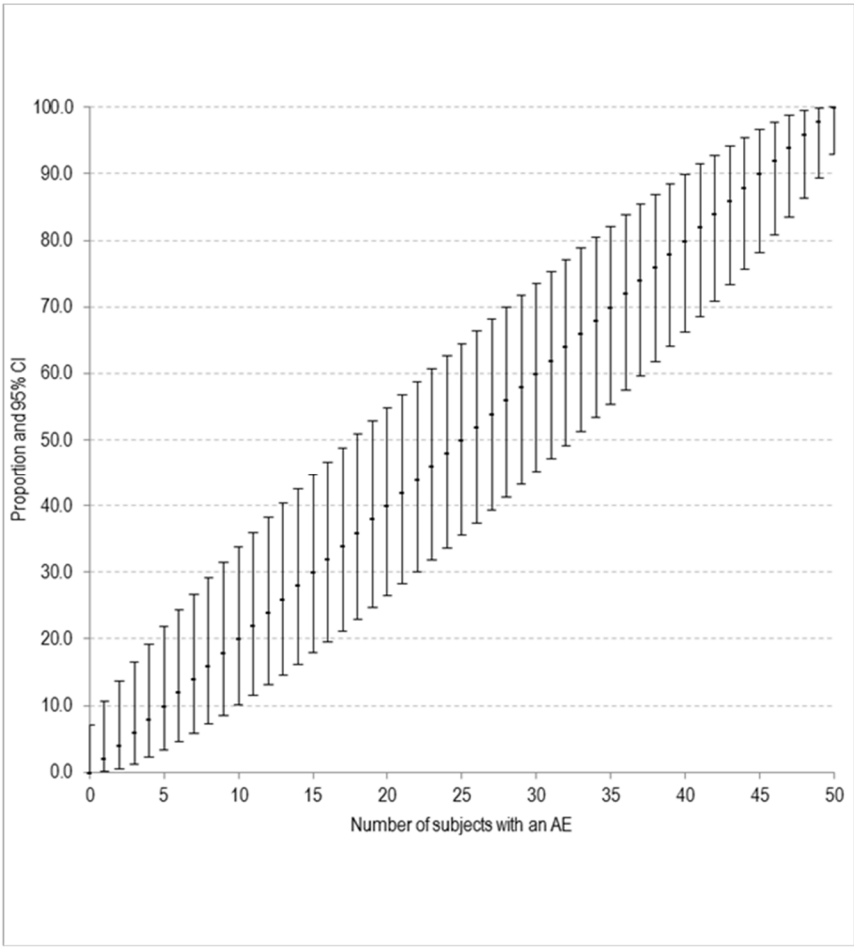
An effect of vaccination on ERD will be monitored very closely. It is anticipated that at least 50% of subjects [Dunn, 2013] will have a negative RSV exposure status (at screening which will be assessed by in-stream serological testing of baseline samples). While the rate of RSV infection could be highly variable by season, a conservative rate of infection of 20% in the first season is assumed [Kutsaya, 2016]. Therefore, with 50 infants in each RSV vaccine group, it is anticipated to observe at least 5 infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in each RSV vaccine group [50×0.5×0.2=5].

With a one-sided type I error of 0.05, and the assumption of a 10% rate of infection progressing to very severe RSV-LRTI (which is a conservative assumption based on the rate in the natural history of disease), 5 infections can provide at least 90% statistical power to demonstrate the progression rate from infection to very severe RSV-LRTI is less than 80%. That is less extreme than that observed in the historic FI-RSV vaccine trial where 80% of RSV RTI cases progressed to hospitalization [Kim, 1969]. During the course of the study, since the actual negative RSV exposure status (at screening based on in-stream baseline serological testing) and infection rates may be lower than 50% and 20%, respectively, the sample size ***may*** be adjusted as needed through additional recruitment in order to achieve ***a sufficient number of*** RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in each RSV vaccine group **(Amended 1 August 2019)**.

If a maximum of 1 out of 5 infections in infants receiving ChAd-155 RSV vaccine progress to very severe RSV-LRTI, then it can be concluded with 95% confidence that the expected progression rate of infection is less than the effect reported in previous FI-RSV trials; if a minimum of 3 out of 5 infections progress to very severe RSV-LRTI then it can be concluded with 95% confidence that the expected progression rate of infection is more than the 10% observed in natural history of infection. The above power analysis is based on the procedure of inequality of one proportion in PASS 12.

With 50 subjects in each RSV vaccine group, the probability of observing at least one SAE would be about 92% if the true incidence rate of SAE is 5%. For estimating the proportion of subjects with AEs, the maximum width of exact 95% confidence interval (CI) would be under 30%, and it could be as large as 35% if attrition rate is 30%. Figure 6 illustrates the precision on the estimate for the proportion of subjects with AEs following vaccination with each RSV formulation based on the number of subjects with AEs observed from 50 subjects.

Figure 6 Exact 95% confidence interval on the proportion of subjects with adverse events following vaccination based on 50 enrolled subjects



11.5. Cohorts for Analyses

11.5.1. Exposed Set

The Exposed Set (ES) will include all subjects with at least one study vaccine administration documented.

A safety analysis based on the ES will include all vaccinated subjects.

An immunogenicity analysis will be conducted on the ES and will include all vaccinated subjects for whom immunogenicity data are available.

The ***ES*** analysis will be performed per treatment actually administered at Dose 1.

11.5.2. *Exposed Set of subjects with a negative RSV exposure status*

The Exposed Set of subjects with a negative RSV exposure status will include all vaccinated subjects assessed as RSV unexposed at screening based on in-stream baseline serological testing.

The safety analysis of incidence of RSV-LRTI will be conducted on the cohort of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) as well as on the entire ES.

11.5.3. Per-protocol Set for analysis of immunogenicity

The per-protocol set (PPS) cohort for analysis of immunogenicity will be defined by timepoint and will consist of all subjects from the ES who complied with eligibility criteria, study procedures up to the end of the study and had immunogenicity results in the epoch as described below.

More specifically, the PPS cohort for analysis of immunogenicity up to Day 61 (Visit 5) /at Visit 7 (end of the first RSV transmission season) will include all evaluable subjects:

- Who met all eligibility criteria (i.e., no protocol violation linked to the inclusion/exclusion criteria, including age).
- Who received study vaccine as scheduled per protocol.
- For whom the administration route and site of the vaccine was as according to protocol.
- Who received the vaccine according to protocol procedures.
- Who complied with the vaccination schedule, as specified in Table 7.
- Who did not receive a concomitant medication/product/vaccine leading to exclusion from a PPS analysis, as described in Section 7.6.2, up to Day 61 (Visit 5) /at Visit 7 (end of the first RSV transmission season).
- Who complied with the timings of the post vaccination blood sampling for immune response evaluation, up to Day 61 (Visit 5) /at Visit 7 (end of the first RSV transmission season), as specified in Table 7.
- For whom post-vaccination immunogenicity results are available for at least one assay up to Day 61 (Visit 5) /at Visit 7 (end of the first RSV transmission season).

Table 24 presents the intervals between study visits that determine subjects' eligibility for inclusion in the PPS analysis.

Table 24 Maximum allowed interval between study visits (Amended 1 August 2019)

Interval	Allowed length of interval
Screening → Visit 1 (Day 1)	0 - 30 days
Visit 1 (Day 1) → Visit 2 (Day 8)	7 - 10 days
Visit 1 (Day 1) → Visit 3 (Day 31)	23 - 44 days[1]
Visit 1 (Day 1) → Visit 5 (Day 61)	60 - 81 days[1]
Visit 3 (Day 31) → Visit 4 (Day 38)	7 - 10 days
Visit 3 (Day 31) → Visit 5 (Day 61) [2]	***30*** - 37 days [1,3]
Visit 5 (Day 61) → Visit 6 (Day 121)[4]	60 - 81 days
Visit 7 (end of the first RSV transmission season)	Defined end of first RSV transmission season[5]
Visit 8 (end of the second RSV transmission season)	Defined end of second RSV transmission season[5]

[1] Subjects will not be eligible for inclusion in the PP cohort for analysis of immunogenicity if they make the study visit outside this interval.

[2] ***Where Synflorix is used as the comparator, a minimum of 30 days between Visit 3 and Visit 5 must be maintained to align with the active comparator vaccination schedule.***

[3] The interval between Visit 1 and Visit 5 must be a minimum of 60 days to be in line with the active comparator vaccination schedules as per the respective approved labels.

[4] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and Menveo will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

[5] ***As soon as possible after the end of the RSV season (approximately within 4 weeks) and in accordance with the active comparator vaccination schedule if applicable. If the active comparator dosing for V7 is later than 4 weeks after the end of the first RSV transmission season, then the recommended timing of the active comparator takes precedence.***

11.5.4. Pooled groups in the study

All subjects in the single dose (1D, $1.5x10^{10}$ vp) RSV + comparator vaccine groups will be pooled together as the pooled 1D RSV group, similarly, all subjects in the two dose (2D, $5x10^{10}$ vp) RSV + comparator vaccine groups will be pooled together as the pooled 2D RSV group, and all subjects in the comparator/Placebo control vaccine alone groups will be pooled together as the pooled comparator group (Table 25).

Table 25 Pooled groups

Study groups		Pooled groups
1D RSV + Bexsero		***Pooled 1D RSV***
1D RSV + Nimenrix		
1D RSV + Synflorix		
1D RSV + Menveo		
1D RSV + Placebo		
2D RSV + *Bexsero*		Pooled ***2D*** RSV
2D RSV + *Nimenrix*		
2D RSV + ***Synflorix***		
2D RSV + *Menveo*		
2D RSV + ***Placebo***		
Bexsero		Pooled comparator
Nimenrix		
Synflorix		
Menveo		
Placebo		

1D: 1 Dose ($1.5x10^{10}$ vp/dose); RSV: ChAd155-RSV vaccine; 2D: 2 Dose ($5x10^{10}$ vp/dose)

11.6. Derived and transformed data

11.6.1. Demography

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

11.6.2. Safety

For a given subject and the analysis of solicited AEs 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 ES 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.

11.6.3. 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. Kinetics will be plotted on subjects with results available at all timepoints.

The geometric mean titers/concentrations (GMTs/GMCs) will be computed by taking the anti-logarithm of the arithmetic mean of the log10 transformed titers/concentrations.

A seronegative subject will be defined as a subject whose antibody titer/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titer/concentration is greater than or equal to the cut-off value of the assay.

Determination of a negative RSV exposure status in infants at 6 to 7 months of age will be based on RSV A and/or B neutralizing antibody titers present in serum at screening (before vaccination with the RSV vaccine) based on in-stream baseline serological testing. At birth, newborns do show positive for neutralizing antibodies due to maternal transfer during gestation. The titer of these antibodies declines over time. At the age of 6 to 7 months a cut-off can be defined below which infants are considered to have a negative RSV exposure status. Infants that show neutralizing antibody titers above this cut-off are suspected to have experienced a recent RSV infection. This cut-off will thus allow the discrimination between a negative RSV exposure status versus RSV infected infants before start of vaccination.

The description of the handling of data below the lower limit of quantification for GMC calculation and fold increase will be described in the statistical analysis plan.

11.6.4. RTI and LRTI

For the analysis of RTI and LRTI, all cases will be definitively classified as either RSV-RTI, RSV-LRTI, severe RSV-LRTI or very severe RSV-LRTI according to the case definitions presented in Table 6, and the association to RSV infection will be assessed by quantitative PCR as primary analysis.

All confirmed LRTI will also be investigated for a panel of respiratory viruses (multiplex PCR; refer to Table 11), as a supplementary analysis of the occurrence of RSV-LRTI diagnosed upon the multiplex PCR.

For the analysis of RTI episode, a new RTI episode will be defined as any occurrence of cough, runny nose, blocked nose with an interval of at least 7 symptom free days since the last episode of RTI that was diagnosed. ***For the analysis of LRTI episode, a new LRTI episode will be defined as a history of cough or difficulty breathing and blood oxygen saturation < 95%, or respiratory rate increase and confirmed RSV infection with an interval of at least 7 symptom free days since the last episode of LRTI that was diagnosed*** **(Amended 1 August 2019)**.

11.7. Analysis of demographics

The analysis of demographics will be performed on the ES and on the PP***S*** cohort for immunogenicity for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups.

Demographic characteristics (age at vaccination in months, sex, country and race and vital signs), cohort description will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable***s*** 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.

Withdrawal status will be summarized by group using descriptive statistics:

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

11.8. Analysis of safety

11.8.1. Within groups assessment

The safety will be descriptively summarized based on the ES. The analysis of local AEs, general AEs and fever will be reported for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups. For the analysis of SAEs and AE of specific interest, the analysis will be performed only on the pooled RSV and pooled comparator groups.

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 will be tabulated with exact 95% confidence interval (CI) after each vaccine dose and overall. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE during the 7-day or 30-day follow-up period will be tabulated, overall vaccination course, with exact 95% CI. The same computations will be done for Grade 3 AEs, for any AEs considered related to vaccination for any Grade 3 AEs considered related to vaccination and AEs resulting in a medically attended visit.

The percentage of subjects reporting each individual solicited local AE (any grade, Grade 2, Grade 3, resulting in a medically attended visit) and 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 (Day 1-7) will be tabulated for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups after each vaccine dose and

overall. Similarly, the percentage of doses followed by each individual solicited local and general AE and their sub-categories, will be tabulated, overall vaccination course, with exact 95% CI.

For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (Day 1-7) will be tabulated for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups after each vaccine dose and overall. Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 (> 40.0°C) causally related fever and for any 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.

For clinical safety laboratory parameters: a listing of laboratory value outside the normal range for the unscheduled visits will be provided as per the toxicity scale. The maximum grading during the study will be tabulated (Refer to APPENDIX C) Laboratory values will be classified according to toxicity criteria. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and assessment of clinical significance **(Amended 1 August 2019)**.

The percentage of subjects with unsolicited AEs within 30 days (Day 1-30) after each vaccine dose (overall doses) with its exact 95% CI will be tabulated RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups and by MedDRA preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and AEs will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subject with episode of spontaneous or excessive bleeding (AE of specific interest), during a 30-day follow-up period after each vaccination will be tabulated according to associated Preferred Term code (to be identified in the Statistical Analysis Plan [SAP]).

The percentage of subjects with RSV-LRTI (AE of specific interest) from Dose 1 up to end of the first RSV transmission season and from Dose 1 up to end of second RSV season will be tabulated according to associated Preferred Term code presented in the SAP.

The percentage of subjects with SAE within 30 days (Day 1-30) after each vaccine dose with its exact 95% CI will be tabulated and by MedDRA preferred term. Similar tables will be generated for SAEs from Dose 1 to end of first RSV season and from Dose 1 to end of the second RSV season.

SAEs reported throughout the study and AE of special interest will be described in detail.

The percentage of subjects using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (Day 1-7) and during the 30-day follow-up period (Day 1-30) will be

summarized by the pooled RSV vaccine and pooled comparator groups after each vaccine dose and overall.

11.8.2. Between groups assessment

Exploratory comparisons between the pooled RSV vaccine group and the pooled comparator group will be done in terms of the percentage of subjects, overall doses, reporting any Grade 2/3 AE during the 7-day follow-up period (Day 1-7) after vaccination, and/ or any fever >39.0°C during the 7-day follow-up period (Day 1-7) after vaccination, and/ or any vaccine-related SAE during the 7-day follow-up period (Day 1-7) after vaccination.

The standardized asymptotic 95% CI for the difference between the pooled RSV group and (minus) the pooled comparator group will be computed.

11.9. Analysis of immunogenicity

The primary analysis will be performed on the PP***S*** for immunogenicity and, if in any pooled group the percentage of vaccinated subjects with serological results excluded from the PPS for immunogenicity is more than 10%, a second analysis will be performed on the ES. The results from immunogenicity analysis will be reported by the pooled RSV vaccine group and the pooled comparator group.

For the final analysis, the Adapted PPS for immunogenicity analysis will be used which allows the summary of immunogenicity results by time point. In summary table on the Adapted PPS for immunogenicity, PPS for immunogenicity at Day 61 will be used for Pre, Day 31 and Day 61 immunogenicity summary and PPS for immunogenicity at Day 365 for Day 365 immunogenicity summary.

The infants are monitored for RSV infection starting from dose 1 and therefore immunogenicity analyses can be adjusted to exclude those infants with an infection prior to sampling.

11.9.1. Within groups assessment

11.9.1.1. Analysis of secondary objectives

For three pooled groups, at each timepoint that blood samples are collected for humoral immune response against the investigational RSV vaccine (neutralizing antibody titers against RSV-A, RSV F antibody concentrations).

- Geometric mean titers/concentrations (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.
- Antibody titers/concentrations will be displayed using reverse cumulative curves.

- The distributions of neutralizing antibody titers/concentrations will be tabulated.
- Percentage of responders in terms of neutralizing antibody titers will be tabulated with exact 95% CI.
- Individual post-vaccination versus pre-vaccination results will be plotted using scatter plots. Results of the comparator group will be used as a reference.
- Geometric mean of ratios of antibody titers/concentrations at each post-vaccination timepoint over pre-vaccination will be tabulated with 95% CI.
- Distribution of the fold increase of the neutralizing antibody titers will be tabulated by pre-vaccination titer category.
- The kinetics of individual antibody titers/antibody concentrations results will be plotted as a function of time for subjects with results available at all timepoints.

An immunogenicity analysis will also be performed on the ES with a negative RSV exposure status (at screening based on in-stream baseline serological testing) for whom immunogenicity data are available.

At study end a sensitivity analysis of immunogenicity will be performed on infants by baseline values.

11.9.1.2. Analysis of tertiary objective

If available, any further exploratory immunology results (including, but not limited to anti-vector immunity and *palivizumab*-competing antibody concentrations) will be reported by timepoint for the two pooled RSV vaccine group***s*** and the pooled comparator group using descriptive summary statistics.

11.10. Analysis of RTI and LRTI

The primary analysis will be performed on the ES of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in the pooled single dose RSV vaccine group, the pooled two dose RSV vaccine group, and the pooled comparator group separately for first and second RSV seasons and overall. A similar analysis will be performed on the entire ES. As primary analysis, the assessment of RSV infection will be performed using the quantitative RT-PCR according to standardized case definitions (see Table 6) based on the available WHO case definitions.

The number of RSV infections within each group and the maximum disease severity of the event will be tabulated. The rate (with 95% CI) of RSV-RTI and RSV-LRTI and infections progressing to hospitalization will be evaluated for each of the three pooled groups.

The ***incidence*** rate of very severe RSV-LRTI among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season will be estimated as well as 95% one-sided lower CI.

The ***incidence rate*** and the relative risk of subjects with RSV-associated RTI (with 95% CI) between each of two pooled RSV vaccine groups and the pooled control group will be calculated for both the cohort of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) on the ES and on the entire ES. The same descriptive analysis will be performed for RSV-associated LRTI and RSV-associated severe LRTI **(Amended 1 August 2019)**.

Descriptive analyses (mean, median, min, max) of viral load assessed by the quantitative RT-PCR (RSV-A/B) of all cases as listed in Table 6 will be tabulated by case category. This analysis will also be done on the three pooled groups.

The incidence rate of all cases as listed in Table 6 (with 95% CI) will be calculated by the three pooled groups. The same descriptive analysis will be performed for all cause LRTI and all cause severe LRTI. These will also be presented for each viral etiology identified by the multiplex PCR.

The incidence rate of asymptomatic RSV infections (with 95% CI) detected by the quantitative PCR (RSV-A/B), will be tabulated by the three pooled groups. Descriptive analyses (mean, median, min, max) of viral load assessed by the quantitative RT-PCR (RSV-A/B) of those asymptomatic RSV infections will also be done on the three pooled groups.

The RVP (Multiplex PCR) on specimens from all RSV-A/B positive and confirmed LRTI cases, according to case definition presented in Table 6 (Figure 3), will be tabulated as a qualitative assessment profiling the potential co-infections occurring in these subjects.

11.11. Interpretation of analyses

For the occurrence of very severe RSV-LRTI among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season, if the upper boundary of the 95% one-sided lower CI of the rate is under 80%, it indicates that the very severe RSV-LRTI rate is less than that of the historic RSV-FI trials [Kim, 1969].

Comparative analyses will be exploratory and should be interpreted with caution considering that there is no adjustment for multiplicity and that group sizes are small for these comparisons.

11.12. 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.

11.12.1. Sequence of analyses

In preparation of the planned iSRC and IDMC evaluations, analyses of all available safety data (i.e., data that are as clean as possible) will be performed (see Section 9.10 for more information). These analyses will be done by an ***independent data analysis center*** to maintain the blinding of the study, and will be documented in a statistical analysis report. Only the outcome of the iSRC and IDMC reviews will be communicated to the RSV study team (no safety signal or safety signal). No clinical study report will be written **(Amended 1 August 2019)**.

The statistical analyses will be performed in 3 steps:

- An analysis will be performed when all data up to Day 61 are available. Additional safety data available at the time of this analysis will be described. At this point, the statistician will be unblinded (i.e., individual subject treatment assignments will be available) and the study will be conducted in a single blind manner, with patients remaining blinded up to the last study visit (end of the second RSV transmission season). Summary results may unblind some specific subjects but no individual listings will be provided and the investigator will not have access to the treatment allocation up to the last study visit (end of the second RSV transmission season), except in case of emergency unblinding (see Section 9.8).
- An analysis will be performed when all data up to Visit 7 (end of the first RSV transmission season) are available. No individual listings will be provided.
- The final analysis will be performed when all data up to study conclusion (end of the second RSV transmission season) are available. An integrated clinical study report containing all data will be written and made available to the investigators at that time.

If the 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.

11.12.2. Statistical considerations for interim analyses

No interim analyses are planned.

12. ADMINISTRATIVE MATTERS

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

12.1. 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 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 storage device containing 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.

12.2. Study Monitoring by GSK Biologicals

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

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

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

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

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

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

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

12.3. 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.

12.4. 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.

12.5. 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 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 pediatric population conducted in at least one EU member state will be posted on publicly available EMA registers within 6 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 6 months in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification. For this multi-country study, summaries of the results will be posted on publicly available EMA registers within 6 months of EoS (as defined in the protocol) in all countries, in order to have sufficient power to answer study objectives.

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.

12.6. 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.

12.7. Data Sharing

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

13. COUNTRY SPECIFIC REQUIREMENTS

13.1. Requirements for Belgium

Belgium will not use placebo, and will only use *Bexsero*.

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APPENDIX A LABORATORY ASSAYS

Assay descriptions could be subjects to change, due to assay re-development and/or qualification.

***RSV A* Neutralization assay**

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

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (***Long,*** 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 ***horse-radish peroxidase (HRP)***, allowing the visualization of plaques ***after coloration with TrueBlue peroxidase substrate.*** Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with Axiovision software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at that dilution and the number of plaques in the virus control wells (no serum added). The serum 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 as described by others [Barbas, 1992; Bates, 2014].

ELISA

- Anti-RSV protein F ELISA

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

- Palivizumab competitive assay

  Palivizumab monoclonal antibody (*Synagis*) is used as a passive treatment that protects against RSV infection by binding to the antigenic site II epitope of the RSV F 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 (horseradish peroxidase-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 horseradish peroxidase-conjugated palivizumab antibodies for binding to the F protein coated antigen. After a washing step, the horseradish peroxidase substrate solution (TMB/H_2O_2) is added and a colored product develops in a manner that is inversely proportional to the amount of palivizumab-like antibodies contained in the test serum. The color 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).

Reverse Transcription Polymerase Chain Reaction (RT-PCR)

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

  Briefly, RSV A and RSV B RNAs extracted from the nasal 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 extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real- time PCR reaction using a calibration curve (absolute quantitation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

- Qualitative multiplex RT-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 acids in nasal swabs from individuals suspected of respiratory tract infections. The following virus types and subtypes can be identified in the assay:

  – Influenza A virus (Flu A)
  – Influenza B virus (Flu 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 respiratory syncytial virus A (RSV A)
  – Human respiratory syncytial virus B (RSV B)

- 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)

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

APPENDIX B CLINICAL LABORATORIES

Table 26 GSK Biologicals' laboratories

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

Table 27 Outsourced laboratories

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

APPENDIX C TOXICITY GRADING FOR HEMATOLOGY AND BIOCHEMISTRY PARAMETERS

Table 28 Toxicity grading scales for hematology and biochemistry parameters applicable for this study

Component	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/dL)	9.0 to < 10.5	8.0 to < 9.0	7.0 to < 8.0	< 7.0
Leukocytes (cell/mm^3)	2500 to < 3500	1500 to < 2500	1000 to < 1500	< 1000
Absolute neutrophil count (cell/mm^3)	1000 to < 1300	750 to < 1000	500 to < 750	< 500
Absolute lymphocyte count (cell/mm^3)	600 to < 650	500 to < 600	350 to < 500	< 350
Platelets (cell//mm^3)	75000 to < 150000	50000 to < 75000	25000 to < 50000	< 25000
Alanine Aminotransferase (increase by factor)	1.1 to < 2.0 xULN	2.0 to < 3.0 xULN	3.00 to ≤ 8.0 xULN	> 8.0 xULN
Aspartate Aminotransferase (increase by factor)	1.1 to < 2.0 xULN	2.0 to < 3.0 xULN	3.00 to ≤ 8.0 xULN	> 8.0 xULN
Creatinine (mg/dL)	0.6 to < 0.9	0.9 to < 1.2	1.2 to ≤ 1.5	> 1.5

Grading scale adapted from Division of AIDS (2003), Division of AIDS (2004) and Division of AIDS (2007).
ULN: upper limit of normal.

APPENDIX D THE SYMPTOMS AND GRADING FOR ASSESSMENT VISITS AND WORSENING VISITS

HISTORY FROM PARENT OR CARER - PART 1		
Symptoms of RTI	*Cough*	*Yes/No (if Yes: start date and end date)*
	Runny nose	*Yes/No (if Yes: start date and end date)*
	Blocked nose	*Yes/No (if Yes: start date and end date)*
	Wheezing	*Yes/No (if Yes: start date and end date)*
	Difficulty in breathing	*Yes/No (if Yes: start date and end date)*
Parental/Carer concern	*Parental concern*	*Yes/No*

*MEDICAL OBSERVATION - PART 2a**	
Temperature	*Record temperature and route of measurement*
Heart rate	*Beats per minute when child is settled*
Respiratory rate	*Breaths per minute counted over one minute*
Lower chest wall indrawing (subcostal recession)	*Yes/No*
SpO_2	*% measured in room air when quiet and not feeding (NB altitude is collected for each participating site)*
Nasal swab taken for testing at central laboratory	*Yes/No*
Specimen taken for RSV and RVP testing at local laboratory	*Yes/No (If Yes specify type of specimen test and result: positive/negative)*
Has a blood sample been taken for assessment of mechanism of illness?	*Yes/No/ Not available*

*MEDICAL OBSERVATION - PART 2b**

Must be completed in full if:

- ***The parent or carer reports wheezing or difficulty in breathing***
- ***The respiratory rate is > 40/minute for subject 12-30 months of age***
- ***Lower chest wall indrawing is observed***
- ***SpO2 measured in room air by pulse oximetry is < 95%***

N.B. May be completed in part or in full for any child attending an assessment visit

Signs of increased respiratory effort	*Audible wheeze*	*Yes/No/Not available*
	Grunting	*Yes/No/Not available*
	Nasal flaring	*Yes/No/Not available*
	Intercostal recession	*Yes/No/Not available*
Signs associated with severity	*Apnea outside medical facility*	*Has an episode of apnea > 20 seconds occurred outside a medical facility? Yes/No/Not available (if Yes provide all details [free text field])*
	Apnea under medical observation	*Has an episode of apnea > 20 seconds occurred during medical observation? Yes/No/Not available (if Yes provide all details [free text field])*
	Peripheral cyanosis	*Yes/No/Not available*
	Central cyanosis	*Yes/No/Not available*
	Irritability/agitation	*0 = content, happy, interactive* *1 = mildly irritable when touched, occasional crying, can be comforted, is interactive* *2 = moderately irritable, intermittently crying, resists comforting, less interactive* *3 = extremely irritable, cannot be comforted, crying throughout examination or not interactive* *Not available*
	Lethargy/excessive sleepiness	*0 = interactive* *1 = mildly lethargic/sleepy is normally interactive when roused* *2 = moderately lethargic/ sleepy, less interactive than normal when roused* *3 = extremely lethargic/sleepy, is not interactive when roused* *Not available*

	Conscious level	***A = The child is awake, alert, and interactive with parents and care providers*** ***V =The child responds only if the care provider or parents call the child's name or speak loudly*** ***P =The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger.*** ***U = The child is unresponsive to all stimuli*** ***Not available***
	Assessment of feeding ability	***0 = Normal feeding*** ***1 = Reduced ability to feed*** ***2 = Unable to feed*** ***Not available***
	Skin turgor	***Yes → > 2 seconds*** ***No → ≤ 2 seconds*** ***Not available***
Findings on auscultation	***Wheeze on auscultation with stethoscope***	***Yes/No/Not available***
	Crackles	***Yes/No/Not available***
Investigations	***Chest X-ray if available*****	***Collected? Yes/No/Not available (If Yes: specify date and specify the presence or absence of the following features: hyperexpansion, peribronchial thickening, interstitial infiltrates, segmental or lobar consolidation, pleural effusion, atelectasis, other: please specify)***
	Blood culture if available**	***Collected? Yes/No (If Yes, specify date and coded results as 1. Pneumococcus, 2. Haemophilus influenza 3. Meningococcus, 4. Salmonella, 5. Other pathogenic organism, 6. Contaminant, 7. No isolate, 8. No result [missing confirmed] and note if 1 to 6: was the period of incubation to positivity detection > 48 hours? Yes/No, if 1, 2, 3 or 4 specify serotype/group, if 5 or 6 specify organism and if 8 comment)***
	Complete blood count If available**	***Collected? Yes/No/Not available (if Yes specify date of collection or tick box if date is same as visit date and specify laboratory name, record results for hematology blood count: hemoglobin, platelets, total white cell count, neutrophil count, lymphocyte count)***
Inpatient care	***Hospitalization indicated? Hospitalization?***	***Yes/No (if Yes, specify start date of hospitalization and total number of calendar days on which the child was hospitalized for at least one hour)***
	If yes: Requirement for monitoring/nursing observation	***Yes/No (if Yes total number of calendar days on which the requirement for monitoring/nursing observation was done for at least one hour)***
	If yes: Requirement for nasogastric or intravenous fluids	***Yes/No (if Yes specify start date of fluids and specify total number of calendar days on which nasogastric or intravenous fluids were given for at least one hour)***
	If yes: Requirement for supplemental oxygen	***Yes/No (if Yes specify start date of oxygen and specify total number of calendar days on which oxygen was administered for at least one hour)***
	If yes: Requirement for respiratory support excluding mechanical ventilation (e.g. high flow, continuous positive airway pressure [CPAP])	***Yes/No (if Yes specify start date of respiratory support and specify total number of calendar days on which respiratory support [excluding mechanical support] was given for at least one hour)***
	If yes: Requirement of mechanical ventilation	***Yes/No (if Yes specify start date of mechanical ventilation and specify total number of calendar days on which mechanical ventilation was given for at least one hour)***

	If yes: Requirement for pediatric intensive care unit management	***Yes/No (if Yes specify start date of pediatric care and specify total number of calendar days on which the child was cared for on pediatric intensive care unit for at least one hour)***
	Was the primary reason for hospitalization social in nature?	***Yes/No***
	In the opinion of the principal investigator and the RSV local result, was RSV-LRTI the principal reason for admission to hospital?	***Yes/No (If No, comment)***

WORSENING INFORMATION OF RTI EPISODE (Worsening episode) - PART 3*

If in the investigator's judgment a deterioration in the clinical status has occurred during the same RTI episode, then the most extreme value of all deteriorated clinical symptoms and signs (as listed in Part 2a and 2b) must be captured

N.B. May be completed in part or in full for any child experiencing a deterioration during the course of a disease episode

Maximum temperature*		***Record temperature and route of measurement***
Maximum respiratory rate*		***Breaths per minute counted over one minute***
Lower chest wall indrawing (subcostal recession)*		***Yes/No/Not available***
Minimum SpO_2 recorded*		***% measured in room air (NB altitude is collected for each participating site)***
Nasal swab taken for testing at central laboratory		***Yes/No***
Specimen taken for RSV and RVP testing at local laboratory (optional sample if the previous swab from the same RTI episode was RSV-positive)		***Yes/No (If Yes specify type of specimen test and result: positive/negative) Not available***
Signs of increased respiratory effort	***Audible wheeze****	***Yes/No/Not available***
	Grunting*	***Yes/No/Not available***
	Nasal flaring*	***Yes/No/Not available***
	Intercostal recession*	***Yes/No/Not available***
Signs associated with severity observed	***Apnea outside medical facility observed during disease episode****	***Has an episode of apnea > 20 seconds occurred outside a medical facility? Yes/No/Not available (if Yes provide all details [free text field])***
	Apnea under medical observation*	***Has an episode of apnea > 20 seconds occurred during medical observation? Yes/No/Not available (if Yes provide all details [free text field])***
	Peripheral cyanosis*	***Yes/No/Not available***
	Central cyanosis*	***Yes/No/Not available***
	Irritability/agitation (record highest score)*	***0 = content, happy, interactive 1 = mildly irritable when touched, occasional crying, can be comforted, is interactive 2 = moderately irritable, intermittently crying, resists comforting, less interactive 3 = extremely irritable, cannot be comforted, crying throughout examination or not interactive Not available***
	Lethargy/excessive sleepiness (record highest score)*	***0 = interactive 1 = mildly lethargic/sleepy is normally interactive when roused 2 = moderately lethargic/ sleepy, less interactive than normal when roused 3 = extremely lethargic/sleepy, is not interactive when roused Not available***

	Conscious level (record lowest level of consciousness)***	***A = The child is awake, alert, and interactive with parents and care providers*** ***V =The child responds only if the care provider or parents call the child's name or speak loudly*** ***P =The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger.*** ***U = The child is unresponsive to all stimuli*** ***Not available***
	Assessment of feeding ability (record highest score)***	***0 = Normal feeding*** ***1 = Reduced ability to feed*** ***2 = Unable to feed*** ***Not available***
	Skin turgor***	***Yes → > 2 seconds*** ***No → ≤ 2 seconds*** ***Not available***
Findings on auscultation	***Wheeze on auscultation******	***Yes/No/Not available***
	Crackles***	***Yes/No/Not available***

**** Observation done by qualified medical/nursing personnel***

***** Test not required per protocol but if taken as part of clinical management result should be recorded***

****** Record if a deterioration in this parameter has occurred relative to that documented at the assessment visit during the course of this disease episode***

APPENDIX E AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D Protocol Amendment 1	
eTrack study number and Abbreviated Title	204894 (RSV PED-011)
IND number	16999
EudraCT number	2018-000431-27
Amendment number:	Amendment 1
Amendment date:	16 July 2018
Co-ordinating author:	• PPD (Scientific Writer)
Rationale/background for changes:	

- In response to feedback from regulatory authorities, this study will evaluate two regimens of the ChAd155-RSV vaccine: either one dose or two doses will be given and the study sample size has been adjusted accordingly. The one dose regimen will administer a single vaccination with a lower dose of $1.5x10^{10}$ viral particles (vp) while the two dose regimen will administer $5x10^{10}$ vp for both vaccinations with a one month interval between doses. Unless the higher $5x10^{10}$ vp dose is not well-tolerated in subjects 12-23 months of age in the ongoing study 204838 (RSV PED-002),we intend to study this high dose as a 1 or 2 dose regimen going forward.
- The meningococcal vaccine *NeisVac-C* was removed and the pneumococcal polysaccharide conjugate vaccine *Synflorix* was added as one of the potential active comparator vaccines to be considered in countries where it is currently licensed.
- A placebo group was added to accommodate this request from countries that were not able to identify a suitable active comparator.
- A cross-reference to the Informed Consent Form (ICF) was added for the local choice of comparator/placebo (Sections 1.2.6 and 3).
- Serological testing of baseline samples to determine exposure status will be performed in-stream to ensure at least 50% of subjects with a negative RSV exposure status at screening based on in-stream baseline serological testing. The sample size will be adjusted as needed through additional recruitment. The discussion on sample size determination has been simplified and assumptions have been further justified (Section 11.4).

• The primary analysis for incidence of LRTI will be conducted in infants with a negative RSV exposure status at screening based on in-stream baseline serological testing.
• Immunogenicity analyses can be adjusted to exclude those infants with an infection prior to sampling. • The wording for the timing of the second dose administration has been adapted for clarity. • A statement has been added that the final confirmation of RSV presence during RTI assessment will be determined by the definitive results from the central testing laboratory. • Clarification was provided that the Respiratory Viral Panel (RVP) testing will qualitatively assess potential co-infections from all RSV-A/B positive and confirmed LRTI cases (Section 6.7.3). • The symptoms and grading for assessment visits and worsening visits have been added (APPENDIX D). • In addition, some typographical errors have been corrected throughout the protocol.

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

On the protocol cover page the other study comparator vaccines were amended.

Other study vaccines	• ***GSK's pneumococcal polysaccharide conjugate vaccine (Synflorix)*** • GSK's meningococcal group A, C, W-135 and Y conjugate vaccine ~~licensed to Pfizer~~ (~~***Nimenrix***~~***Menveo***) • ~~Pfizer's meningococcal group C polysaccharide conjugate vaccine (*NeisVac-C*)~~ • ~~Saline~~***Placebo*** (Formulation buffer S9b)

The detailed title was amended.

Detailed title	A Phase 1/2, randomized, observer-blind, controlled, multi-center study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' respiratory syncytial virus (RSV) investigational vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A), when administered intramuscularly ***as a single dose or as two doses*** according to a 0, 1-month schedule**,** to infants aged 6 and 7 months.

On the protocol cover page and on the Sponsor Signatory Approval page the **Contributing authors** have been added.

Contributing authors	• PPD ***(Clinical Research and Development Lead)*** • PPD ***(Project Statistician)*** • PPD ~~(Study Delivery Lead)~~ • PPD (Study Delivery Lead) • PPD (Study Delivery Lead) • PPD ***(Study Delivery Lead)*** • PPD ***(Clinical Read-out Team Leader)*** • PPD (Clinical and Epidemiology Research and Development Project Lead) • PPD ***(Clinical and Epidemiology Research and Development Project Lead)***

On the Signatory Approval page the EudraCT number was added and the **Sponsor signatory** has been replaced.

EudraCT number	~~2018-000431-27~~
Sponsor signatory	PPD ~~, Director~~***Antonio Gonzalez Lopez*** ***(***Clinical and Epidemiology Research & Development Project Lead***)***

In the **Synopsis**, the following changes have been made:

Rationale for the study and study design	• **Rationale for the study** GSK Biologicals is developing the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) to protect infants from RSV diseases. The purpose of this study is to provide critical information on the safety, reactogenicity and immunogenicity profile of the ChAd155-RSV vaccine in infants likely to be unexposed to RSV before moving to a ~~dose selection and a~~ proof-of-concept trial in infants. ~~This~~ ***An important aspect of this phase I/II*** study will ***be to compare a single lower dose of 1.5x10^{10} viral particles (vp) and two higher doses of 5x10^{10} vp according to a 0, 1 month schedule administered to infants aged 6 and 7 months likely to be unexposed to RSV, which is powered to statistically exclude*** a ***level of*** risk of

'vaccine-induced enhanced RSV disease' ~~after vaccination of infants aged 6 and 7 months, likely to be unexposed to RSV~~, ***associated*** with ~~the ChAd155-~~***historic FI-***RSV vaccine ***trials***. **(Amended 16 July 2018)**

- **Rationale for the study design**

Study population: The immunogenicity, safety and reactogenicity of the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) has been evaluated in healthy adults aged 18 to 45 years (study 201974 [RSV PED-001; NCT02491463]). A clinical study is currently being conducted in RSV-seropositive infants aged 12 to 23 months (study 204838 [RSV PED-002]). The safety profile of the ChAd155-RSV vaccine in adults (study 201974 [RSV PED-001; NCT02491463]) has been evaluated ***and determined to be*** satisfactory by an Independent Data Monitoring Committee (IDMC). ~~At the condition of~~***Should there be a*** satisfactory safety profile of the ChAd155-RSV vaccine in RSV-seropositive infants, as evaluated by an IDMC on Day 60 data (i.e., ~~Day~~ 30 ***days*** post-~~d~~***D***ose 2 of the highest dose level) of the study RSV PED-002, the present study will be performed. This study will be conducted ~~on~~***in*** infants aged 6 and 7 months, ***(***having a low chance of natural exposure to RSV before inclusion in the study~~,~~***). The primary analysis for incidence of LRTI will be conducted in infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing). This study will support the decision to*** ~~allow~~ age de-escalat~~ion~~***e*** to the targeted population (infants as from 6 weeks of age~~).~~) ***in the subsequent study***.

C*ontrol *vaccine*s:** Active ~~**controls:** Active controls~~comparators*** are included as a control for the reactogenicity, safety and immunogenicity assessments. The choice of one of four ~~meningococcal~~***control*** vaccines, as active comparators has been driven by the fact that, in most countries at least one of these vaccines meet the criteria of being of medical benefit, and where possible licensed for infants and used with a similar dose and schedule as the investigational RSV vaccine, while not being part of a national immunization program. The choice of which active control ~~meningococcal~~ comparator vaccine ~~will~~***to*** be used will be done at the country level and will be used according to its approved label.

~~To provide benefit to all trial participants and to maintain the study blind until the end of follow up, the ChAd155-RSV~~

~~vaccine recipients will also receive immunization with the selected meningococcal vaccine.~~

A placebo group was added to accommodate a request from countries that were not able to identify a suitable active comparator.

- **Regimen, dose and route of administration:** ~~A vaccination regimen based on~~

This study will evaluate two ~~intramuscular (IM) injections (in the anterolateral thigh) of 5 x 10^{10} viral particles (vp)~~***regimens of the ChAd155-RSV vaccine; either one lower dose of 1.5x10^{10} vp or two doses of 5x10^{10} vp will be administered*** ~~according to a 0, 1 month~~ ***. For the two dose schedule*** ~~(4-week~~***, an interval of approximately one month between*** ~~vaccinations) will be~~ ***dosing will be used. A single dose arm was added in this 6-7 month-old study population before going to target population in subsequent studies.***

The dose levels to be evaluated in this study~~. This dose level is the same as the highest dose~~ ***have previously been*** administered to RSV-seropositive infants aged 12 to 23 months (study RSV PED-002 [204838]) ***and will have been*** shown to have a satisfactory safety profile ***and reviewed*** by the IDMC. ~~This dose~~Th***ese*** dose***s*** might be modified following review by the IDMC of the safety data from study RSV- PED-002 (204838). However if no significant safety concerns are identified with the highest ChAd155-RSV vaccine dose of 5x10^{10} vp administered in the RSV PED-002 study, ~~it~~***that dose*** will be ***the highest does level*** evaluated in this study.

~~The 4-week interval regimen has been tested in preclinical models and results from a~~***In the*** bovine RSV challenge model in ~~which~~ seronegative, colostrum-restricted newborn calves ~~were vaccinated with~~ ***, both a single and two*** ~~doses~~***dose regimen*** of 5x10^{10} vp ChAd155-RSV~~,~~ ***have been evaluated. The two dose regimen was given at an interval of*** four weeks apart***. Both regimens showed*** ~~that dose regimen was immunogenic and protected calves from~~ ***a similar level of protection against challenge with bovine RSV*** ~~disease and infection and~~***, but the two dose regimen showed higher immunogenicity. Neither regimen was*** ~~not~~ ***associated*** ~~to~~***with*** pulmonary pathology.

~~A Phase I clinical trial evaluated a simian adenoviral vector-based RSV vaccine with the same insert as ChAd155-RSV candidate vaccine (PanAd3-RSV) [RSV001 Interim Study~~

~~Report, 2014]. Data from this trial, with 42 subjects, showed that a vaccination regimen based on two IM injections, separated by four weeks, was safe and immunogenic.~~

In this study, infants aged 6 and 7 months will be administered ~~with Dose 1~~***the first dose*** of the ChAd155-RSV vaccine before the RSV season to increase the probability of enrolling infants unexposed to RSV, and then followed up through the RSV season. ***The second dose will be given one month after the first dose.***

Objectives

Primary

- To evaluate the safety and reactogenicity of the RSV investigational vaccine ~~($5x10^{10}$ vp)~~ when administered IM ***as one ($1.5x10^{10}$ vp) dose or as two*** ~~IM~~***($5x10^{10}$ vp) doses according to a 0, 1-month*** schedule***,*** up to ~~30~~***6***0 days after Dose ~~2~~***1*** (i.e., Day 61) in infants aged 6 and 7 months.

Secondary

- To evaluate the occurrence of RSV respiratory tract infections ***of any severity*** from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season, in infants aged 6 and 7 months.
- To evaluate the safety of ~~two IM doses of~~ ***the RSV investigational vaccine*** ~~($5x10^{10}$ vp)~~ ***when administered IM as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses according to a 0, 1-month*** schedule***,*** from study start (Day 1) up to the end of the second RSV transmission season~~,~~ in infants aged 6 and 7 months.
- ***To evaluate the occurrence of very severe RSV LRTI from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season in RSV infected infants aged 6 and 7 months with a negative RSV exposure status (at screening based on in-stream baseline serological testing).***
- To evaluate the humoral immunogenicity induced by ~~two IM doses of~~ the RSV investigational vaccine ~~($5x10^{10}$ vp)~~ when administered IM ***as one ($1.5x10^{10}$ vp) dose or as two ($5x10^{10}$ vp) doses*** according to a 0, 1-month schedule, ***from study start (Day 1)*** up to the end of the first RSV transmission season, in infants aged 6 and 7 months.

Tertiary

- If deemed necessary, to further characterize the immune response of the RSV investigational vaccine when ***one (1.5x10^{10} vp) dose or two*** ~~IM~~***(5x10^{10} vp) doses*** are ***administered IM*** according to a 0, 1-month schedule ~~in~~***to*** infants aged 6 and 7 months.

Study design

- Experimental design: Phase I/II, observer-blind, randomized, controlled, multi-centric study with ~~two~~***three*** parallel groups.
  - Epoch 004: follow-up starting after Visit 7 (end of the ~~second~~***first*** RSV transmission season)* and ending at Visit 8 (end of the second RSV transmission season).
- End of Study (EoS): Last testing results released of samples collected at Visit 8 (end of the second RSV transmission season) ***related to primary and secondary endpoints.****

  * Up to Visit 8 (end of the second RSV season), there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season ~~and~~***or*** if following active or a passive surveillance contacts, a subject presents symptoms of respiratory tract infection (RTI), a nasal swab will be collected.

Synopsis Table 1 Study groups and epochs foreseen in the study

~~Old Synopsis Table 1~~

Study groups	Number of subjects*	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
RSV + *Bexsero*	15 **	6 – 7 months	x	x	x	x
RSV + *Nimenrix*	15 **	6 – 7 months	x	x	x	x
RSV + *Menveo*	15 **	6 – 7 months	x	x	x	x
RSV + *NeisVac-C*	5 **	6 – 7 months	x	x	x	x
Bexsero	15 **	6 – 7 months	x	x	x	x
Nimenrix	15 **	6 – 7 months	x	x	x	x
Menveo	15 **	6 – 7 months	x	x	x	x
NeisVac-C	5 **	6 – 7 months	x	x	x	x

New Synopsis Table 1

Study groups	Numbers of subjects*	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
1D RSV + Bexsero	***50*** **	6 – 7 months	***N/A***	***x***	***x***	***x***
1D RSV + Nimenrix		6 – 7 months	***N/A***	***x***	***x***	***x***
1D RSV + Synflorix		***6 – 7 months***	***N/A***	***x***	***x***	***x***
1D RSV + Menveo		6 – 7 months	***N/A***	***x***	***x***	***x***
1D RSV + Placebo		***6 – 7 months***	***N/A***	***x***	***x***	***x***
2D RSV + Bexsero	***50*** **	6 – 7 months	***N/A***	x	x	x
2D RSV + Nimenrix		6 – 7 months	***N/A***	x	x	x
2D RSV + Synflorix		***6 – 7 months***	***N/A***	***x***	***x***	***x***
2D RSV + Menveo		6 – 7 months	***N/A***	x	x	x
2D RSV + Placebo		***6– 7 months***	***N/A***	***x***	***x***	***x***
Bexsero	***50*** **	6 – 7 months	***N/A***	x	x	x
Nimenrix		6 – 7 months	***N/A***	x	x	x
Synflorix		***6 – 7 months***	***N/A***	***x***	***x***	***x***
Menveo		6 – 7 months	***N/A***	x	x	x
Placebo		***6 – 7 months***	***N/A***	***x***	***x***	***X***

1D: 1 Dose (1.5x10[10] vp/dose); **RSV**: ChAd155-RSV vaccine; ***2D: 2 Dose (5x10[10] vp~~).~~/dose); N/A: Not Applicable***.

* Note that ~~across all~~***for both 1D and 2D*** RSV ***vaccine + active comparator/placebo*** groups the total number of subjects is ~~50~~***10***0 and that for ~~each~~***both*** RSV ***vaccine*** + active comparator/***placebo groups*** there will be a 1:1***:1*** ratio maintained with the ~~same~~corresponding active comparator/***placebo group***.

** Note that the~~se~~ ***numbers of subjects anticipated to receive the control vaccines within participating countries are*** ~~approximation of~~***not yet known, but*** the distribution and supplies will be prepared to allow flexible enrolment across countries (for any comparator the range of subjects is 0 – ***50*** may be enrolled) but the overall total of ***15***~~0~~0 subjects will be respected.

Synopsis Table 2 Study groups and treatment foreseen in the study

~~Old Synopsis Table 2~~

Treatment name	Vaccine/ Product name	Study Groups							
		RSV + *Bexsero*	RSV + *Nimenrix*	RSV + *Menveo*	RSV + *NeisVac-C*	*Bexsero*	*Nimenrix*	*Menveo*	*NeisVac-C*
RSV ChAd	ChAd155-RSV	x	x	x	x				
Saline	FB					x	x	x	x
Bexsero	*Bexsero*	x				x			
Nimenrix	*Nimenrix*		x				x		
Menveo				x				x	
NeisVac-C	*Neiss Vac-C*				x				x

New Synopsis Table 2

Treatment name	***1D RSV ChAd***	***2D RSV ChAd***	***Bexsero***	***Nimenrix***	***Synflorix***	***Menveo***	***FB***
Vaccine/ Product name	***1D ChAd155-RSV 1.5X10^{10} vp/dose***	***2D ChAd155-RSV 5X10^{10} vp/dose***	***Bexsero***	***Nimenrix***	***Synflorix***	***Menveo***	***FB***
Study Groups							
1D RSV + Bexsero	***x***		***x***				***x***
1D RSV + Nimenrix	***x***			***x***			***x***
1D RSV + Synflorix	***x***				***x***		***x***
1D RSV + Menveo	***x***					***x***	***x***
1D RSV + Placebo	***x***						***x***
2D RSV + Bexsero		***x***	***x***				
2D RSV + Nimenrix		***x***		***x***			
2D RSV + Synflorix		***x***			***x***		
2D RSV + Menveo		***x***				***x***	
2D RSV + Placebo		***x***					
Bexsero			***x***				***x***
Nimenrix				***x***			***x***
Synflorix					***x***		***x***
Menveo						***x***	***x***
Placebo							***x***

ChAd155-**RSV**: Chimpanzee Adenovirus Type 155 RSV vaccine ~~(5x10^{10} vp)~~; **FB**: Formulation buffer S9b; **RSV ChAd**: Treatment with ChAd155-RSV vaccine; ***1D: 1 Dose (1.5x10^{10} vp/dose); 2D: 2 Dose (5x10^{10} vp)./dose)***.

– ~~Control: meningococcal vaccine~~ Control***s***: active ~~controls~~***comparator vaccines*** (*Bexsero*, or *Nimenrix*, ***or Synflorix,*** or *Menveo*, ***or*** ~~NeisVac-C) and saline (~~***Placebo*** (***Formulation buffer*** ~~S9b).*~~***[FB])****

* The choice of active ~~control~~ comparator vaccine ***or Placebo*** is done at the country level.

- Vaccination schedules:
  - RSV investigational vaccine:
    - ***In the 1 Dose (1D) groups, a*** single ***lower*** dose ***of 1.5x10^{10} vp will be administered IM at Day 1***

(Visit 1). Formulation buffer will be administered in the 1D groups at Day 31 (Visit 3). In the 2 Dose (2D) groups, two ~~IM vaccine~~ doses ***of 5x10^{10} vp will be administered IM*** according to a 0, 1-month schedule, (i.e., at Day 1 ***[Visit 1]*** and Day 31~~)~~ ~~(~~ ***[Visit 3]***) ***(see Synopsis Table 3).*** Dose 1 will be administered before the first RSV season~~.~~ ***and the second dose will be given one month after the first dose*** (RSV seasons will be determined for each country based on local epidemiological data and documented in the Study Procedures Manual ~~(SPM).~~***[SPM]. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years.*** For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable.).

- ***Comparator or Placebo***:
  - ***In countries where*** *Bexsero* ***or*** *Nimenrix*~~For *Bexsero, Nimenrix,* and *NeisVac-C*~~ ***is used as a control***, two ~~primary~~ doses will be administered IM with at least a 2 month interval ~~with a~~***between these primary doses***. ***A*** booster dose ***will be*** administered IM in the second year of life ~~(~~at ***Day 365*** (Visit 7), with an interval of at least 2 months between the primary series and booster dose. ***The first Bexsero or Nimenrix dose will be administered at Day 1 (Visit 1) (in the groups receiving only Bexsero or Nimenrix, respectively). In the groups receiving only Bexsero or Nimenrix, the second dose will be at Day 61 (Visit 5). The first Bexsero or Nimenrix dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of Bexsero or Nimenrix in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits*** (see Synopsis Table ~~4).~~ ***3***).
  - ***In countries where Synflorix is used as a control, two doses will be administered IM with at least a 1 month interval between these primary doses. A***

booster dose will be administered IM in the second year of life at Day 365 (Visit 7). The first Synflorix dose will be administered at Day 31 (Visit 3) (in the group receiving only Synflorix). In the group receiving only Synflorix, the second dose will be at Day 61 (Visit 5). The first Synflorix dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of Synflorix in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Synopsis Table 3).

- In countries where *Menveo* is used as a control, two doses will be administered IM at least 3 months apart with the second dose in the second year of life~~.~~ ***at Day 365 (Visit 7)***. The first *Menveo* dose will be administered ~~as a comparator~~ at ***Day 31 (***Visit 3 ~~(opposing the second RSV vaccine dose) from 7 months of age.~~***) (in the group receiving only Menveo)***. The first *Menveo* dose to be administered to the ***1D and 2D*** RSV group***s*** will be at ***Day 61 (***Visit 5~~,~~***)***, following the ***1 or 2*** RSV vaccine ~~administrations.~~***doses, respectively***. Since the second *Menveo* dose has to be administered in the second year of life~~,~~ ***at Day 365 (Visit 7)***, no administration will be performed at ***Day 121*** ~~and therefore in those countries the second *Menveo* dose~~***(Visit 6). Formulation buffer will be*** ~~at Visit 7, at the end of the first RSV season (refer to~~ ***administered, when neither RSV vaccine nor comparator is scheduled, at the 4 vaccination visits*** (***see*** Synopsis Table 3).
- ***In countries where Placebo is used as a control, one dose will be administered IM at Day 31 (Visit 3) in the 1D RSV + Placebo group and two IM doses will be administered IM according to a 0, 1-month schedule at Day 1 (Visit 1) and Day 31 (Visit 3) in the Placebo group (see Synopsis Table 3).***

Synopsis Table 3 Vaccines administered and vaccination schedules

~~Old Synopsis Table 3~~

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	**7-8 / (V3, D31)**	**8-9 / (V5, D61)**	**10-11 / (V6, D121)****	**14-18 / (V7)**
RSV + *Bexsero*	RSV ChAd	RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	Saline	*Bexsero*	Saline	*Bexsero*
RSV + *Nimenrix*	RSV ChAd	RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	Saline	*Nimenrix*	Saline	*Nimenrix*
RSV + *Menveo*	RSV ChAd	RSV ChAd	*Menveo*		*Menveo*
Menveo	Saline	*Menveo*	Saline		*Menveo*
RSV + *NeisVac-C*	RSV ChAd	RSV ChAd	*NeisVac-C*	*NeisVac-C*	*NeisVac-C*
NeisVac-C	*NeisVac-C*	Saline	*NeisVac-C*	Saline	*NeisVac-C*

New Synopsis Table 3

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	**7-8 / (V3, D31)**	**8-9 / (V5, D61)**	**10-11 / (V6, D121)****	**14-18 / (V7, D365)**
1D RSV + Bexsero	***1D RSV ChAd***	***FB***	***Bexsero***	***Bexsero***	***Bexsero***
2D RSV + *Bexsero*	***2D*** RSV ChAd	***2D*** RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	***FB***	*Bexsero*	***FB***	*Bexsero*
1D RSV + Nimenrix	***1D RSV ChAd***	***FB***	***Nimenrix***	***Nimenrix***	***Nimenrix***
2D RSV + *Nimenrix*	***2D*** RSV ChAd	***2D*** RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	***FB***	*Nimenrix*	***FB***	*Nimenrix*
1D RSV + Synflorix	***1D RSV ChAd***	***FB***	***Synflorix***	***Synflorix***	***Synflorix***
2D RSV + ***Synflorix***	***2D*** RSV ChAd	***2D*** RSV ChAd	***Synflorix***	***Synflorix***	***Synflorix***
Synflorix	***FB***	***Synflorix***	***Synflorix***	***FB***	***Synflorix***
1D RSV + Menveo	***1D RSV ChAd***	***FB***	***Menveo***		***Menveo***
2D RSV + Menveo	***2D RSV ChAd***	***2D RSV ChAd***	***Menveo***		***Menveo***
Menveo	***FB***	***Menveo***	***FB***		***Menveo***
1D RSV + Placebo	***1D RSV ChAd***	***FB***			
2D RSV + ***Placebo***	***2D*** RSV ChAd	***2D*** RSV ChAd			
Placebo	***FB***	***FB***			

V: Visit; **D:** Day; ***1D: 1 Dose (1.5x10^{10} vp/dose); 2D: 2 Dose (5x10^{10} vp/dose)***; **RSV ChAd**: Treatment with ChAd155-RSV vaccine ~~(5x10^{10} vp)~~; **~~V:~~ Visit.*; FB: Formulation buffer S9b***.

* Assumes enrolled at 6 and 7 months of age for the vaccine Dose 1 to be administered before the first RSV season (RSV seasons will be determined for each country based on local epidemiological data).

** In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7.

- Treatment allocation: infants will be randomized using a centralized randomization system on internet (SBIR) before first vaccination and after assessment of eligibility (i.e., after screening conclusion). The randomization algorithm will use a minimization procedure accounting for country~~.~~ ***as a minimization factor and the grouping comparator/placebo as a stratification factor.***

  - Nasal swab: there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season and if following active or a passive surveillance contacts, a subject presents symptoms of respiratory tract infection (RTI), a nasal swab will be collected ***(as well as a sample for local testing i.e., the type of sample to be determined locally [e.g., swab, etc.]).***

- Study visits: Other than the screening visit and assessment visits for active/passive surveillance, there will be 8 study visits except in countries where *Menveo* ***or Placebo*** is used as a control where there will be 7 study visits.

  - In countries where *Menveo* is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and ~~it~~***Menveo*** will be administered at the end of the first RSV season at Visit 7.

  - ***In countries where Placebo is used as a control, no vaccine administration will be performed after Visit 3 and therefore in those countries there will be no Visit 6. There will be a Visit 5 and Visit 7 for countries using Placebo and all other study procedures will occur at these visits except vaccination.***

  - ***Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (Day 730) (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.***

- Surveillance for spontaneous or excessive bleeding.

  Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination, in order to detect any thrombocytopenic petechiae or purpura. ***The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets.***

Case definition

During the analysis of the study, all cases identified during the surveillance of RSV-RTI will be definitively classified as either RTI, LRTI, severe LRTI or very severe LRTI according to the standardized case definitions (see Synopsis Table ~~7~~***5***) based on the available World Health Organization (WHO) case definitions.

Synopsis Table 5 Case definitions for data analysis

Case	*At sea level up to 2500 meters elevation*	*Above 2500 meters elevation*
RSV-RTI	Runny nose OR blocked nose OR cough AND Confirmed RSV infection [4]	***Same***
RSV-LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3] AND Confirmed RSV infection [4]	***Same but with SpO2 <92%***
~~**RSV**~~ **severe *RSV*-LRTI**	Meeting the case definition of RSV-LRTI AND SpO_2 < 93% [2], OR lower chest wall in-drawing	***Same but with SpO2 <90%***
~~**RSV**~~ **very severe *RSV*-LRTI**	Meeting the case definition of RSV-LRTI AND SpO_2 < 90% [2], OR inability to feed, OR failure to respond / unconscious	***Same but with SpO2 <88%***
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]	***Same***
All-cause LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3]	***Same but with SpO2 <92%***

Definitions based on [Modjarrad, 2016]

LRTI = lower respiratory tract infections; **RR** = respiratory rate; **RTI** = respiratory tract infections; **SpO2** = Blood oxygen saturation by pulse oximetry.

[1] Based on history reported by parents~~/LARs and includes difficulty breathing (e.g., showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnoea) associated with nasal obstruction.~~

Number of subjects The target will be to enroll approximately ***150***~~0~~ infants likely to be unexposed to RSV ~~to ensure that~~***with about 50 infants*** ~~receive~~***for each of three randomization groups. If necessary, the sample size will be increased through additional recruitment in order to achieve at least*** ~~one dose of~~***5 RSV*** ~~investigational~~ ***infected infants***, ***with a negative RSV exposure status (at screening based on in-stream baseline serological testing), in each RSV vaccine group.*** Dose 1 of the ChAd155-RSV vaccine should be administered before the first RSV season ***and second dose will be given one month after the first dose*** (RSV seasons will be determined for each country based on local epidemiological data ***and documented in the SPM***. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable).

Endpoints

Secondary

- ***Occurrence of RSV-RTI, RSV-LRTI, severe RSV-LRTI and very severe RSV-LRTI (according to standardized case definitions) as from first vaccination (Day 1) up to the end of the second RSV transmission season.***
- ***Occurrence of very severe RSV-LRTI* (*according to standardized case definitions) among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season.***
- ~~Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61):~~
  - ~~Palivizumab-competing antibody concentrations.~~

Tertiary

- ***Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61).***
  - ***Palivizumab-competing antibody concentrations.***

The LIST OF ABBREVIATIONS has been amended as follows:

ES:	***Exposed Set***
FB:	***Formulation buffer (S9b)***
HRP:	***Horse-Radish Peroxidase***
PP*S*:	Per-Protocol ***Set***
SAP:	***Statistical Analysis Plan***
TLR:	***Toll-like receptor***
~~**TCV:**~~	~~Total Vaccinated Cohort~~
UK:	***United Kingdom***

The following terms have been amended or added to the **GLOSSARY OF TERMS**

End of Study ***(Synonym of End of Trial)***	~~Synonymous with 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, study completion 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. Study completion must be achieved no later than 8 months after LSLV.***
Exposed Set	***All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.***
Per Protocol Set	***All subjects who received at least 1 dose of the study treatment to which they are randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion.***

The **TRADEMARKS** have been amended as follows:

Trademarks of the GSK group of companies	Generic description
Synflorix	***Pneumococcal polysaccharide conjugate vaccine (adsorbed)***

Trademarks not owned by the GSK group of companies	Generic description
~~*NeisVac-C* (Pfizer)~~	~~Meningococcal group C polysaccharide conjugate vaccine (tetanus toxoid protein conjugate)~~
TrueBlue (SeraCare)	***Peroxidase substrate***

In Section 1.1.3.2. Serum immune responses to the FI-RSV vaccine and to subsequent RSV infection, the following changes have been made:

When the sera of these infants and children were later compared with those of infants and children with natural RSV infection, it could be observed that FI-RSV vaccination induced high total IgG antibody ~~titres~~***titers***, but a relatively low level of neutralising antibody ~~titres~~***titers*** [Murphy, 1986].

In Section 1.1.3.4. Animal models for "FI-RSV enhanced RSV disease", the following changes was made:

In general, animal models suggest that the immunopathology seen with the FI-RSV vaccine was a result of a poor functional antibody response [Graham, 2011; Openshaw, 2002] An unbalanced cellular immune response skewed towards Th2 (disturbed Th1/Th2 balance) could also ***be*** observed in mouse models [Connors, 1992; Connors, 1994; Waris, 1996], but is not consistently supported by data from other model animals [Antonis, 2003; Castilow, 2008; Phipps, 2007].

The Section 1.1.6. Pre-clinical experience. the following statement was added:

Please refer to the current IB for information regarding the pre-clinical studies of GSK Biologicals' investigational ChAd155-RSV vaccine.

The Section 1.1.7. Clinical experience, the following statement was amended:

Please refer to the current IB for information regarding the ~~pre-clinical and~~ clinical studies of GlaxoSmithKline (GSK) Biologicals' investigational ChAd155-RSV vaccine.

The Section 1.2.1. Rationale for the study, the following changes were made:

The purpose of this study is to provide critical information on the safety, reactogenicity and immunogenicity profile of the ChAd155-RSV vaccine in infants likely to be unexposed to RSV before moving to a ~~dose-selection and a~~ proof-of-concept trial in infants. ~~This~~ ***An important aspect of this phase I/II*** study will ***be to compare a single lower dose of 1.5x10^{10} viral particles (vp) and two higher doses of 5x10^{10} vp according to a 0, 1 month schedule administered to infants aged 6 and 7 months likely to be unexposed to RSV, which is powered to statistically exclude*** a ***level of*** risk of 'vaccine-induced enhanced RSV disease' ~~after vaccination of infants aged 6 and 7 months, likely to be unexposed to RSV~~,~~-~~***associated*** with ~~the ChAd155-~~***historic FI-***RSV vaccine ***trials*** ~~in young infants~~ [Kim, 1969].

The Section 1.2.2.1. Study population, the following changes were made:

The immunogenicity, safety and reactogenicity of the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) has been evaluated in healthy adults aged 18 to 45 years (study 201974 [RSV PED-001; NCT02491463]). A clinical study is currently being conducted in RSV-seropositive infants aged 12 to 23 months (study 204838 [RSV PED-002]). The safety profile of the ChAd155-RSV vaccine in adults (study 201974 [RSV PED-001; NCT02491463]) has been evaluated satisfactory by an Independent Data Monitoring Committee (IDMC). ~~At the condition of~~***Should there*** be a satisfactory safety profile of the ChAd155-RSV vaccine in RSV-seropositive infants, as evaluated by an IDMC on Day 60 data (i.e., ~~Day~~ 30 ***days*** post-Dose 2 of the highest dose level) of the study RSV PED-002, the present study will be performed. This study will be conducted on infants aged 6 and 7 months (having a low chance of natural exposure to RSV before inclusion in the study~~),~~). ***The primary analysis for incidence of LRTI will be conducted in infants with a negative RSV exposure status (at screening based on in-stream serological testing). This study will support the decision to*** ~~allow~~ age de-escalat~~ion~~***e*** to the targeted population (infants as from 6 weeks of age).

The Section 1.2.2.2. Choice of study population, the following change was made:

Infants of this age are more likely to be unexposed to RSV compared to older infants. ~~Most of the infants (50% to 70%) are estimated to be RSV-exposed at one year of age.~~ ***[Dunn, 2013]***.

The Section 1.2.2.3. In-stream serological testing of baseline samples to determine exposure status, was added:

Subjects will not be screened for serostatus as criterion for enrolment in the study, due to the potential presence and detection of residual maternal antibodies (Refer to Section 6.7.3 for more details on the determination of a negative RSV exposure status). The assumption is that the majority of infants are previously unexposed (see Section 1.2.2.2). Serological testing of baseline samples to determine exposure status will be performed in-stream to ensure at least 50% of infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) and the sample size will be adjusted as needed through additional recruitment (Section 11.4).

The Section 1.2.3. Rationale for regimen, dose and route of administration, was amended as follows:

~~A vaccination regimen based on~~ ***This study will evaluate two*** ~~IM injections (in the anterolateral thigh) of 5 x 10^{10} viral particles (vp)~~***regimens of the ChAd155-RSV vaccine; either one dose of 1.5x10^{10} vp or two doses of 5x10^{10} vp will be administered*** ~~according to a 0, 1 month~~ ***. For the two dose schedule*** ~~(4 week~~***an interval of approximately one month between*** ~~vaccinations)~~***dosing will be*** ~~evaluated~~***used. A single dose arm was added in this*** ~~study. This dose level is the same as the highest dose~~***6-7 month-old study population before going to target population in subsequent studies.***

The dose level***s to be evaluated in this study have previously been*** administered to RSV-seropositive infants aged 12 to 23 months (study RSV PED-002 [204838]) ***and will have been*** shown to have a satisfactory safety profile ***and reviewed*** by the IDMC. ~~This dose~~Th***ese*** dose***s*** might be modified following review by the IDMC of the safety data from study RSV PED-002 (204838). However~~,~~ if no significant safety concerns are identified with the highest ChAd155-RSV vaccine dose of 5x10^{10} vp administered in the RSV PED-002 study, ~~it~~***that dose*** will be ***the highest does level*** evaluated in this study.

~~The 4-week interval regimen has been tested in preclinical models and results from a~~***In the*** bovine RSV challenge model in which seronegative, colostrum-restricted newborn calves~~ were vaccinated with~~***, both a single and two*** ~~doses~~***dose regimen*** of 5x10^{10} vp ChAd155-RSV ***have been evaluated. The two dose regimen was given at an interval of*** four weeks apart***. Both regimens showed*** ~~that dose regimen was immunogenic and protected calves from~~ ***a similar level of protection against challenge with bovine RSV*** ~~disease and infection and~~***, but the two dose regimen showed higher immunogenicity. Neither regimen was*** ~~not~~ ***associated*** ~~to~~***with*** pulmonary pathology. ***Low or potentially suboptimal dosing could be associated with lack of efficacy but is not likely to be associated with ERD; this is supported by animal data evaluating protection against a delayed challenge after a period of waning immunity. Non-clinical calf data showed that a challenge 4 months after the second dose or a challenge after a single dose did***

not induce any sign of ERD and demonstrated similar efficacy against LRTI. Despite waning immunity after 4 months, animals were fully protected upon challenge.

~~Using a different adenovector, PanAd3, the 5 x 10^{10} vp dose regimen was shown to be safe in toxicology studies in mice. Preclinical data in different species (mice, cotton rats, non-human primates, and seronegative newborn calves) have shown that this regimen induces both anti-RSV F neutralizing antibodies and systemic T-cell responses [Taylor, 2015; Pierantoni, 2015].~~

~~A Phase I clinical trial evaluated a simian adenoviral vector-based RSV vaccine with the same insert as ChAd155-RSV candidate vaccine (PanAd3-RSV) [, 2014]. Data from this trial, with 42 subjects, showed that a vaccination regimen based on two IM injections, separated by four weeks, was safe and immunogenic.~~

Similarly, the selected one dose level of $1.5x10^{10}$ vp is the same as the mid-dose administered to RSV-seropositive infants in the RSV PED-002 study that will have been shown to have a satisfactory safety profile and reviewed by the IDMC. The rationale for using the mid-dose level is to collect safety and immunogenicity data on a lower dose and on the one-dose regimen in 6-7 months RSV-naïve infants before progressing to the target population i.e. infants as of 6 weeks of age.

***If tolerated, both candidate regimens would be evaluated in the target population to determine immune response and evaluate efficacy.*)**

In this study, infants aged 6 to 7 months will be administered with ~~Dose 1~~***the first dose*** of the ChAd155-RSV vaccine before the RSV season to increase the probability of enrolling infants unexposed to RSV, and then followed up through the RSV season. ***The second dose will be given one month after the first dose.***

In the Section 1.2.4.1.Rationale for RSV disease surveillance the following paragraph was deleted:

~~Subjects will not be screened for serostatus as criterion for enrolment in the study, due to the potential presence and detection of residual maternal antibodies. The assumption is that the majority of infants are previously unexposed (see Section). Infants will be administered with Dose 1 of the ChAd155-RSV vaccine before the RSV season and then followed up through the RSV season.~~

The Section 1.2.5. Rationale for study blinding, was amended as follows:

Given the different appearance and storage conditions of the investigational RSV vaccine and the active control comparator vaccines / ~~saline solution~~***Placebo***, double blinding is not possible and the study will be conducted in an observer-blind manner.

*Refer to the SPM for RSV seasons per ~~site~~ ***country***.

In the Section 1.2.6. Rationale for the use of ~~active~~ controls, the following changes have been made:

~~Active comparators~~***The comparator / Placebo groups are included as a control for the reactogenicity, safety and immunogenicity assessments. The choice of control between an active comparator or Placebo will be done at country level. Refer to the Informed Consent Form (ICF) for the local choice of comparator/Placebo.***

Active comparators are included as a control for the reactogenicity, safety and immunogenicity assessments. The choice of one of four ~~meningococcal~~***control*** vaccines, as active comparators has been driven by the fact that, in most countries at least one of these vaccines meet the criteria of being of medical benefit, and where possible licensed for infants and used with a similar dose and schedule as the investigational RSV vaccine, while not being part of a national immunization program. The choice of which active control ~~meningococcal~~ comparator vaccine will be used will be done at the country level and will be used according to its approved label.

Since the immunization schedule for the ~~meningococcal~~***active*** comparator vaccines for infants between 6 and 18 months of age is slightly different, infants in the active control group will be administered ~~saline~~***FB*** at the time of administration of the first dose of the investigational RSV vaccine (for ***either*** *Menveo* ***or Synflorix***) or the second dose of the investigational RSV vaccine (for either *Bexsero* or *Nimenrix* ~~or *NeisVac-C*~~). To accommodate the various vaccination schedules of the ~~meningococcal~~***active comparator*** vaccines across countries, ~~saline~~***FB*** may also be offered once during the two to three additional vaccinations given to complete the comparator vaccine schedule in the study (~~refer to~~ ***see Figure 1 and*** Table 2).

The Section 1.2.7. Rationale for ChAd155 RSV vaccine recipients receiving ~~meningococcal~~ *active comparator* vaccine, was amended as follows:

To provide benefit to all trial participants and to maintain the study blind until the end of follow up, the ChAd155-RSV vaccine recipients will also receive immunization with the selected ~~meningococcal~~***active comparator*** vaccine.

The Section 1.3. Benefit : Risk Assessment, was amended as follows:

~~Half~~***Approximately two thirds*** of the infants (~~50~~***10***0) in this study will be exposed to the ChAd155-RSV vaccine, whereas all infants will receive ***either*** an active control comparator vaccine (*Bexsero,* or *Nimenrix, **or Synflorix,*** or *Menveo~~,~~*), ***or*** ~~*NeisVac-C*~~)~~*~~***Placebo*** (see Figure 1 and Table 2).

~~*~~ The choice of active ~~control~~ comparator vaccine ***or Placebo*** is done at the country level.

Please refer to the current IB for the summary of potential risks and benefits of ChAd155-RSV vaccine.

Please refer to the local Prescribing Information for information regarding the summary of potential risks and benefits of *Bexsero*, *Nimenrix,* ***Synflorix*** and *Menveo* ~~and *NeisVac-C*~~.

In Section 1.3.1. Risk Assessment, was amended as follows:

~~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.~~

A broad safety hematology and biochemistry evaluation was performed at each study visit in adults during study RSV PED-001 (201974). In this study, no significant safety concerns were identified up to 30 days post Dose 2 ***in healthy adults aged 18 to 45 years*** (refer to Section ***1.1.7*** and to the current IB). Hematology and biochemistry parameters are also being intensively evaluated in RSV-seropositive infants aged 12 to 23 months during study RSV PED-002 (204838).

~~No significant safety concerns were identified up to 30 days post Dose 2 in study RSV PED-001 with the ChAd155-RSV vaccine in healthy adults aged 18 to 45 years (refer to Section and to the current IB).~~

Risks linked to the active control comparator ~~meningococcal~~ vaccines

Refer to the local Prescribing Information for potential risks and contraindications related to *Bexsero*, *Nimenrix,* ***Synflorix or*** *Menveo* ~~or *NeisVac-C*~~ vaccines.

The Section 1.3.2. Benefit Assessment, was amended as follows

The choice of ~~meningococcal~~***active comparator*** vaccine (*Bexsero*, *Nimenrix,* ***Synflorix, or*** *Menveo* ~~or *NeisVac-C*~~) for each participating country ensures that the vaccine may be given according to the local label and provides medical benefit in the country. ~~All~~***Within a given participating country, a***ll infants in both groups of this study will receive the full locally recommended vaccination course of ~~meningococcal~~***active comparator*** vaccine where possible and may be immunized against ***either*** invasive meningococcal disease caused by *Neisseria meningitidis*~~.~~ ***(with the meningococcal vaccines Bexsero, Nimenrix or Menveo); or against invasive pneumococcal disease and acute otitis media caused by Streptococcus pneumoniae (with the pneumococcal vaccine Synflorix)***.

The Section 1.3.3. Overall Benefit:Risk Conclusion, was amended as follows

The four ~~meningococcal comparator~~***control*** vaccines administered to all participants in this study as active ~~controls~~***comparators***, are licensed for infants in the particular country where possible, and therefore have demonstrated medical benefit in the prevention of invasive meningococcal disease caused by *Neisseria meningitidis*~~.~~ ***(for the meningococcal vaccines Bexsero, Nimenrix, Menveo); or against invasive pneumococcal disease and acute otitis media caused by Streptococcus pneumoniae (for the pneumococcal vaccine Synflorix)***.

The Section 2.1. Primary objectives~~s~~ was amended as follows:

- To evaluate the safety and reactogenicity of the RSV investigational vaccine ~~(5x10^{10} vp)~~ when administered ***IM as one (1.5x10^{10} vp) dose or as two*** ~~IM~~***(5x10^{10} vp) doses according to a 0, 1-month*** schedule***,*** up to ~~30~~ ***6***0 days after Dose ~~2~~***1*** (i.e., Day 61) in infants aged 6 and 7 months.

The Section 2.2. Secondary objectives was amended as follows:

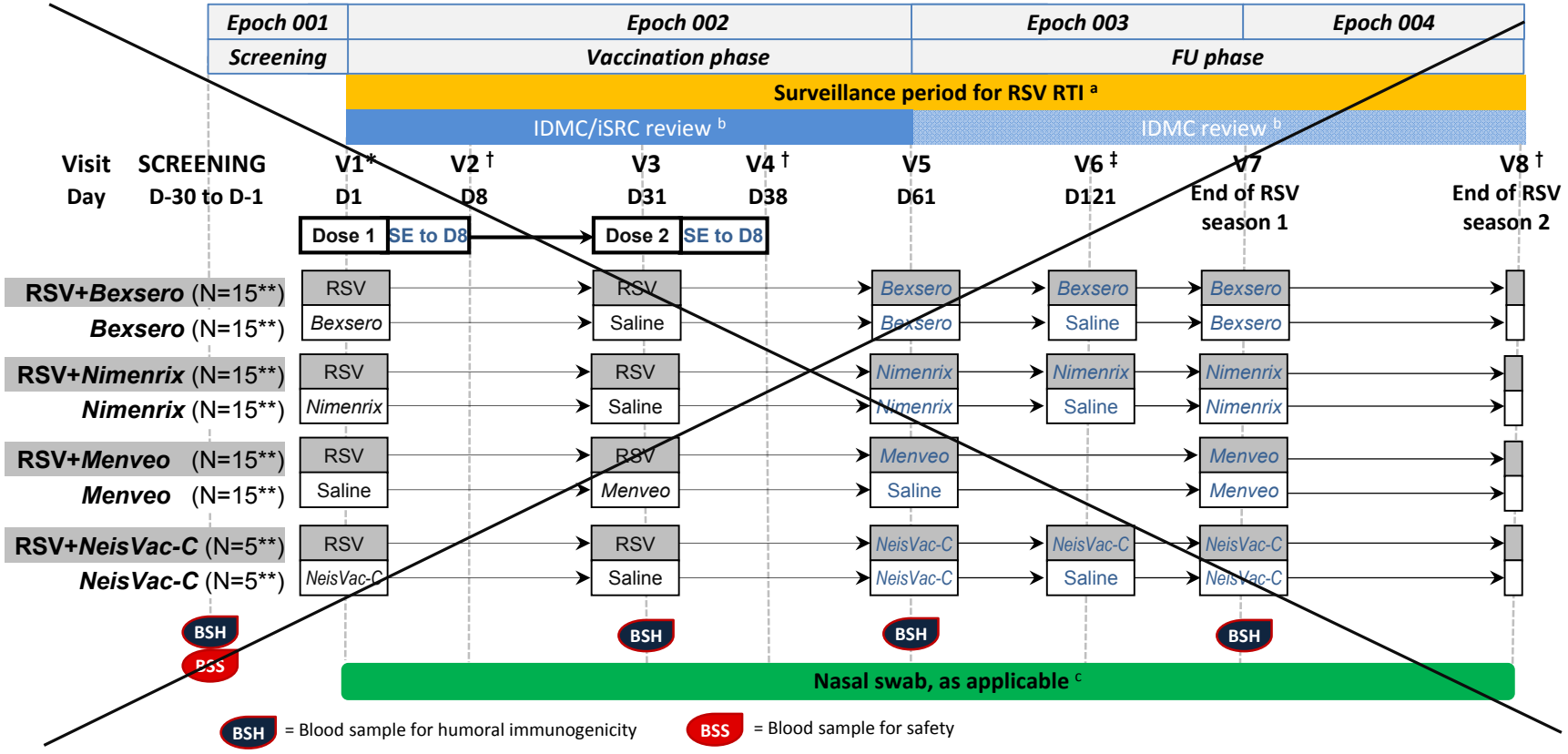
- To evaluate the occurrence of RSV respiratory tract infections ***of any severity*** from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season, in infants aged 6 and 7 months.
- To evaluate the safety of ~~two IM doses of~~ the RSV investigational vaccine ~~(5x10^{10} vp)~~ when administered ***IM as one (1.5x10^{10} vp) dose or as two (5x10^{10} vp) doses*** according to a 0, 1-month schedule, from study start (Day 1) up to the end of the second RSV transmission season in infants aged 6 and 7 months.
- ***To evaluate the occurrence of very severe RSV-LRTI from Visit 1 (Day 1, after Dose 1) up to the end of the first RSV transmission season in RSV infected infants aged 6 and 7 months with a negative RSV exposure status (at screening based on in-stream baseline serological testing).***
- To evaluate the humoral immunogenicity induced by ~~two IM doses of~~ the RSV investigational vaccine ~~(5x10^{10} vp)~~ when administered ***IM as one (1.5x10^{10} vp) dose or as two (5x10^{10} vp) doses*** according to a 0, 1-month schedule, ***from study start (Day 1)*** up to the end of the first RSV transmission season, in infants aged 6 and 7 months.

The Section 2.3. Tertiary objectives~~s~~ was amended as follows:

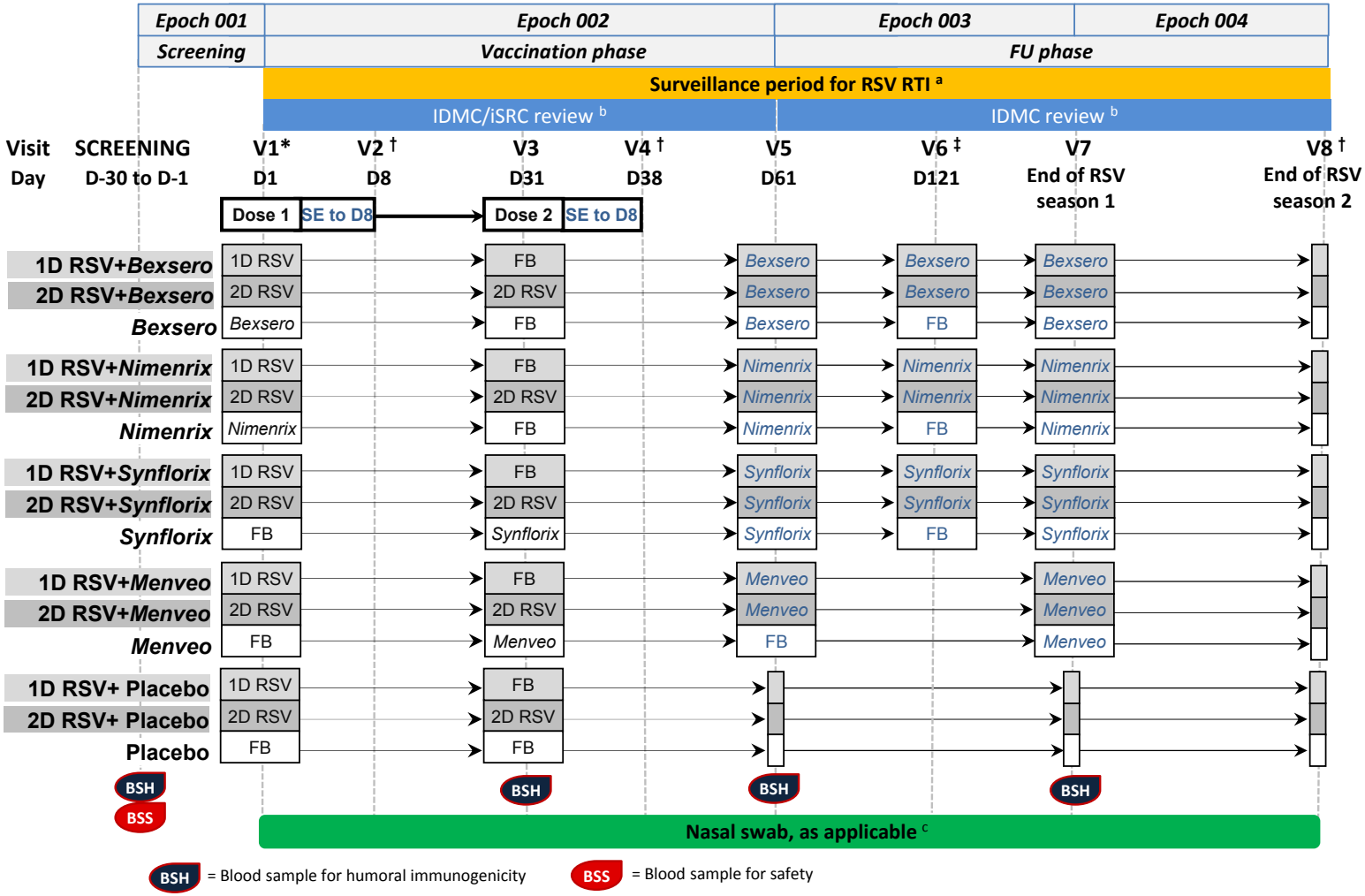
- If deemed necessary, to further characterize the immune response of the RSV investigational vaccine when ***one (1.5x10^{10} vp) dose or*** two ~~IM~~***(5x10^{10} vp)*** doses are administered ***IM*** according to a 0, 1-month schedule ~~in~~***to*** infants aged 6 and 7 months.

The Section 3. STUDY DESIGN OVERVIEW was amended as follows:

~~Old Study Design Figure 1~~



New Study Design Figure 1



D: Day; **FU**: follow-up; **IDMC**: Independent Data Monitoring Committee; **iSRC***:* internal Safety Review Committee; **RSV**: respiratory syncytial virus; **RTI:** respiratory tract infection; **SE**: solicited events; **V**: Visit ***1D: 1 Dose (1.5x10[10] vp/dose); 2D: 2 Dose (5x10[10] vp/dose); FB: Formulation buffer S9b***.

***** Vaccine Dose 1 at Day 1 will be administered before the first RSV season (refer to Section 5.1 for definition of RSV season).

~~** Total number of infants in administered the ChAd155-RSV vaccine = approximately 50 and in the active control comparator groups = approximately 50.~~

† Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8~~ (Day 730)~~ (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator***. For the United Kingdom (UK) only, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.***)

‡ In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

[a] Surveillance for RSV-RTI comprises monthly nasal swab collected to detect asymptomatic RSV infections during RSV season and active and passive surveillance contacts for RSV symptomatic RTI. Of note the swab may be omitted if a nasal swab has been taken at a symptomatic visit in the same month (see Section 9.2). Data about RSV–RTI incidence will be reviewed monthly by an IDMC.

[b] An iSRC will review all accumulating safety data monthly until the IDMC reviews has reviewed all safety data up to 30 days after administration of Dose 2 (i.e., Day 61). The IDMC will review all accumulating safety data monthly throughout the period of vaccination and accumulating SAEs until the end of the second RSV transmission season. Refer to Sections 9.10.2 and 9.10.3.

[c] Refer to Section 6.6.12.3.

~~Old Vaccines administered and vaccination schedules Table 2~~

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	**7-8 / (V3, D31)**	**8-9 / (V5, D61)**	**10-11 / (V6, D121)****	**14-18 / (V7)**
RSV + *Bexsero*	RSV ChAd	RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	Saline	*Bexsero*	Saline	*Bexsero*
RSV + *Nimenrix*	RSV ChAd	RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	Saline	*Nimenrix*	Saline	*Nimenrix*
RSV + *Menveo*	RSV ChAd	RSV ChAd	*Menveo*		*Menveo*
Menveo	Saline	*Menveo*	Saline		*Menveo*
RSV + *NeisVac-C*	RSV ChAd	RSV ChAd	*NeisVac-C*	*NeisVac-C*	*NeisVac-C*
NeisVac-C	*NeisVac-C*	Saline	*NeisVac-C*	Saline	*NeisVac-C*

New Vaccines administered and vaccination schedules Table 2

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	**7-8 / (V3, D31)**	**8-9 / (V5, D61)**	**10-11 / (V6, D121)****	**14-18 / (V7, D365)**
1D RSV + Bexsero	***1D RSV ChAd***	***FB***	***Bexsero***	***Bexsero***	***Bexsero***
2D RSV + *Bexsero*	***2D*** RSV ChAd	***2D*** RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	***FB***	*Bexsero*	***FB***	*Bexsero*
1D RSV + Nimenrix	***1D RSV ChAd***	***FB***	***Nimenrix***	***Nimenrix***	***Nimenrix***
2D RSV + *Nimenrix*	***2D*** RSV ChAd	***2D*** RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	***FB***	*Nimenrix*	***FB***	*Nimenrix*
1D RSV + Synflorix	***1D RSV ChAd***	***FB***	***Synflorix***	***Synflorix***	***Synflorix***
2D RSV + ***Synflorix***	***2D*** RSV ChAd	***2D*** RSV ChAd	***Synflorix***	***Synflorix***	***Synflorix***
Synflorix	***FB***	***Synflorix***	***Synflorix***	***FB***	***Synflorix***
1D RSV + Menveo	***1D RSV ChAd***	***FB***	***Menveo***		***Menveo***
2D RSV + Menveo	***2D RSV ChAd***	***2D RSV ChAd***	***Menveo***		***Menveo***
Menveo	***FB***	***Menveo***	***FB***		***Menveo***
1D RSV + Placebo	***1D RSV ChAd***	***FB***			
2D RSV + ***Placebo***	***2D*** RSV ChAd	***2D*** RSV ChAd			
Placebo	***FB***	***FB***			

V: Visit; **D:** Day; ***1D: 1 Dose (1.5x10^{10} vp/dose); 2D: 2 Dose (5x10^{10} vp/dose)*; RSV ChAd**: ~~Treatment with~~ ChAd155-RSV vaccine ~~(5x10^{10} vp);~~ **~~V:~~** ~~Visit.~~*; FB: Formulation buffer S9b*.

* Assumes enrolled at 6 and 7 months of age for the vaccine Dose 1 to be administered before the first RSV season; ***the second dose will be given one month after the first dose***. (RSV seasons will be determined for each country based on local epidemiological data [The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. Refer to the SPM for RSV seasons per ~~site.]~~***country***.])

** In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7.

- Experimental design: Phase I/II, ~~N/A~~***observer-blind***, randomized, controlled, multi-centric study with ~~two~~***three*** parallel groups.

  – Epoch 004: follow-up starting after Visit 7 (end of the ~~second~~***first*** RSV transmission season)* and ending at Visit 8 (end of the second RSV transmission season).

  *Any safety, immunogenicity and disease surveillance data collected beyond Visit 5 (Day 61) will be collected in Epoch 003. Any safety, immunogenicity and disease surveillance data collected beyond Visit 7 (end of the first RSV transmission season) will be collected in Epoch 004. ***Refer to the SPM for RSV transmission seasons per country***.

  ~~** Refer to the SPM for RSV transmission seasons per site.~~

- Primary Completion Date (PCD): Visit 5 (Day 61).

Refer to glossary of terms for the definition of PCD.

- End of Study (EoS): Last testing results released of samples collected at Visit 8 (end of the second RSV transmission season~~).*~~) ***related to primary and secondary endpoints.*)**

  * Up to Visit 8 (end of the second RSV season), there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season ~~and~~***or*** if following active or a passive surveillance contacts, a subject presents symptoms of respiratory tract infection (RTI), a nasal swab will be collected.

Refer to ***the*** glossary of terms for the definition of EoS.

~~Old Study groups and epochs foreseen in the study Table 3~~

Study groups	Number of subjects*	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
RSV + *Bexsero*	15 **	6 – 7 months	x	x	x	x
RSV + *Nimenrix*	15 **	6 – 7 months	x	x	x	x
RSV + *Menveo*	15 **	6 – 7 months	x	x	x	x
RSV + *NeisVac-C*	5 **	6 – 7 months	x	x	x	x
Bexsero	15 **	6 – 7 months	x	x	x	x
Nimenrix	15 **	6 – 7 months	x	x	x	x
Menveo	15 **	6 – 7 months	x	x	x	x
NeisVac-C	5 **	6 – 7 months	x	x	x	x

New Study groups and epochs foreseen in the study Table 3

Study groups	Numbers of subjects*	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
1D RSV + Bexsero	***50****	6 – 7 months	***N/A***	***x***	***x***	***x***
1D RSV + Nimenrix		6 – 7 months	***N/A***	***x***	***x***	***x***
1D RSV + Synflorix		***6 – 7 months***	***N/A***	***x***	***x***	***x***
1D RSV + Menveo		6 – 7 months	***N/A***	***x***	***x***	***x***
1D RSV + Placebo		***6 – 7 months***	***N/A***	***x***	***x***	***x***
2D RSV + Bexsero	***50****	6 – 7 months	***N/A***	x	x	x
2D RSV + Nimenrix		6 – 7 months	***N/A***	x	x	x
2D RSV + Synflorix		***6 – 7 months***	***N/A***	***x***	***x***	***x***
2D RSV + Menveo		6 – 7 months	***N/A***	x	x	x
2D RSV + Placebo		***6– 7 months***	***N/A***	***x***	***x***	***x***
Bexsero	***50****	6 – 7 months	***N/A***	x	x	x
Nimenrix		6 – 7 months	***N/A***	x	x	x
Synflorix		***6 – 7 months***	***N/A***	***x***	***x***	***x***
Menveo		6 – 7 months	***N/A***	x	x	x
Placebo		***6 – 7 months***	***N/A***	***x***	***x***	***x***

1D: 1 Dose (1.5x10[10] vp/dose); **RSV**: ChAd155-RSV vaccine; ***2D: 2 Dose (5x10[10] vp~~).~~/dose); N/A: Not Applicable***.

* Note that ~~across all~~***for both 1D and 2D*** RSV ***vaccine + active comparator/placebo*** groups the total number of subjects is ~~50~~***10***0 and that for ~~each~~***both*** RSV ***vaccine*** + active comparator***/placebo groups*** there will be a 1:1***:1*** ratio maintained with the ~~same~~corresponding active comparator***./placebo group***.)

** Note that the~~se~~ ***numbers of subjects anticipated to receive the control vaccines within participating countries are*** ~~approximation of~~***not yet known, but*** the distribution and supplies will be prepared to allow flexible enrolment across countries (for any comparator the range of subjects is 0 – ***50*** may be enrolled) but the overall total of ***15***~~0~~0 subjects will be respected.

~~Old Study groups and treatment foreseen in the study Table 4~~

Treatment name	Vaccine/ Product name	Study Groups							
		RSV + *Bexsero*	RSV + *Nimenrix*	RSV + *Menveo*	RSV + *NeisVac-C*	*Bexsero*	*Nimenrix*	*Menveo*	*NeisVac-C*
RSV ChAd	ChAd155-RSV	x	x	x	x				
Saline	FB					x	x	x	x
Bexsero	*Bexsero*	x				x			
Nimenrix	*Nimenrix*		x				x		
Menveo				x				x	
NeisVac-C	*Neiss Vac-C*				x				x

New Study groups and treatment foreseen in the study Table 4

Treatment name	***1D RSV ChAd***	***2D RSV ChAd***	***Bexsero***	***Nimenrix***	***Synflorix***	***Menveo***	***FB***
Vaccine/ Product name	***1D ChAd155-RSV 1.5X10[10] vp/dose***	***2D ChAd155-RSV 5X10[10] vp/dose***	***Bexsero***	***Nimenrix***	***Synflorix***	***Menveo***	***FB***
Study Groups							
1D RSV + Bexsero	***x***		***x***				***x***
1D RSV + Nimenrix	***x***			***x***			***x***
1D RSV + Synflorix	***x***				***x***		***x***
1D RSV + Menveo	***x***					***x***	***x***
1D RSV + Placebo	***x***						***x***
2D RSV + Bexsero		***x***	***x***				
2D RSV + Nimenrix		***x***		***x***			
2D RSV + Synflorix		***x***			***x***		
2D RSV + Menveo		***x***				***x***	
2D RSV + Placebo		***x***					
Bexsero			***x***				***x***
Nimenrix				***x***			***x***
Synflorix					***x***		***x***
Menveo						***x***	***x***
Placebo							***x***

ChAd155-RSV: Chimpanzee Adenovirus Type 155 RSV vaccine ~~(5x1010 vp);~~ **FB**: Formulation buffer S9b; **RSV ChAd**: ~~Treatment with~~ ChAd155-RSV vaccine; ***1D: 1 Dose (1.5x10[10] vp/dose); 2D: 2 Dose (5x10[10] vp~~).~~/dose)***.

- ~~Control: meningococcal vaccine~~Control***s***: active ~~controls~~***comparator vaccines*** (*Bexsero*, or *Nimenrix*, ***or Synflorix,*** or *Menveo*, or ~~*NeisVac-C*) and saline (Formulation buffer S9b).~~*Placebo ***(FB)****.

  * The choice of active ~~control~~ comparator ~~meningococcal~~ vaccine (Bexsero, Nimenrix, **Synflorix**, or Menveo) **or** ~~NeisVac-C)~~**Placebo** is done at the country level. **Refer to the ICF for the local choice of comparator/Placebo.**

- Vaccination schedules:

  – RSV investigational vaccine:

    o ***In the 1 Dose (1D) groups, a*** single ***lower*** dose ***of 1.5x10[10] vp will be administered IM at Day 1 (Visit 1). Formulation buffer will be administered in the 1D groups at Day 31 (Visit 3). In the 2 Dose (2D) groups,*** two ~~IM vaccine~~ doses ***of 5x10[10] vp will be administered IM*** according to a 0, 1-month schedule, (i.e., at Day 1 ***[Visit 1]*** and Day 31 ***[Visit 3]***) ***(see Figure 1 and Table 2)*** ~~(~~Dose 1 will be administered before the first RSV season ~~[~~***and the second dose will be given one month after the first dose*** (RSV seasons will be determined for each country based on local epidemiological data~~.~~ ***and documented in the Study Procedures Manual [SPM].*** The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable~~. Refer to the SPM for RSV seasons per site.]~~).

- ***Comparator*** or ***Placebo***:
  - ***In countries where*** *Bexsero* ***or*** *Nimenrix* ~~For *Bexsero, Nimenrix,* and *NeisVac-C*~~ ***is used as a control***, two ~~primary~~ doses will be administered IM with at least a 2 month interval ~~with a~~***between these primary doses***. ***A*** booster dose ***will be*** administered IM in the second year of life ~~(~~at ***Day 365*** (Visit 7), with an interval of at least 2 months between the primary series and booster dose. ***The first Bexsero or Nimenrix dose will be administered at Day 1 (Visit 1) (in the groups receiving only Bexsero or Nimenrix, respectively). In the groups receiving only Bexsero or Nimenrix, the second dose will be at Day 61 (Visit 5). The first Bexsero or Nimenrix dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of Bexsero or Nimenrix in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits*** (see ***Figure 1 and Table 2***).
  - ***In countries where Synflorix is used as a control, two doses will be administered IM with at least a 1 month interval between these primary doses. A booster dose will be administered IM in the second year of life at Day 365*** (***Visit 7). The first Synflorix dose will be administered at Day 31 (Visit 3) (in the group receiving only Synflorix). In the group receiving only Synflorix, the second dose will be at Day 61 (Visit 5). The first Synflorix dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of Synflorix in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Figure 1 and Table 2).***
  - In countries where *Menveo* is used as a control, two doses will be administered IM at least 3 months apart with the second dose in the second year of life~~.~~ ***at Day 365*** (***Visit 7)***. The first *Menveo* dose will be administered ~~as a comparator~~ at ***Day 31 (***Visit 3~~ (opposing the second RSV vaccine dose) from 7 months of age.~~***) (in the group receiving only Menveo)***. The first *Menveo* dose to be administered to the ***1D and 2D*** RSV group***s*** will be at ***Day 61 (***Visit 5***)***, following the ***1 or 2*** RSV vaccine ~~administrations.~~***doses, respectively***. Since the second *Menveo* dose has to be administered in the second year of life~~,~~ ***at Day 365*** (***Visit 7)***, no administration will be performed at ***Day 121*** ~~and therefore in those countries the second *Menveo* dose~~***(Visit 6). Formulation buffer will be*** ~~at Visit 7, at the end of the first RSV season (refer to~~***administered, when neither RSV vaccine or comparator is scheduled, at the 4 vaccination visits*** (***see Figure 1 and*** Table 2).
  - ***In countries where Placebo is used as a control, one dose will be administered IM at Day 31 (Visit 3) in the 1D RSV + Placebo group and two IM doses will be administered IM according to a 0, 1-month schedule at Day 1 (Visit 1) and Day 31 (Visit 3) in the Placebo group (see Figure 1 and Table 2).***

- Treatment allocation: infants will be randomized using a centralized randomization system on internet (SBIR) before first vaccination and after assessment of eligibility (i.e., after screening conclusion) (refer to Section 6.2.2 for details about randomization of treatment). The randomization algorithm will use a minimization procedure accounting for country~~.~~ ***as a minimization factor and the grouping comparator/placebo as a stratification factor.***
- Sampling schedule:
  - Nasal swab: there will be monthly nasal swab to detect asymptomatic RSV infections during the RSV season and if following active or a passive surveillance contacts, a subject presents symptoms of RTI, a nasal swab will be collected~~.~~ ***(as well as a sample for local testing i.e., the type of sample to be determined locally [e.g., swab, etc.]) (Refer to the SPM)***.
- Study visits: Other than the screening visit and assessment visits for active/passive surveillance, there will be 8 study visits except in countries where *Menveo* ***or Placebo*** is used as a control where there will be 7 study visits.
  - In countries where *Menveo* is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7). ~~Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (Day 730) (no blood sampling for immune response and~~
  - ***In countries where Placebo is used as a control, no vaccine administration***~~)~~ ~~may take place~~ ***will be performed after Visit 3 and therefore in*** ~~the subject's home or~~***those countries there will be no Visit 6. There will be a Visit 5 and Visit 7 for countries using Placebo and all other study procedures will occur at*** ~~the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.~~***these visits except vaccination.***
  - ***Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (Day 730) (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.***
    - ***For the United Kingdom (UK) only, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.***

Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination, in order to detect any thrombocytopenic petechiae or purpura. ***The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets.***

In the Section 4.1. RTI case definitions, the Case definitions for data analysis Table 6 was amended as follows:

Case	*At sea level up to 2500 meters elevation*	*Above 2500 meters elevation*
RSV-RTI	Runny nose OR blocked nose OR cough AND Confirmed RSV infection [4]	***Same***
RSV-LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3] AND Confirmed RSV infection [4]	***Same but with SpO2 <92%***
~~**RSV-** **severe *RSV*-LRTI**	Meeting the case definition of RSV-LRTI AND SpO_2 < 93% [2], OR lower chest wall in-drawing	***Same but with SpO2 <90%***
~~**RSV-** **very severe *RSV*-LRTI**	Meeting the case definition of RSV-LRTI AND SpO_2 < 90% [2], OR inability to feed, OR failure to respond / unconscious	***Same but with SpO2 <88%***
RSV hospitalization	Confirmed RSV infection [5] AND Hospitalized for acute medical condition [6]	***Same***
All-cause LRTI	History of cough OR difficulty breathing [1] AND SpO_2 < 95% [2], OR RR increase [3]	***Same but with SpO2 <92%***

LRTI = lower respiratory tract infections; **RR** = respiratory rate; **RTI** = respiratory tract infections; **SpO2** = blood oxygen saturation.

Based on [Modjarrad, 2016]

[1] Based on history reported by parents~~/LARs and includes difficulty breathing (e.g., showing signs of wheezing or stridor, tachypnoea, flaring [of nostrils], chest in-drawing, apnoea) associated with nasal obstruction.~~

In Section 5. STUDY COHORT, the Section 5.1. Number of subjects was amended as follows:

The target will be to enroll approximately ***150***~~0~~ infants ~~(50 infants in the vaccine group and 50 infants in the control group) aged 6 and 7 months at the time of first vaccination,~~ likely to be ***previously*** unexposed to RSV~~.~~ ***with about 50 infants for each of three randomization groups. If necessary, the sample size will be increased through additional recruitment in order to achieve at least 5 RSV infected infants***, ***with a negative RSV exposure status (at screening based on in-stream serological testing), in each RSV vaccine group.*** Dose 1 administration should be completed before the first RSV season ***and second dose will be given one month after the first dose*** (RSV seasons will be determined for each country based on local epidemiological data ~~[~~***and documented in the SPM***. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. Refer to the SPM for RSV seasons per ~~site.])~~.***country***. Refer to Section 11.4 for the determination of sample size.

In the Section 5.3. Exclusion criteria for enrolment the following changes have been made:

- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day (for pediatric subjects), or equivalent. ~~Inhaled and topical~~***T***opical steroids are allowed.
- History of recurrent wheezing. ~~(~~***("Recurrent wheezing" is defined as ≥ 2 episodes of wheezing ~~in the past 12 months~~).*** Wheezing should have been verified on auscultation by doctor).
- History of any reaction or hypersensitivity ~~likely~~ to ~~be exacerbated by~~ any component of the vaccine***s (investigational or control) or placebo used in this study or any contraindication to them.***
- Concurrently participating in another clinical study, at any time during the study period, in which the subject ***or mother*** has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- ***For Thailand only, subjects who have received Synflorix prior to enrolment.***)

In the Section 6.2.2.2. Treatment allocation to the subject the following change was made:

The treatment numbers will be allocated by ~~dose.~~***components***.

The Section 6.2.2.2.1. Study group and treatment number allocation was amended as follows:

The target will be to enroll approximately ***150***~~0~~ infants~~ to ensure that 50 infants receive at least one dose of RSV investigational vaccine.~~ Approximately 50 infants likely to be ***previously*** unexposed to RSV will be randomly assigned to receive ***2 doses at 0, 1 month schedule of*** 0.5 mL of the ChAd155-RSV vaccine ($5x10^{10}$ vp) ***[the 2D RSV + comparator group], approximately 50 infants likely to be previously unexposed to RSV will be randomly assigned to receive a single dose of 0.5 mL of ChAd155-RSV vaccine ($1.5x10^{10}$ vp) [the 1D RSV + comparator group],*** and approximately 50 infants likely to be ***previously*** unexposed to RSV will be randomly assigned to receive 0.5 mL of the ~~active~~comparator***/Placebo control*** ~~comparator~~ vaccine~~.~~ ***[the comparator/Placebo control alone group]***.

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR) operated at the study level.

The randomization algorithm will assign each subject to ~~either an~~***the 2 doses of*** RSV ***vaccine*** + comparator ~~vaccine~~ group***, the single dose of RSV vaccine + comparator group,*** or its corresponding active control comparator group with the aim of keeping the ratio between the pooled ***2 dose*** RSV ~~group~~ ***+ comparator*** group***, the pooled single dose RSV + comparator group*** and the pooled comparator group at 1:1***:1*** in the entire study (see Table 25 for a description of pooled groups).

Countries will be grouped into ~~four~~***five*** levels according to the choice of comparator vaccine ~~and the grouping factor will be applied as a single factor (the only factor) in the minimization~~ ***or Placebo, the randomization algorithm will use a minimization procedure accounting for country as a minimization factor and the grouping comparator/placebo as a stratification factor*** to ~~assure that~~***attempt to maintain*** a 1:1***:1*** ratio ~~is maintained~~***as well*** within each level in the assignment of RSV + comparator vaccine versus comparator~~-~~***/Placebo control*** vaccine alone.

The actual randomization assignment the subject received (to one of ~~four~~ ***five 2 dose of*** RSV + comparator vaccine groups~~ or~~***, to one of*** ~~four active control~~ ***five single dose of RSV + comparator vaccine groups, or to one of five comparator/Placebo control*** alone groups) will be able to be identified in SBIR.

In Section 6.5. Outline of study procedures, the **List of study procedures Table 7** had the following key changes:

Epoch	**Epoch 001**	**Epoch 002**					**Epoch 003**		**Epoch 004**				
Age	**6-7 months**	**6-9 months**											
Type of contact	**Screening**	**Visit 1**	**Visit 2** [b]	**Visit 3**	**Visit 4** [b]	**Visit 5**	**Visit 6** [c]	**Visit 7**	**Visit 8** [b]	**Unscheduled visit for safety** [e]	**Contact for active/ passive surveillance** [f]	**Surveillance for asymptomatic RSV-RTI** [g]	**Assessment of potential RSV-RTI** [h]
Timepoints	**D -30 to D-1** [a]	**D1**	**D8**	**D31**	**D38**	**D61**	**D121**	**D365 end of the 1st RSV season** [d]	**D730 end of the 2nd RSV season** [d]		**Monthly or Weekly**	**Monthly**	
30 minutes post-vaccination observation for additional comparator/~~saline~~***FB*** vaccinations						O	O	O					
Surveillance for RSV-RTI, difficulty in breathing and wheezing		O	O	O	O	O	O	O	O		~~●~~***O***	~~●~~***O***	
Recording of AESI (spontaneous or excessive bleeding) [z]		●	●	●	●	●				●			
Reporting of easy bruising, or rash/petechiae monitored by parent(s)/LAR(s) [z]		***O***	***O***	***O***	***O***	***O***							

AE: adverse event; AESI: Adverse Events of Special Interest; ***FB: Formulation buffer S9b***; LRTI: lower respiratory tract infection; RSV: respiratory syncytial virus; RTI: respiratory tract infection, RVP: respiratory viral panel SAE: serious adverse event.

[b] ***Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (Day 730) (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator. Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator.***

[c] In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Figure 1 and ~~).~~Table 2***).***

[d] Refer to the SPM for RSV seasons per ~~site.~~***country***.

[r] ***If no blood sample was collected for humoral immunogenicity at the screening visit, an additional blood sample will be taken at Visit 1 that must***~~Samples to~~ ***be taken before vaccination.***

[s] Samples ***must*** be taken before vaccination.

[z] Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination, in order to detect any thrombocytopenic petechiae or purpura~~.~~ ***(see*** Table 19***).***

The footnotes in the Intervals between study visits Table 8 have been amended as follows:

[1] Visit 1 should take place no longer than 30 days after the Screening visit. When applicable, a re-screening visit may be scheduled at any time (but only once to assess eligibility~~; blood for humoral response will not be re-sampled).~~ All screening procedures need to be performed within 30 days of Visit 1.

[2] In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Figure 1and Table 2).

In Section 6.6.11. Study vaccines administration, the following change has been made:

The subjects will be observed closely (visual follow-up as well as measurement of resting vital signs) for at least 60 minutes following the administration of the vaccines at Visit 1 and Visit 3, with appropriate medical treatment readily available in case of anaphylaxis. Vital signs are body temperature, HR and RR. Vital signs are preferably measured when the infant is calm. After administration of comparator vaccines or ~~saline~~***FB*** at Visit 5, Visit 6 and Visit 7, the subjects will be observed closely (visual follow-up as well as measurement of resting vital signs) for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

In Section 6.6.12.1. Blood sampling for humoral immunity, the following changes have been made:

- Blood sampling for humoral response will not be repeated in case of insufficient volume, at any timepoint~~.~~ ***except if no blood sample for humoral immunogenicity was collected at the screening visit. In that case an additional blood sample will be taken at Visit 1 that must be taken before vaccination***.

In Section 6.6.12.2. Blood sampling for hematology and biochemistry, the following changes have been made:

*Note: Blood ~~can~~**may** be re-sampled for hematology and biochemistry assessment **during a re-screening visit (as described above) or during an Unscheduled Visit** where there is clinical indication for additional testing.*

In Section 6.6.12.3. Nasal swab ~~and~~*or* other specimen for ~~local~~*PCR* assay, the following changes have been made:

Nasal swab ~~and~~*or* other specimen for ~~local~~*PCR* assay collected during assessment visit

Real time assessment of potential RSV-LRTI cases is important for the timely monitoring of safety.

If during passive or active surveillance contact, the investigator/study staff assesses that an infant presents a potential RSV-RTI (refer to Section 9.2), a nasal swab ~~and~~***or*** another specimen for ~~local~~ assay will be collected during an assessment visit:

- The nasal swab will allow assessing the potential RSV infection by quantitative RT-PCR ***and respiratory viral panel (RVP)*** at sponsor laboratory.

- The specimen for local assay will allow assessing the potential RSV infection and ~~respiratory viral panel (~~***RVP***~~)~~ at a local routine laboratory, where available. The specimen type will depend on the assay run locally.

Nasal swab collected *for PCR assay* to detect asymptomatic RSV infections

During RSV season, there will be monthly nasal swabs to detect asymptomatic RSV infections. These nasal swabs will allow assessing the potential RSV infection by quantitative RT-PCR ~~at~~***performed centrally at the*** sponsor laboratory. This swab may be omitted upon investigator discretion if a swab has been taken for a symptomatic episode in the previous 4 weeks.

In the Section 6.7.2. Biological samples the Biological samples Table 9 was amended as follows:

Sample	Timepoint	Type of sample†	Subject	Number of subjects	Quantity
Blood	Screening	Blood sample for hematology and biochemistry	All infants	≥ 1***5***0	2.3 mL
		Blood sample for humoral response #	All infants	≥ 1***5***0	2.5 mL
		Total volume of blood collected for each subject			**4.8 mL**
	Visit 3 (Day 31)	Blood sample for humoral response	All infants	~1***5***0	2.5 mL
	Visit 5 (Day 61)	Blood sample for humoral response	All infants	~***150***	2.5 mL
	Total volume of blood collected for each subject from Screening to Visit 5 (Day 61)*				**9.8 mL**
	Visit 7 (end of the first RSV transmission season)	Blood sample for humoral response	All infants	~1***5***0	2.5 mL
	Assessment of potential RSV-RTI	Blood sampling for assessment of mechanisms of illness (potential ERD)	Hospitalization for RSV-LRTI (only for RSV-positive subjects using a locally available RSV test)	Hospitalization for RSV-LRTI (only for RSV-positive subjects using a locally available RSV test)	2.5 mL
	Unscheduled visit for safety	Blood sample for hematology and biochemistry	Event-driven	Event-driven	2.3 mL
	Total volume of blood collected for each subject from Screening to Visit 8 (end of the second RSV transmission season)*				**12.3 mL**
Nasal swab	Assessment of potential RSV-RTI	Nasal swab**	Event-driven	Event-driven	-
	Surveillance for asymptomatic RSV-RTI	Nasal swab***	All infants	~1***5***0	-

† The priority ranking in blood sampling is hematology > biochemistry > humoral response.

Venipuncture will not be repeated for humoral response in case of insufficient volume, at any timepoint~~.~~ ***except if no blood sample for humoral immunogenicity was collected at the screening visit. In that case an additional blood sample will be taken at Visit 1 that must be taken before vaccination***.

* Total quantity of blood for each subject excludes any optional or unscheduled hematology and biochemistry blood sampling or blood sample for assessment of mechanism of illness collected if a subject has been hospitalized for RSV-LRTI.

** If during passive or active surveillance contact, the investigator/study staff assesses that an infant presents a potential RSV-RTI (refer to Table 6 for definition), the potential RSV infection will be assessed by quantitative RT-PCR of nasal swab specimens taken at an assessment visit.

*** During RSV season, there will be monthly nasal swabs to detect asymptomatic RSV infections. These swabs will be tested by quantitative RT-PCR at sponsor laboratory.

These assays will be performed only on enrolled infants~~.~~ ***and samples from non-enrolled subjects will be discarded.***

In Section 6.7.3. Laboratory assays, the following changes have been made:

Determination of a negative RSV exposure status in infants at 6 to 7 months of age will be based on RSV A and/or B neutralizing antibody titers present in serum at screening (before vaccination with the RSV vaccine) based on in-stream baseline serological testing. At birth, newborns do show positive for neutralizing antibodies due to maternal transfer during gestation. The titer of these antibodies declines over time. At the age of 6 to 7 months a cut-off can be defined below which infants are considered to have a negative RSV exposure status. Infants that show neutralizing antibody titers above this cut-off are suspected to have experienced a recent RSV infection. This cut-off will thus allow the discrimination between a negative RSV exposure status versus RSV infected infants before start of vaccination.

The following laboratory assays are planned:

- Functional (neutralizing) antibody titers against RSV-A will be measured by a neutralization assay on serum samples (Table 10).
- ~~RSV F protein antibody concentrations and palivizumab-competing antibody concentrations will be determined by in-house ELISA on serum sample.~~
- RTI will be assessed by:
  - Quantitative RT-PCR that is able to discriminate RSV-A and RSV-B subtypes (Table 11).
  - Qualitative multiplex PCR for detection of a panel of viruses (Table 11).
  - Local RSV assay, and local RVP where available (Table 11).

Final confirmation of RSV presence will be obtained through the definitive results from the central test.

The Humoral Immunity (Antibody determination) Table 10 was amended as follows:

System	Component	Method	Kit / Manufacturer	Unit	Cut-off*	Laboratory**
SERUM	Respiratory Syncytial Virus A Ab	NEUTRALIZATION	In-house	ED60	To be defined	GSK Biologicals[1] ~~or NÉOMED-LABS~~
SERUM	Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	ELISA	In-house	EU/ml	To be defined	~~GSK Biologicals[1] or~~ NÉOMED-LABS[1]

System	Component	Method	Kit / Manufacturer	Unit	Cut-off*	Laboratory**
~~SERUM~~	~~Respiratory Syncytial Virus F protein Ab.IgG (Palivizumab competing Ab)~~	~~ELISA~~	~~In house~~	~~µg/ml~~	~~To be defined~~	~~GSK Biologicals[1] or NÉOMED-LABS~~

Ab: antibody; **ELISA**: enzyme-linked immunosorbent assay; **IgG**: immunoglobulin G; **RSV**: respiratory syncytial virus
* Assay cut-off and unit might be subject to change ~~during the course of the study~~ (e.g., in case of requalification, revalidation or standardization). In this case, this will be documented in the clinical report.

The Molecular Biology (PCR tests) Table 11 was amended as follows:

System	Component	Kit / Manufacturer	Method	Unit	Laboratory*
Nasal swab	RSV A RNA RSV B RNA	In-house	Quantitative RT-PCR	Copies/ml	GSK Biologicals[1] ~~or designated 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) [2]	*Allplex* Respiratory Panel (Seegene) or equivalent [2]	Multiplex PCR (Luminex)	Qualitative assay (positive/ negative)	GSK Biologicals[1] ~~or designated laboratory~~

Additional testing may include, but is not limited to, the following:

- Anti-vector immunity: neutralization.
- ***RSV F protein antibody concentrations and palivizumab-competing antibody concentrations will be determined by in-house ELISA on serum sample.***

The Hematology and biochemistry tests Table 12 was amended as follows:

System	Discipline	Component	Timepoint	Method	Scale	Laboratory
Whole blood	Hematology	Hemoglobin	Screening	As per local practice	Quantitative	Local laboratory
		Leukocytes (White Blood Cells)				
		Lymphocytes				
		Neutrophils				
		Platelets				
Serum	Biochemistry	Alanine Aminotransferase	Screening	As per local practice	Quantitative	
		Aspartate Aminotransferase				
		Creatinine				

At screening repeat testing may be performed once according to Figure 2. At any time during the trial additional hematology and/or biochemistry testing may be performed for the further investigation of a potential AE.

~~Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.~~

The Immunological read-outs Table 13 was amended as follows:

Blood sampling timepoint			No. subjects	Component	Components priority rank
Type of contact and timepoint	**Sampling timepoint**	**System**			
Screening (Day -30 to Day -1)	Pre-Vaccination	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2
				~~Respiratory Syncytial Virus F protein Ab.IgG (Palivizumab competing Ab)~~	~~3~~
Visit 3 (Day 31)	Post-Vaccination 1	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2
				~~Respiratory Syncytial Virus F protein Ab.IgG (Palivizumab competing Ab)~~	~~3~~
Visit 5 (Day 61)	Post-Vaccination 2	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2
				~~Respiratory Syncytial Virus F protein Ab.IgG (Palivizumab competing Ab)~~	~~3~~
Visit 7 (end of the first RSV transmission season)	Post-Vaccination 2	Serum	~ 150	Anti-RSV A Neutralizing Antibody	1
				Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	2

Ab: Antibody; **IgG**: immunoglobulin G; **RSV**: respiratory syncytial virus.

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 13.

The RVP (Multiplex PCR) on specimens from all RSV-A/B positive and confirmed LRTI cases, according to case definition presented in Table 6 (Figure 3), will qualitatively assess the potential co-infections occurring in these subjects. The panel of viruses profiled is presented in Table 14.

The Molecular biology for nasal swab and specimen analysis Table 14 was amended as follows:

~~Blood sampling~~Sampling timepoint			No. subjects	Component	Components priority rank
Type of contact and timepoint	**Sampling timepoint**	**System**			
Surveillance for asymptomatic RSV-RTI	Monthly contact during the RSV season	Nasal swab	~ 150	Quantitative RT-PCR (RSV A RNA and RSV B RNA)	Not applicable

In Section 7.1. Description of study vaccines, the **Study vaccines** Table 15 was amended as follows:

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
1D RSV ChAd	***1D* ChAd155-RSV**	**ChAd155-RSV=3*10^{10}vp/mL**	***Liquid in monodose vial*** †	**0.5 ml**	*1*
2D RSV ChAd	2D ChAd155-RSV	ChAd155-RSV=1*10^{11}vp/mL	Liquid in monodose vial †	0.5 ml	2
~~*Saline*~~ ***Formulation buffer (FB)***	***Formulation buffer S9b***	***Na_2HPO_4=1.3mg; KH_2PO_4=186µg; NaCl=3.85mg; KCl=100µg; $MgCl_2$=50µg***	Clear liquid	0.5 ml	0***, 1*** or 2 ‡
Placebo	***Formulation buffer S9b***	***Na_2HPO_4=1.3mg; KH_2PO_4=186µg; NaCl=3.85mg; KCl=100µg; $MgCl_2$=50µg***	***Clear liquid***	***0.5 ml***	***2***
Bexsero	*Bexsero*	Recombinant Neisseria meningitidis group B NHBA fusion protein=50µg; Recombinant Neisseria meningitidis group B NadA protein=50µg; Recombinant Neisseria meningitidis group B fHbp fusion protein=50µg; Outer membrane vesicles (OMV) from Neisseria meningitidis group B strain NZ98/254=25µg; $Al(OH)_3$=500µg Al3+	White opalescent liquid suspension for injection in pre-filled syringe	0.5 ml	3
Nimenrix	*Nimenrix* § MenACWY-TT	PSA=5µg TT; PSC=5µg TT; PSW_{135}=5µg TT; PsY=5µg TT; TT~=44µg	White powder or cake in a single dose glass vial	0.5 ml	3
	Nimenrix § NaCl	NaCl=150mM	Sodium chloride as a clear liquid for suspension		
Menveo	*Menveo* ¥ MenA lyo	MenA=10µg,CRM197=16.7-33.3µg; KH_2PO_4=5mM; Sucrose=12.5mg	Lyophilized component in a vial	0.5 ml	2
	Menveo ¥ MenCWY liquid	MenC=5µg,CRM197=7.1-12.5µg; MenW=5µg,CRM197=3.3-8.3µg; MenY=5µg,CRM197=5.6-10µg; NaCl=4.5mg; Na_3PO_4=10mM; NaH_2PO_4=2.5mM; Na_2HPO_4=7.5mM; water=0.5ml	Liquid component in a vial		

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
~~*NeisVac-C*~~ ***Synflorix***	~~*Neiss Vac-C*~~ ***Synflorix 10Pn-PD-DiT***	~~MenC=10µg TT, TT=10-20µg; Al=500µg~~ ***PS1=1µg PD; PS4=3µg PD; PS5=1µg PD; PS6B=1µg PD; PS7F=1µg PD; PS9V=1µg PD; PS14=1µg PD; PS18C=3µg TT; PS19F=3µg DT; PS23F=1µg PD; PD=9-16µg; DT=3-6µg; TT=5-10µg; $AlPO_4$=500µg Al3+***	~~Semi-opaque~~ ***Turbid white*** ~~to off-white~~ ***suspension***	***0.5 ml***	***3***

† Clear, colorless solution free from visible particles.

‡ The number of ~~Saline~~***Formulation buffer*** doses depends on the study arm and study country (see Table 2).

§ MenACWY-TT, a white powder or cake, is resuspended with a NaCl solution, to make *Nimenrix*.

¥ MenA lyo, a lyophilized component, is resuspended with MenCWY liquid, to make *Menveo*.

**** Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the vaccination visits (see Figure 1, Table 2 and Table 16).***

In Section 7.2. Storage and handling of study vaccine, the following changes were made:

For the ~~saline~~***Placebo [S***aline***]*** (Formulation buffer S9b) and for the active control comparator ~~meningococcal~~ vaccines (*Bexsero*, *Nimenrix,* ***Synflorix*** and *Menveo* ~~and *NeisVac-C*~~) any temperature excursion outside the range of 2.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) and for the ChAd155-RSV vaccine any temperature excursion above -60°C (for ≤ -60°C/≤ -76°F label storage condition) ~~or below -80.0°C~~ must be reported in the appropriate (electronic) temperature excursion decision form. The impacted investigational medicinal products (IMPs) must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

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.

Refer to the SPM for more details on aspects vaccine handling including disposal of waste and management of accidental spills.

In Section 7.3. Dosage and administration of study vaccines, the following changes were made:

The first IM dose of ChAd155-RSV vaccine must be administered before the first RSV season ~~(RSV seasons will be determined for each country based on local epidemiological data.~~ ***while the second dose (when applicable) will be given one month after the first dose. The volume to be administered for each IM vaccination will be 0.5 mL in the anterolateral thigh. The preferable side for administration is the left side. If for some reason the left side cannot be used, please ensure the subsequent doses are administered on the same side as the first dose. In the second year of life at Day 365 (Visit 7) if the muscle size is adequate, the site of administration can be the deltoid on the left side.***

The Dosage and administration Table 16 was amended as follows:

~~Old Dosage and administration Table 16~~

Type of contact and timepoint	Volume to be administered	Study group	Treatment name[4]	Route[1]	Site		
					Location	Direction	Laterality
Visit 1 (Day 1)	0.5 ml	RSV + *Bexsero*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Nimenrix*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Menveo*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *NeisVac-C*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	*Bexsero*	*Bexsero*	IM	Antlat Thi	NA	Left
	0.5 ml	*Nimenrix*	*Nimenrix*	IM	Antlat Thi	NA	Left
	0.5 ml	*Menveo*	Saline	IM	Antlat Thi	NA	Left
	0.5 ml	*NeisVac-C*	*NeisVac-C*	IM	Antlat Thi	NA	Left
Visit 3 (Day 31)	0.5 ml	RSV + *Bexsero*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Nimenrix*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Menveo*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *NeisVac-C*	RSV ChAd	IM	Antlat Thi	NA	Left
	0.5 ml	*Bexsero*	Saline	IM	Antlat Thi	NA	Left
	0.5 ml	*Nimenrix*	Saline	IM	Antlat Thi	NA	Left
	0.5 ml	*Menveo*	*Menveo*	IM	Antlat Thi	NA	Left
	0.5 ml	*NeisVac-C*	Saline	IM	Antlat Thi	NA	Left
Visit 5 (Day 61)	0.5 ml	RSV + *Bexsero*	*Bexsero*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Nimenrix*	*Nimenrix*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Menveo*	*Menveo*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *NeisVac-C*	*NeisVac-C*	IM	Antlat Thi	NA	Left
	0.5 ml	*Bexsero*	*Bexsero*	IM	Antlat Thi	NA	Left
	0.5 ml	*Nimenrix*	*Nimenrix*	IM	Antlat Thi	NA	Left
	0.5 ml	*Menveo*	Saline	IM	Antlat Thi	NA	Left
	0.5 ml	*NeisVac-C*	*NeisVac-C*	IM	Antlat Thi	NA	Left
Visit 6 (Day 121) [5]	0.5 ml	RSV + *Bexsero*	*Bexsero*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Nimenrix*	*Nimenrix*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *NeisVac-C*	*NeisVac-C*	IM	Antlat Thi	NA	Left
	0.5 ml	*Bexsero*	Saline	IM	Antlat Thi	NA	Left
	0.5 ml	*Nimenrix*	Saline	IM	Antlat Thi	NA	Left
	0.5 ml	*NeisVac-C*	Saline	IM	Antlat Thi	NA	Left
Visit 7 (end of the first RSV transmission season)	0.5 ml	RSV + *Bexsero*	*Bexsero*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Nimenrix*	*Nimenrix*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *Menveo*	*Menveo*	IM	Antlat Thi	NA	Left
	0.5 ml	RSV + *NeisVac-C*	*NeisVac-C*	IM	Antlat Thi	NA	Left
	0.5 ml	*Bexsero*	*Bexsero*	IM	Antlat Thi	NA	Left
	0.5 ml	*Nimenrix*	*Nimenrix*	IM	Antlat Thi	NA	Left
	0.5 ml	*Menveo*	*Menveo*	IM	Antlat Thi	NA	Left
	0.5 ml	*NeisVac-C*	*NeisVac-C*	IM	Antlat Thi	NA	Left

New Dosage and administration Table 16

Type of contact and timepoint	Study group	Treatment name[1]	Volume to be administered *(0.5 mL)*	Route[2] (*IM*)	Site	
					Location (*Anterolateral Thigh*) [3]	Laterality [4] (Left)
Visit 1 (Day 1)	***1D RSV + Bexsero***	***1D RSV ChAd***	0.5 mL	IM	Anterolateral Thigh	Left
	1D RSV + Nimenrix	***1D RSV ChAd***				
	1D RSV + Synflorix	***1D RSV ChAd***				
	1D RSV + Menveo	***1D RSV ChAd***				
	1D RSV + Placebo	***1D RSV ChAd***				
	2D RSV + *Bexsero*	***2D*** RSV ChAd				
	2D RSV + *Nimenrix*	***2D*** RSV ChAd				
	2D RSV + Synflorix	***2D*** RSV ChAd				
	2D RSV + Menveo	***2D RSV ChAd***				
	2D RSV + Placebo	***2D*** RSV ChAd				
	Bexsero	*Bexsero*				
	Nimenrix	*Nimenrix*				
	Synflorix	***FB***				
	Menveo	***FB***				
	Placebo	***FB***				
Visit 3 (Day 31)	***1D RSV + Bexsero***	***FB***				
	1D RSV + Nimenrix	***FB***				
	1D RSV + Synflorix	***FB***				
	1D RSV + Menveo	***FB***				
	1D RSV + Placebo	***FB***				
	2D RSV + *Bexsero*	***2D*** RSV ChAd				
	2D RSV + *Nimenrix*	***2D*** RSV ChAd				
	2D RSV + Synflorix	***2D*** RSV ChAd				
	2D RSV + Menveo	***2D*** RSV ChAd				
	2D RSV + Placebo	***2D*** RSV ChAd				
	Bexsero	***FB***				
	Nimenrix	***FB***				
	Synflorix	***Synflorix***				
	Menveo	***Menveo***				
	Placebo	***FB***				
Visit 5 (Day 61)	***1D RSV + Bexsero***	***Bexsero***				
	1D RSV + Nimenrix	***Nimenrix***				
	1D RSV + Synflorix	***Synflorix***				
	1D RSV + Menveo	***Menveo***				
	2D RSV + *Bexsero*	*Bexsero*				
	2D RSV + *Nimenrix*	*Nimenrix*				
	2D RSV + Synflorix	***Synflorix***				
	2D RSV + Menveo	*Menveo*				
	Bexsero	*Bexsero*				
	Nimenrix	*Nimenrix*				
	Synflorix	***Synflorix***				
	Menveo	***FB***				

Type of contact and timepoint	Study group	Treatment name[1]	Volume to be administered *(0.5 mL)*	Route[2] (*IM*)	Site	
					Location (*Anterolateral Thigh*) [3]	Laterality [4] (Left)
Visit 6 (Day 121) [5]	***1D RSV + Bexsero***	***Bexsero***	0.5 mL	IM	Anterolateral Thigh	Left
	1D RSV + Nimenrix	***Nimenrix***				
	1D RSV + Synflorix	***Synflorix***				
	2D RSV + Bexsero	*Bexsero*				
	2D RSV + Nimenrix	*Nimenrix*				
	2D RSV + Synflorix	***Synflorix***				
	Bexsero	***FB***				
	Nimenrix	***FB***				
	Synflorix	***FB***				
Visit 7 (end of the first RSV transmission season)	***1D RSV + Bexsero***	***Bexsero***				
	1D RSV + Nimenrix	***Nimenrix***				
	1D RSV + Synflorix	***Synflorix***				
	1D RSV + Menveo	***Menveo***				
	2D RSV + Bexsero	*Bexsero*				
	2D RSV + Nimenrix	*Nimenrix*				
	2D RSV + Synflorix	***Synflorix***				
	2D RSV + Menveo	*Menveo*				
	Bexsero	*Bexsero*				
	Nimenrix	*Nimenrix*				
	Synflorix	***Synflorix***				
	Menveo	*Menveo*				

~~**Antlat Thi**: Anterolateral thigh; **ChAd155-RSV**: Chimpanzee Adenovirus Type 155 RSV vaccine ($5x10^{10}$ vp); **NA**: not applicable; **Saline**: formulation buffer S9b.~~

~~[1] **IM:** Intramuscular.~~

~~[2] Directionality is a qualifier for further detailing the location of the vaccine administration location (e.g., Upper, Lower).~~

1D: 1 Dose ($1.5x10^{10}$ vp/dose); 2D: 2 Dose ($5x10^{10}$ vp/dose); **RSV ChAd:** Chimpanzee Adenovirus Type 155 RSV vaccine; **NA**: not applicable**;** ***FB***: ***F***ormulation buffer S9b.

[1] The choice of active comparator vaccine or Placebo control is done at the country level (see Table 2).

[2] **IM:** Intramuscular.

[3] In the second year of lifeon Day 365 (Visit 7) if the muscle size is adequate, the site of administration can be the deltoid on the left side.

[4] The preferable side for administration ***is the left side***. If for some reason the left side cannot be used, please ensure the subsequent doses are administered on the same side as the first dose.

[5] In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Figure 1, Table 2 and Table 7).

~~Minimizing environmental contamination with genetically modified organisms~~

~~Each product will be used in accordance with the local applicable genetically modified organism regulations.~~

~~To minimize release of the recombinant vectored vaccine virus into the environment, each vaccine is produced under good manufacturing practice conditions with the handling of live material in appropriate laboratory facilities. This is to ensure that any release of modified organism is contained, inactivated and incinerated, using single use equipment as much as possible, to avoid release of modified genetic material into the environment.~~

~~Refer to the SPM for more details on aspects vaccine handling including disposal of waste and management of accidental spills.~~

In Section 9.2. Surveillance for RSV-RTI, difficulty in breathing and wheezing episodes, the following cross-reference was added:

Refer to APPENDIX D for the symptoms and grading for assessment visits and worsening visits.

In Section 9.2.1. Passive surveillance, the following change was made:

All subjects' parent(s)/LAR(s) will be instructed to contact investigator/study staff in case of any new ***or worsened*** RTI symptoms (cough, runny nose or blocked nose) or in case of any new difficulty in breathing or wheezing. They will be also reminded to record the start date and the end date of the RTI symptoms on the RTI episode card.

In Section 9.2.2. Surveillance for asymptomatic RSV-RTI, the following changes were made:

In order to detect asymptomatic RSV-RTI, monthly nasal swabs for analysis at sponsor laboratory will be performed for all subjects during the RSV season~~.~~ ***who are 'RTI symptom free' within an approximate 30 day period***. Upon investigators discretion ~~this~~***, the asymptomatic visit may be omitted*** if a nasal swab has been taken for a potential disease episode in ***the*** previous 4 weeks~~. This~~ ***(please refer to the SPM for an example of when to schedule the visit). The asymptomatic*** nasal swab will be tested by quantitative PCR**.**

In Section 9.2.3. Active surveillance, the following changes were made:

There will be contact between the investigator/study staff and subject's parent(s)/LAR(s) on a regular basis (weekly during the RSV season and every month outside the RSV season). If there has not been a contact through a clinic visit (i.e., Visits 1, 2, 3, 4, 5, 6*, 7, 8~~, 9~~), a passive surveillance contact (refer to Section 9.2.1), an assessment visit (refer to Section 9.2.4) or a surveillance for asymptomatic RSV infection (refer to Section 9.2.2), then the investigator/study staff will contact the subject's parent(s)/LAR(s). The active surveillance will be performed by phone, mobile phone or e-mail.

* In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

During each active follow-up contact, the investigator/study staff will:

- Confirm with the subjects' parent(s)/LAR(s), if the subject has developed new RTI symptoms (cough, runny nose or blocked nose) and if he/she has developed any symptoms of difficulty in breathing or wheezing (during and between contacts).
  - **If there is** any new or on-going difficulty in breathing, wheezing or parental concern, the investigator/study staff will schedule an assessment visit as soon as possible (refer to Section 9.2.4), but no later than 24 hours after the contact to ensure prompt assessment of the need for medical care. ~~***The investigator/study***~~

~~***staff will remind subjects' parent(s)/LAR(s) to record the start date and the end date of the RTI symptoms on the RTI episode card.***~~

- **If there is <u>no</u> suspicion** of difficulty in breathing, nor wheezing, nor parental concern, but any new symptoms of an RTI (cough, runny nose or blocked nose) are present, the investigator/study staff will schedule an assessment visit as soon as possible (refer to Section 9.2.4), but no later than 72 hours after the contact.

- ***Performing the visit as soon as possible is important to assess the need for medical care, to ensure that early symptoms are captured, and also to collect a nasal swab for the detection of RSV.***
- ***The investigator/study staff will remind subjects' parent(s)/LAR(s) to record the start date and the end date of the RTI symptoms on the RTI episode card.***

In Section 9.3.3.2.1. Assessment of intensity, the footnote of **Table 20 Intensity scales for solicited symptoms in infants** has been changed as follows:

* Fever is defined as temperature ≥ 38.0°C / 100.4° F ***by any route***. The preferred location for measuring temperature in this study will be the axilla for subjects ≥ 1 and < 5 years of age and the rectum for subjects < 12 months of age.

The Section 9.3.3.2.2. Assessment of causality, the following change was made:

The investigator is obligated to assess the relationship between study vaccines and the occurrence of each AE/SAE using clinical judgement. ~~In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e., investigational, control or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the AE to be related to all products.~~

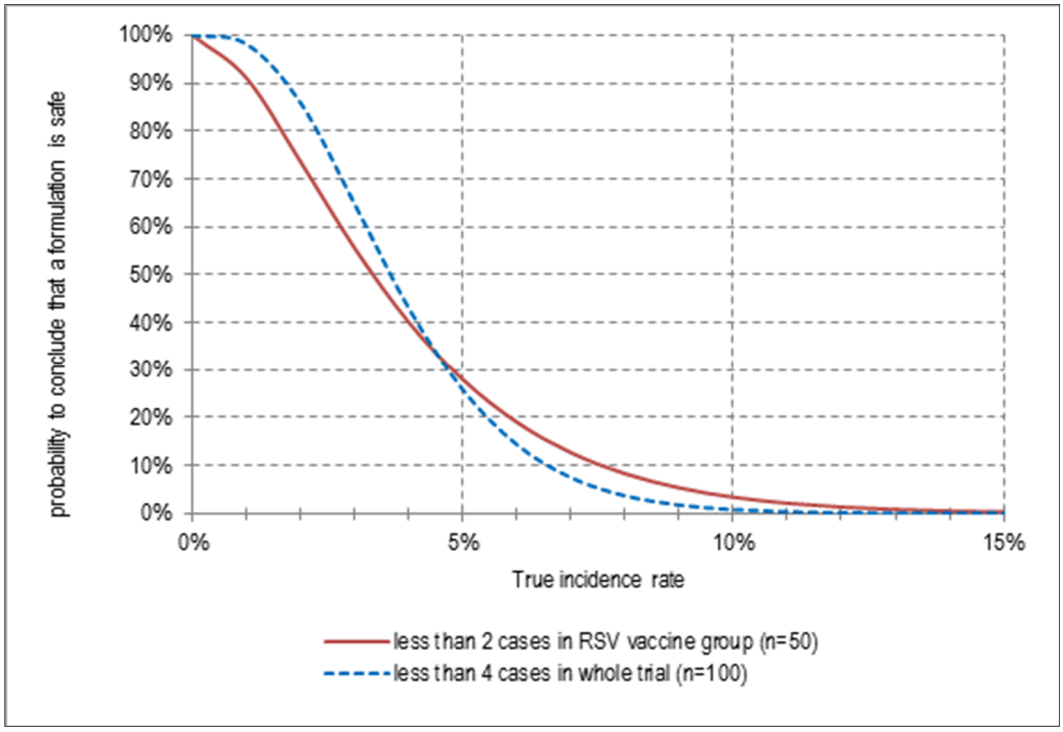
In Section 9.10.4. Holding rules, Table 23 Holding rules during the planned iSRC or IDMC evaluation has been amended as follows:

Holding Rule	Event	Number of infants
2a	Any Grade 3 solicited local AE lasting 48 hours or more following administration of an investigational RSV vaccine, within the 7-day (Days 1-7) post-vaccination period.	≥ 25% & ≥ 2 infants in ~~th~~***any of two*** pooled RSV vaccine group***s***
2b	Any Grade 3 solicited general AE lasting 48 hours or more following administration of an investigational RSV vaccine, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Days 1-7) post-vaccination period.	≥ 25% & ≥ 2 infants in ~~th~~***any of two*** pooled RSV vaccine group***s***
2c	Any ≥ Grade 3 unsolicited AE following administration of an investigational RSV vaccine, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Days 1-7) post-vaccination period	≥ 25% & ≥ 2 infants in ~~th~~***any of two*** pooled RSV vaccine group***s***
2d	Infants hospitalized for RSV-LRTI	≥ 4***6*** (in the combination of ~~th~~***two*** pooled RSV vaccine and the pooled comparator/***Placebo*** groups)

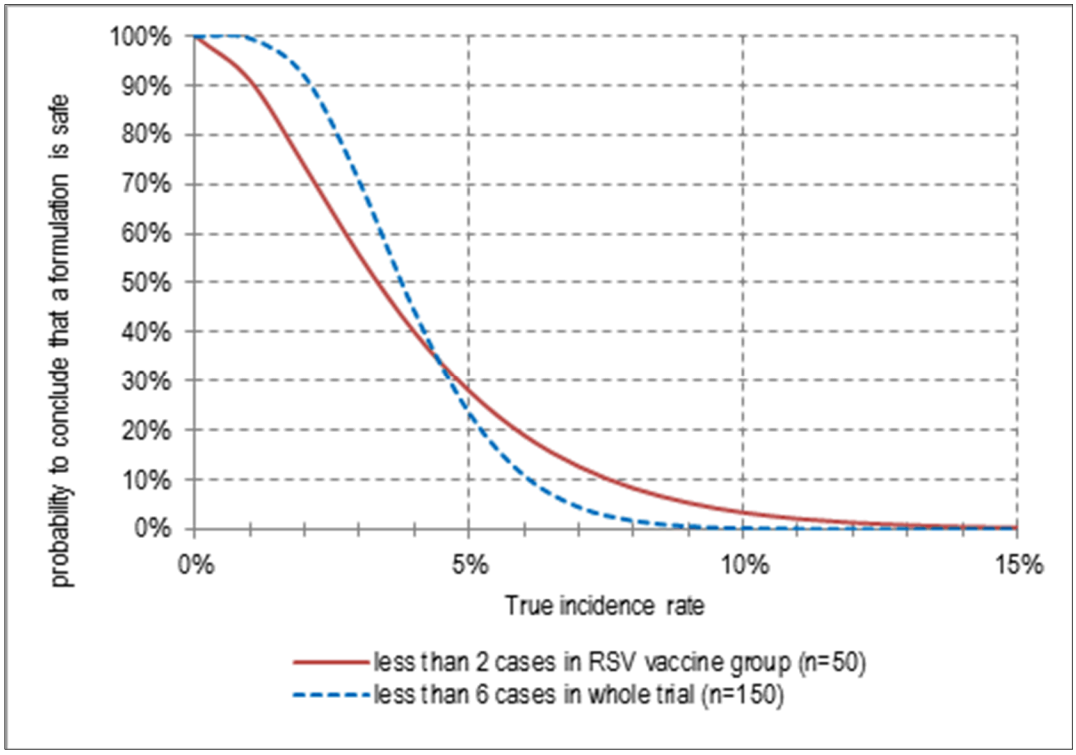
Figure 5 on the **Evaluations based on 50 subjects per group - Risk assessment curve for one formulation based on the proposed safety holding rules during the planned IDMC evaluation** has been changed:

Figure 5 gives the probability of not meeting holding rule assessed during the planned IDMC evaluation when 50 subjects are enrolled per study group and 1**5**0 subjects in the whole trial.

~~Old Figure 5~~



New Figure 5



In Section 11. STATISTICAL METHODS, the following changes have been made:

In Section 11.2. Secondary endpoints, the following changes were made:

- ***Occurrence of RSV-RTI, RSV-LRTI, severe RSV-LRTI and very severe RSV-LRTI (according to standardized case definitions) as from first vaccination (Day 1) up to the end of the second RSV transmission season.***
- ***Occurrence of very severe RSV-LRTI (according to standardized case definitions) among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season.***
- ~~Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61):~~
  - ~~Palivizumab-competing antibody concentrations.~~

In Section 11.3. Tertiary endpoints, the following changes were made:

- ***Humoral response to the investigational RSV vaccine, pre-vaccination (Screening), post-Dose 1 (Day 31) and post-Dose 2 (Day 61).***
  - ***Palivizumab-competing antibody concentrations.***

In Section 11.4. Determination of sample size, the following changes have been made:

The sample size determination is based on the minimum number of subjects needed to allow detection of a serious ERD signal ~~of ERD of the~~ ***having a magnitude similar to that*** ~~occurred in association with~~***of the historic FI-RSVvaccine trials [Kim, 1969]. A total of 150 infants will be enrolled and randomized with 1:1:1 ratio*** ~~into~~***to receive either*** ~~receiving~~***1 dose of the 1.5x10^{10} vp/dose ChAd-155 RSV vaccine [the 1D RSV + comparator group], 2 doses of the 5x10^{10} vp/dose ChAd-155 RSV vaccine [the 2D RSV + comparator group], or no ChAd-155 RSV vaccine [the comparator/Placebo control*** ~~.~~ ***alone group].***

An effect of vaccination on ERD will be monitored very closely. It is anticipated that ~~prior to the transmission season approximately 70% of infants 6 months~~***at least 50% of subjects [Dunn, 2013] will*** ~~be RSV naïve i.e., ~~***have*** ~~not experienced an RSV RTI previously [, 2014]. If the magnitude of ERD risk in RSV naïve children is as extreme as that observed in the FI trial (80% of RSV RTI progress to hospitalization), and in contrast~~***a negative RSV*** ~~experienced children follow a usual clinical course of infection (5% of RSV RTI require hospitalization) then in this cohort including RSV experienced and naive infants an overall rate of 60% RSV RTI requiring hospitalization is derived [, 1969]. RSV hospitalization is not an objective measure of RSV disease severity and so the progression of infection to very severe RSV LRTI~~***exposure status (at screening which will be assessed*** ~~.~~ ***by in-stream serological testing of baseline samples). While the rate of RSV infection could be highly variable by season, a conservative rate of infection of 20% in the first season is assumed [Kutsaya***~~taken. Therefore, a total of 10 infected infants would be expected from 50 RSV vaccine recipients.~~***, 2016]. Therefore, with 50 infants in each RSV vaccine group, it is anticipated to observe at least 5 infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in each RSV vaccine group [50×0.5×0.2=5].***

With a one-sided type I error of 0.05, and the assumption of ~~the~~***a 10% rate of*** ~~10%~~ ***infection progressing to very severe RSV-LRTI*** ~~,~~ ***(which is a conservative assumption based on the rate in the natural history of disease),*** ~~10~~***5 infections can provide at least 90% statistical power to demonstrate the progression rate from infection to very severe RSV-LRTI is less than 80%. That is less extreme than that observed in the historic FI-RSV vaccine trial where 80% of RSV RTI cases progressed to hospitalization [Kim, 1969]. During the*** ~~60%.~~***course of the study, since the actual negative RSV exposure status (at screening based on in-stream baseline serological testing) and infection rates may be lower than 50% and 20%, respectively, the sample size will be adjusted as needed through additional recruitment in order to achieve at least 5 RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in each RSV vaccine group.***

If a maximum of ~~2~~***1*** out of ~~10~~***5*** infections in infants receiving ChAd-155 RSV vaccine progress to very severe RSV-LRTI, then it can be concluded with 95% confidence that the expected progression rate of infection is less than the effect reported in previous FI-RSV trials; if a minimum of 4***3*** out of ~~10~~5 infections progress to very severe RSV-LRTI then it can be concluded with 95% confidence that the expected progression rate of

infection is more than the 10% observed in natural history of infection. The above power analysis is based on the procedure of inequality of one proportion in PASS 12.

With 50 subjects in ***each*** RSV vaccine group, the probability of observing at least one SAE would be about 92% if the true incidence rate of SAE is 5%. For estimating the proportion of subjects with AEs, the maximum width of exact 95% confidence interval (CI) would be under 30%, and it could be as large as 35% if attrition rate is 30%. Figure 6 illustrates the precision on the estimate for the proportion of subjects with AEs following vaccination with each RSV formulation based on the number of subjects with AEs observed from 50 subjects.

~~In addition, relative risks for enhanced RSV-LRTI of RSV vaccine versus control will be monitored and evaluated. Under the assumption of 5% of annual LRTI event rate in control group, a one year follow up, and one-sided type I error of 0.1, the current sample size is able to provide about 80% statistical power to rule out the relative risk of at least 8.5 (vaccine vs. control) in absence of vaccine efficacy. The power analysis is based on Two Independent Proportions (Superiority by a Margin) in PASS 12.~~

In Section 11.5. Cohorts for Analyses, the following changes have been made:

The Section 11.5.1. heading has been changed from ~~**Total vaccinated cohort**~~ to **Exposed Set**

The ~~total vaccinated cohort (TVC~~***Exposed Set (ES***) will include all subjects with at least one study vaccine administration documented.

A safety analysis based on the ~~TVC~~***ES*** will include all vaccinated subjects.

An immunogenicity analysis ~~based~~***will be conducted on the*** ~~TVC~~***ES and*** will include all vaccinated subjects for whom immunogenicity data are available.

The ~~TVC~~***ES*** analysis will be performed per treatment actually administered at Dose 1.

The Section 11.5.2. ***Exposed Set of subjects with a negative RSV exposure status*** has been added:

The Exposed Set of subjects with a negative RSV exposure status will include all vaccinated subjects assessed as RSV unexposed at screening based on in-stream baseline serological testing.

The safety analysis of incidence of RSV-LRTI will be conducted on the cohort of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) as well as on the entire ES.

The Section 11.5.3. Per-protocol ~~cohort~~Set for analysis of immunogenicity (formerly Section 11.5.2.), has been amended as follows:

The per-protocol ~~(PP~~***set*** (PP***S***) cohort for analysis of immunogenicity will be defined by timepoint and will consist of all subjects from the ~~TVC~~***ES*** who complied with eligibility criteria, study procedures up to the end of the study and had immunogenicity results in the epoch as described below.

More specifically, the PP***S*** cohort for analysis of immunogenicity up to ***Day 61 (***Visit 5 ~~(Day 61)/~~***)*** /at ***Day 365 (***Visit 7***)*** (end of the first RSV transmission season) will include all evaluable subjects:

- Who met all eligibility criteria (i.e., no protocol violation linked to the inclusion/exclusion criteria, including age).
- Who received ~~at least one dose of~~ ***study vaccine~~.~~ as scheduled per protocol***.
- For whom the administration route and site of the vaccine was as according to protocol.
- Who received the vaccine according to protocol procedures.
- Who complied with the vaccination schedule, as specified in Table 7.
- Who did not receive a concomitant medication/product/vaccine leading to exclusion from a PP***S*** analysis, as described in Section 7.6.2, up to ***Day 61 (***Visit 5~~(~~***)*** /at ***Day***~~61)/up to~~ ***365 (***Visit 7***)*** (end of the first RSV transmission season).
- Who complied with the timings of the post vaccination blood sampling for immune response evaluation, up to ***Day 61 (***Visit 5~~ (Day 61)/~~***)*** /at ***Day 365 (***Visit 7***)*** (end of the first RSV transmission season), as specified in Table 7.
- For whom post-vaccination immunogenicity results are available for at least one assay up to ***Day 61 (***Visit 5~~ (Day 61)/~~***)*** /at ***Day 365 (***Visit 7***)*** (end of the first RSV transmission season).

Table 24 presents the intervals between study visits that determine subjects' eligibility for inclusion in the PPS analysis.

Footnote 3 of the Maximum allowed interval between study visits Table 24 was amended as follows:

[3] In countries where *Menveo* ***or Placebo*** is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

The Pooled groups Table 25 was amended as follows:

Study groups	Pooled groups
1D RSV + Bexsero	***Pooled 1D RSV***
1D RSV + Nimenrix	
1D RSV + Synflorix	
1D RSV + Menveo	
1D RSV + Placebo	
2D RSV + ~~*NeisVac-C*~~*Bexsero*	Pooled ***2D*** RSV
2D RSV + *Nimenrix*	
2D RSV + ***Synflorix***	
2D RSV + ***Menveo***	
2D RSV + ***Placebo***	
Bexsero	Pooled comparator
Nimenrix	
Synflorix	
Menveo	
~~*NeisVac-C*~~***Placebo***	

1D: 1 Dose ($1.5x10^{10}$ vp/dose); RSV: ChAd155-RSV vaccine; 2D: 2 Dose ($5x10^{10}$ vp/dose)

In the Section 11.6. Derived and transformed data, the **Section 11.6.2. Safety** had the following change:

For a given subject and the analysis of solicited AEs 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~~***ES*** will include only vaccinated subjects with documented safety data (i.e., symptom screen completed)

The Section 11.6.3. Immunogenicity was amended as follows:

Determination of a negative RSV exposure status in infants at 6 to 7 months of age will be based on RSV A and/or B neutralizing antibody titers present in serum at screening (before vaccination with the RSV vaccine) based on in-stream baseline serological testing. At birth, newborns do show positive for neutralizing antibodies due to maternal transfer during gestation. The titer of these antibodies declines over time. At the age of 6 to 7 months a cut-off can be defined below which infants are considered to have a negative RSV exposure status. Infants that show neutralizing antibody titers above this cut-off are suspected to have experienced a recent RSV infection. This cut-off will thus allow the discrimination between a negative RSV exposure status versus RSV infected infants before start of vaccination.

The Section 11.6.4. RTI and LRTI, was amended as follows:

For the analysis of RTI and LRTI, all cases will be definitively classified as either ***RSV-***RTI, ***RSV-***LRTI, ***severe RSV-LRTI*** or very severe ***RSV-***LRTI according to the case definitions presented in Table 6, and the association to RSV infection will be assessed by quantitative PCR as primary analysis.

The Section 11.7. Analysis of demographics was amended as follows:

The analysis of demographics will be performed on the ~~TVC~~***ES*** and on the PP***S*** cohort for immunogenicity for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups.

Demographic characteristics (age at vaccination in months, sex, country and race~~)~~ ***and vital signs***), cohort description will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable***s*** such as race.

In the Section 11.8. Analysis of safety, the **Section 11.8.1. Within groups assessment** had the following changes:

The safety will be descriptively summarized based on the ~~TVC~~***ES***. The analysis of local AEs, general AEs and fever will be reported for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups. For the analysis of SAEs ***and AE of specific interest***, the analysis will be performed only on the pooled RSV and pooled comparator groups.

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 will be tabulated with exact 95% confidence interval (CI) after each vaccine dose and overall. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE during the 7-day or 30-day follow-up period will be tabulated, overall vaccination course, with exact 95% CI. The same computations will be done for Grade 3 AEs, for any AEs considered related to vaccination ~~and~~ for any Grade 3 AEs considered related to vaccination~~.~~ ***and AEs resulting in a medically attended visit***.

The percentage of subjects with **unsolicited** AEs within 30 days (Day 1-30) after each vaccine dose (overall doses) with its exact 95% CI will be tabulated RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups and by MedDRA preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and AEs will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term. ***The percentage of subject with episode of spontaneous or excessive bleeding (AE of specific interest), during a 30-day follow-up period after each vaccination will be tabulated according to associated Preferred Term code (to be identified in the Statistical Analysis Plan [SAP]).***

The percentage of subjects with RSV-LRTI (AE of specific interest) from Dose 1 up to end of the first RSV transmission season and from Dose 1 up to end of second RSV season will be tabulated according to associated Preferred Term code presented in the SAP.

The percentage of subjects with SAE within 30 days (Day 1-30) after each vaccine dose with its exact 95% CI will be tabulated and by MedDRA preferred term. Similar tables will be generated for SAEs from Dose 1 to end of first RSV season and from Dose 1 to end of the second RSV season.

The Section 11.9. Analysis of immunogenicity was amended as follows:

The primary analysis will be performed on the ~~PP cohort~~PP***S*** for immunogenicity and, if in any group the percentage of vaccinated subjects with serological results excluded from the ~~PP cohort~~PP***S*** for immunogenicity is more than 10%, a second analysis will be performed on the ~~TVC~~***ES***. The results from immunogenicity analysis will be reported by the pooled RSV vaccine group and the pooled comparator group.

For the final analysis, the Adapted PPS for immunogenicity analysis will be used which allows the summary of immunogenicity results by time point. In summary table on the Adapted PPS for immunogenicity, PPS for immunogenicity at Day 61 will be used for Pre, Day 31 and Day 61 immunogenicity summary and PPS for immunogenicity at Day 365 for Day 365 immunogenicity summary.

The infants are monitored for RSV infection starting from dose 1 and therefore immunogenicity analyses can be adjusted to exclude those infants with an infection prior to sampling.

In the Section 11.9.1. Within groups assessment, the **Section 11.9.1.1. Analysis of secondary objectives** had the following changes:

For ~~both~~***three*** pooled groups, at each timepoint that blood samples are collected for humoral immune response against the investigational RSV vaccine (neutralizing antibody titers against RSV-A, RSV F antibody concentrations~~ and palivizumab-competing antibody concentrations):~~).

An immunogenicity analysis will also be performed on the ES with a negative RSV exposure status (at screening based on in-stream baseline serological testing) for whom immunogenicity data are available.

The Section 11.9.1.2. Analysis of tertiary objective was amended as follows:

If available, any further exploratory immunology results (including, but not limited to anti-vector immunity ***and palivizumab-competing antibody concentrations***) will be reported by ***timepoint for*** the ***two*** pooled RSV vaccine group***s*** and the pooled comparator group ~~and timepoint~~ using descriptive summary statistics.

The Section 11.10. Analysis of RTI and LRTI was amended as follows:

The ***primary*** analysis will be performed ***on the*** ~~TVC~~***ES of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in*** the pooled ***single dose*** RSV vaccine group***, the pooled two dose RSV vaccine group,*** and the pooled comparator group separately for first and second RSV seasons and overall. ***A similar analysis will be performed on the entire ES.*** As primary analysis, the assessment of RSV infection will be performed using the quantitative RT-PCR according to standardized case definitions (see Table 6) based on the available WHO case definitions.

The number of RSV infections within each group and the maximum disease severity of the event will be tabulated. The rate (with 95% ***CI***) of RSV***-RTI and RSV-LRTI and infections progressing to hospitalization*** will be evaluated ~~both~~***for each of the three*** pooled groups. ~~RSV infection (symptomatic or asymptomatic) will be assessed by either central quantitative RT-PCR (RSV-A/B) or locally available test.~~

The rate of very severe RSV-LRTI among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season will be estimated as well as 95% one-sided lower CI.

The proportion and the relative risk of subjects with at least one RSV-associated RTI (with 95% CI) ~~will be calculated.~~***between each of two pooled RSV vaccine groups and the pooled control group*** will be ***calculated for both the cohort of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) on the ES and on the entire ES.*** The same descriptive analysis will be performed for subjects with at least one RSV-associated LRTI and those with at least one RSV-associated severe LRTI.

Descriptive analyses (mean, median, min, max) of viral load assessed by the quantitative RT-PCR (RSV-A/B) of ~~RSV-RTI, RSV-associated LRTI and severe LRTI~~***all cases as listed in Table 6*** will be tabulated~~.~~ ***by case category***. This analysis will also be done on the ~~two~~***three*** pooled groups.

The incidence rate of ***all*** ~~cause RTI~~ ***cases as listed in Table 6*** (with 95% CI) will be calculated by ~~both~~***the three*** pooled groups. The same descriptive analysis will be performed for all cause LRTI and all cause severe LRTI. These will also be presented for each viral etiology identified by the multiplex PCR.

The incidence rate of asymptomatic RSV infections (with 95% CI) detected by the quantitative PCR (RSV-A/B), will be tabulated by the ~~two~~***three*** pooled groups. Descriptive analyses (mean, median, min, max) of viral load assessed by the quantitative RT-PCR (RSV-A/B) of those asymptomatic RSV infections will also be done on the ~~two~~***three*** pooled groups.

The RVP (Multiplex PCR) on specimens from all RSV-A/B positive and confirmed LRTI cases, according to case definition presented in Table 6 (Figure 3), will be tabulated as a qualitative assessment profiling the potential co-infections occurring in these subjects.

The Section 11.11. Interpretation of analyses was amended as follows:

For the occurrence of very severe RSV-LRTI among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season, if the upper boundary of the 95% one-sided lower CI of the rate is under 80%, it indicates that the very severe RSV-LRTI rate is less than that of the historic RSV-FI trials [Kim, 1969].

The Section 11.12.1. Sequence of analyses was amended as follows:

In preparation of the planned iSRC and IDMC evaluations, analyses of all available safety data (i.e., data that are as clean as possible) will be performed (see Section 9.10 for more information). These analyses will be done by an unblinded statistician outside GSK to maintain the ***blinding of the*** study ~~blind~~, and will be documented in a statistical analysis report. Only the outcome of the iSRC and IDMC reviews will be communicated to the RSV study team (no safety signal or safety signal). No clinical study report will be written.

In the Section 12. ADMINISTRATIVE MATTERS, the **Section 12.1. electronic Case Report Form instructions** had the following change:

The investigator will be provided with a ~~CD-ROM of~~***storage device containing*** 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.

In the new Section 13. COUNTRY SPECIFIC REQUIREMENTS, the new **Section 13.1. Requirements for Belgium** had the following statement:

Belgium will not use placebo, and will only use Bexsero.

The Section 14. REFERENCES (formely Section 13.) was amended as follows:

~~Chu HY, Steinhoff MC, Magaret A, et al. Respiratory syncytial virus transplacental antibody transfer and kinetics in mother-infant pairs in Bangladesh. J Infect Dis. 2014; 210(10): 1582-9.~~

Dunn SR, Ryder AB, Tollefson et al. Seroepidemiologies of human metapneumovirus and respiratory syncytial virus in young children, determined with a new recombinant fusion protein enzyme-linked immunosorbent assay. Clin Vaccine Immunol. 2013; (10): 1654-6.

Kutsaya A, Teros-Jaakkola T, Kakkola L, et al. Prospective clinical and serological follow-up in early childhood reveals a high rate of subclinical RSV infection and a relatively high reinfection rate within the first 3 years of life. Epidemiol Infect. 2016; 144(8): 1622-33.

~~Pierantoni A, Esposito ML, Ammendola V et al. Mucosal delivery of a vectored RSV vaccine is safe and elicits protective immunity in rodents and nonhuman primates. *Mol Ther Methods Clin Dev*. 2015; 2, 15018.~~

~~Taylor G, Thom M, Capone S, et al. Efficacy of a virus-vectored vaccine against human and bovine respiratory syncytial virus infections. *Sci Transl Med*. 2015; 7: 300.~~

The Section APPENDIX A LABORATORY ASSAYS was amended as follows:

RSV A **Neutralization assay**

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

~~First, v~~ *V*irus neutralization is performed by incubating a fixed amount of RSV-A ~~long~~ strain (***Long,*** 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,~~***horse-radish peroxidase (HRP)***, allowing the visualization of plaques ~~by immunofluorescence.~~***after coloration with TrueBlue peroxidase substrate***. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with Axiovision software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at that dilution and the number of plaques in the virus control wells (no serum added). The serum 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 as described by others [Barbas, 1992; Bates, 2014].

ELISA

- Anti-RSV protein F ELISA

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

~~PCR~~ ***Reverse Transcription Polymerase Chain Reaction (RT-PCR)***

- Quantitative ***RT-***PCR able to discriminate RSV-A and RSV-B subtypes:

  Briefly, RSV A and RSV B RNAs extracted from the nasal 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 extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real- time PCR reaction using a calibration curve (absolute quantitation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

- Qualitative multiplex ***RT-***PCR for detection of a panel of viruses:

The APPENDIX D, indicating **THE SYMPTOMS AND GRADING FOR ASSESSMENT VISITS AND WORSENING VISITS,** was added:

HISTORY FROM PARENT OR CARER - PART 1		
Symptoms of RTI	***Cough***	***Yes/No (if Yes: start date and end date)***
	Runny nose	***Yes/No (if Yes: start date and end date)***
	Blocked nose	***Yes/No (if Yes: start date and end date)***
	Wheezing	***Yes/No (if Yes: start date and end date)***
	Difficulty in breathing	***Yes/No (if Yes: start date and end date)***
Parental/Carer concern	***Parental concern***	***Yes/No***
MEDICAL OBSERVATION - PART 2a*		
Temperature		***Record temperature and route of measurement***
Heart rate		***Beats per minute when child is settled***
Respiratory rate		***Breaths per minute counted over one minute***
Lower chest wall indrawing (subcostal recession)		***Yes/No***
SpO_2		***% measured in room air when quiet and not feeding (NB altitude is collected for each participating site)***
Nasal swab taken for testing at central laboratory		***Yes/No***
Specimen taken for RSV and RVP testing at local laboratory		***Yes/No (If Yes specify type of specimen test and result: positive/negative)***
Has a blood sample been taken for assessment of mechanism of illness?		***Yes/No/ Not available***
MEDICAL OBSERVATION - PART 2b*		
Must be completed in full if: • ***The parent or carer reports wheezing or difficulty in breathing*** • ***The respiratory rate is > 40/minute for subject 12-30 months of age*** • ***Lower chest wall indrawing is observed*** • ***SpO2 measured in room air by pulse oximetry is < 95%*** ***N.B. May be completed in part or in full for any child attending an assessment visit***		
Signs of increased respiratory effort	***Audible wheeze***	***Yes/No/Not available***
	Grunting	***Yes/No/Not available***
	Nasal flaring	***Yes/No/Not available***
	Intercostal recession	***Yes/No/Not available***
Signs associated with severity	***Apnea outside medical facility***	***Has an episode of apnea > 20 seconds occurred outside a medical facility? Yes/No/Not available (if Yes provide all details [free text field])***
	Apnea under medical observation	***Has an episode of apnea > 20 seconds occurred during medical observation? Yes/No/Not available (if Yes provide all details [free text field])***
	Peripheral cyanosis	***Yes/No/Not available***
	Central cyanosis	***Yes/No/Not available***
	Irritability/agitation	***0 = content, happy, interactive*** ***1 = mildly irritable when touched, occasional crying, can be comforted, is interactive*** ***2 = moderately irritable, intermittently crying, resists comforting, less interactive*** ***3 = extremely irritable, cannot be comforted, crying throughout examination or not interactive*** ***Not available***
	Lethargy/excessive sleepiness	***0 = interactive*** ***1 = mildly lethargic/sleepy is normally interactive when roused*** ***2 = moderately lethargic/ sleepy, less interactive than normal when roused*** ***3 = extremely lethargic/sleepy, is not interactive when roused*** ***Not available***

	Conscious level	***A = The child is awake, alert, and interactive with parents and care providers*** ***V =The child responds only if the care provider or parents call the child's name or speak loudly*** ***P =The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger.*** ***U = The child is unresponsive to all stimuli*** ***Not available***
	Assessment of feeding ability	***0 = Normal feeding*** ***1 = Reduced ability to feed*** ***2 = Unable to feed*** ***Not available***
	Skin turgor	***Yes → > 2 seconds*** ***No → ≤ 2 seconds*** ***Not available***
Findings on auscultation	***Wheeze on auscultation with stethoscope***	***Yes/No/Not available***
	Crackles	***Yes/No/Not available***
Investigations	***Chest X-ray if available*****	***Collected? Yes/No/Not available (If Yes: specify date and specify the presence or absence of the following features: hyperexpansion, peribronchial thickening, interstitial infiltrates, segmental or lobar consolidation, pleural effusion, atelectasis, other: please specify)***
	Blood culture if available**	***Collected? Yes/No (If Yes, specify date and coded results as 1. Pneumococcus, 2. Haemophilus influenza 3. Meningococcus, 4. Salmonella, 5. Other pathogenic organism, 6. Contaminant, 7. No isolate, 8. No result [missing confirmed] and note if 1 to 6: was the period of incubation to positivity detection > 48 hours? Yes/No, if 1, 2, 3 or 4 specify serotype/group, if 5 or 6 specify organism and if 8 comment)***
	Complete blood count If available**	***Collected? Yes/No/Not available (if Yes specify date of collection or tick box if date is same as visit date and specify laboratory name, record results for hematology blood count: hemoglobin, platelets, total white cell count, neutrophil count, lymphocyte count)***
Inpatient care	***Hospitalization indicated? Hospitalization?***	***Yes/No (if Yes, specify start date of hospitalization and total number of calendar days on which the child was hospitalized for at least one hour)***
	If yes: Requirement for monitoring/nursing observation	***Yes/No (if Yes total number of calendar days on which the requirement for monitoring/nursing observation was done for at least one hour)***
	If yes: Requirement for nasogastric or intravenous fluids	***Yes/No (if Yes specify start date of fluids and specify total number of calendar days on which nasogastric or intravenous fluids were given for at least one hour)***
	If yes: Requirement for supplemental oxygen	***Yes/No (if Yes specify start date of oxygen and specify total number of calendar days on which oxygen was administered for at least one hour)***
	If yes: Requirement for respiratory support excluding mechanical ventilation (e.g. high flow, continuous positive airway pressure [CPAP])	***Yes/No (if Yes specify start date of respiratory support and specify total number of calendar days on which respiratory support [excluding mechanical support] was given for at least one hour)***
	If yes: Requirement of mechanical ventilation	***Yes/No (if Yes specify start date of mechanical ventilation and specify total number of calendar days on which mechanical ventilation was given for at least one hour)***

	If yes: Requirement for pediatric intensive care unit management	*Yes/No (if Yes specify start date of pediatric care and specify total number of calendar days on which the child was cared for on pediatric intensive care unit for at least one hour)*
	Was the primary reason for hospitalization social in nature?	*Yes/No*
	In the opinion of the principal investigator and the RSV local result, was RSV-LRTI the principal reason for admission to hospital?	*Yes/No (If No, comment)*

*WORSENING INFORMATION OF RTI EPISODE (Worsening episode) - PART 3**

If in the investigator's judgment a deterioration in the clinical status has occurred during the same RTI episode, then the most extreme value of all deteriorated clinical symptoms and signs (as listed in Part 2a and 2b) must be captured

N.B. May be completed in part or in full for any child experiencing a deterioration during the course of a disease episode

*Maximum temperature****		*Record temperature and route of measurement*
*Maximum respiratory rate****		*Breaths per minute counted over one minute*
*Lower chest wall indrawing (subcostal recession)****		*Yes/No/Not available*
*Minimum SpO_2 recorded****		*% measured in room air (NB altitude is collected for each participating site)*
Nasal swab taken for testing at central laboratory		*Yes/No*
Specimen taken for RSV and RVP testing at local laboratory (optional sample if the previous swab from the same RTI episode was RSV-positive)		*Yes/No (If Yes specify type of specimen test and result: positive/negative) Not available*
Signs of increased respiratory effort	*Audible wheeze****	*Yes/No/Not available*
	*Grunting****	*Yes/No/Not available*
	*Nasal flaring****	*Yes/No/Not available*
	*Intercostal recession****	*Yes/No/Not available*
Signs associated with severity observed	*Apnea outside medical facility observed during disease episode****	*Has an episode of apnea > 20 seconds occurred outside a medical facility? Yes/No/Not available (if Yes provide all details [free text field])*
	*Apnea under medical observation****	*Has an episode of apnea > 20 seconds occurred during medical observation? Yes/No/Not available (if Yes provide all details [free text field])*
	*Peripheral cyanosis****	*Yes/No/Not available*
	*Central cyanosis****	*Yes/No/Not available*
	*Irritability/agitation (record highest score)****	*0 = content, happy, interactive 1 = mildly irritable when touched, occasional crying, can be comforted, is interactive 2 = moderately irritable, intermittently crying, resists comforting, less interactive 3 = extremely irritable, cannot be comforted, crying throughout examination or not interactive Not available*
	*Lethargy/excessive sleepiness (record highest score)****	*0 = interactive 1 = mildly lethargic/sleepy is normally interactive when roused 2 = moderately lethargic/ sleepy, less interactive than normal when roused 3 = extremely lethargic/sleepy, is not interactive when roused Not available*

	Conscious level (record lowest level of consciousness)***	***A = The child is awake, alert, and interactive with parents and care providers*** ***V =The child responds only if the care provider or parents call the child's name or speak loudly*** ***P =The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger.*** ***U = The child is unresponsive to all stimuli*** ***Not available***
	Assessment of feeding ability (record highest score)***	***0 = Normal feeding*** ***1 = Reduced ability to feed*** ***2 = Unable to feed*** ***Not available***
	Skin turgor***	***Yes → > 2 seconds*** ***No → ≤ 2 seconds*** ***Not available***
Findings on auscultation	***Wheeze on auscultation******	***Yes/No/Not available***
	Crackles***	***Yes/No/Not available***

**** Observation done by qualified medical/nursing personnel***

***** Test not required per protocol but if taken as part of clinical management result should be recorded***

****** Record if a deterioration in this parameter has occurred relative to that documented at the assessment visit during the course of this disease episode***

GlaxoSmithKline Biologicals SA	
Vaccines R &D	
Protocol Amendment 2	
eTrack study number and Abbreviated Title	204894 (RSV PED-011)
IND number	16999
EudraCT number	2018-000431-27
Amendment number:	Amendment 2
Amendment date:	24 January 2019
Co-ordinating author:	• PPD (Scientific Writer)
Rationale/background for changes:	
• In response to a request received from the English Competent Authority (MHRA) on 2 January 2019, added clarification that hypersensitivity to any component of comparator or control vaccines used in this study or contraindication to them is an exclusion criterion.	

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

In the Section 5.3. Exclusion criteria for enrolment the following changes have been made:

- History of any reaction or hypersensitivity ~~likely~~ to ~~be exacerbated by~~ any component of the vaccine***s (investigational or control) or placebo used in this study or any contraindication to them.***

GlaxoSmithKline Biologicals SA	
Vaccines R &D	
Protocol Amendment 3	
eTrack study number and Abbreviated Title	204894 (RSV PED-011)
IND number	16999
EudraCT number	2018-000431-27
Amendment number:	Amendment 3
Amendment date:	21 March 2019
Co-ordinating author:	• PPD (Scientific Writer)
Rationale/background for changes:	
• The indication of pneumonia was added for *Synflorix* (Sections 1.3.2 and 1.3.3). • References to Day 365 and Day 730 for Visits 7 and 8, respectively, were removed in Tables 8 and 24 and throughout. • Clarification was added to the exclusion criterion on recurrent wheezing to specify in the subject's lifetime. • A hyperlink reference was added to include World Health Organization (WHO) weight percentile guidelines for girls and boys ages 5 years and under (https://www.who.int/childgrowth/standards/weight_for_age/en/). • The exclusion criterion related to mothers participating in another clinical study was clarified to specify if breastfeeding. • The cut-off for the neutralization assay was added (Table 10). • Revised Section 9.10.3 to reflect that an additional analysis may be conducted after subjects complete a full RSV season when there are 5 infections among subjects with a negative RSV exposure status (at screening) in each randomization group. • Section 9.10.5 was revised to clarify the roles of the iSRC and VSMB. • In addition, some typographical errors have been corrected throughout the protocol.	

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

On the **protocol cover page the Coordinating author** has been added:

Co-ordinating authors • PPD ***(Scientific Writer)***

On the **protocol cover page** the **Contributing author** has been added.

Contributing authors • PPD ***(Study Delivery Lead)***

In the **Synopsis**, the following changes were made:

Synopsis Table 1 Study groups and epochs foreseen in the study (Amended 21 March 2019)

Study groups	*Target* Numbers of subjects*	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
1D RSV + Bexsero	50**	6 – 7 months	N/A	x	x	x
1D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
1D RSV + Synflorix		6 – 7 months	N/A	x	x	x
1D RSV + Menveo		6 – 7 months	N/A	x	x	x
1D RSV + Placebo		6 – 7 months	N/A	x	x	x
2D RSV + Bexsero	50**	6 – 7 months	N/A	x	x	x
2D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
2D RSV + Synflorix		6 – 7 months	N/A	x	x	x
2D RSV + Menveo		6 – 7 months	N/A	x	x	x
2D RSV + Placebo		6– 7 months	N/A	x	x	x
Bexsero	50**	6 – 7 months	N/A	x	x	x
Nimenrix		6 – 7 months	N/A	x	x	x
Synflorix		6 – 7 months	N/A	x	x	x
Menveo		6 – 7 months	N/A	x	x	x
Placebo		6 – 7 months	N/A	x	x	x

1D: 1 Dose ($1.5x10^{10}$ vp/dose)***;*** **RSV**: ChAd155-RSV vaccine; ***2D:*** 2 Dose ($5x10^{10}$ vp/dose)***; N/A:*** Not Applicable.

~~* Note that for both 1D and 2D RSV vaccine + active comparator/placebo groups the total number of subjects is 100 and that for both RSV vaccine + active comparator/placebo groups there will be a 1:1:1 ratio maintained with the corresponding active comparator/placebo group.~~

~~** Note that the numbers of subjects anticipated to receive the control vaccines within participating countries are not yet known, but the distribution and supplies will be prepared to allow flexible enrolment across countries (for any comparator the range of subjects is 0 – 50 may be enrolled) but the overall total of 150 subjects will be respected~~

- Vaccination schedules:

  RSV investigational vaccine:

  – In the 1 Dose (1D) groups, a single lower dose of $1.5x10^{10}$ vp will be administered IM at Day 1 (Visit 1). Formulation buffer will be administered in the 1D groups at Day 31 (Visit 3). In the 2 Dose (2D) groups, two doses of $5x10^{10}$ vp will be administered IM according to a 0, 1-month schedule, (i.e., at Day 1 [Visit 1] and Day 31 [Visit 3]) (see Synopsis Table 3). Dose 1 will be administered before the first RSV season and the second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the Study Procedures Manual [SPM]. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the

season, rather than approximation to the nearest month, this is desirable. **(Amended 21 March 2019**)

Comparator or Placebo:

- In countries where Bexsero or Nimenrix is used as a control, two doses will be administered IM with at least a 2 month interval between these primary doses. A booster dose will be administered IM in the second year of life at ~~Day 365 (~~Visit 7~~)~~, with an interval of at least 2 months between the primary series and booster dose. The first Bexsero or Nimenrix dose will be administered at Day 1 (Visit 1) (in the groups receiving only Bexsero or Nimenrix, respectively). In the groups receiving only Bexsero or Nimenrix, the second dose will be at Day 61 (Visit 5). The first Bexsero or Nimenrix dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of Bexsero or Nimenrix in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5***th*** vaccination visits (see Synopsis Table 3) **(Amended 21 March 2019)**.
- In countries where *Synflorix* is used as a control, two doses will be administered IM with at least a 1 month interval between these primary doses. A booster dose will be administered IM in the second year of life at ~~Day 365 (~~Visit 7~~)~~. The first *Synflorix* dose will be administered at Day 31 (Visit 3) (in the group receiving only *Synflorix*). In the group receiving only *Synflorix,* the second dose will be at Day 61 (Visit 5). The first *Synflorix* dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of *Synflorix* in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Synopsis Table 3) **(Amended 21 March 2019)**.
- In countries where Menveo is used as a control, two doses will be administered IM at least 3 months apart with the second dose in the second year of life at ~~Day 365 (~~Visit 7~~)~~. The first Menveo dose will be administered at Day 31 (Visit 3) (in the group receiving only Menveo). The first Menveo dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. Since the second Menveo dose has to be administered in the second year of life at ~~Day 365 (~~Visit 7~~)~~, no administration will be performed at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 4 vaccination visits (see Synopsis Table 3) **(Amended 21 March 2019)**.
- In countries where Placebo is used as a control, one dose will be administered IM at Day 31 (Visit 3) in the 1D RSV + Placebo group and two IM doses will be

– administered IM according to a 0, 1-month schedule at Day 1 (Visit 1) and Day 31 (Visit 3) in the Placebo group (see Synopsis Table 3).

Synopsis Table 3 Vaccines administered and vaccination schedules (Amended 21 March)

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	**7-8 / (V3, D31)**	**8-9 / (V5, D61)**	**10-11 / (V6, D121)****	**14-18 / ~~(V7, D365)~~**
1D RSV + *Bexsero*	1D RSV ChAd	FB	*Bexsero*	*Bexsero*	*Bexsero*
2D RSV + *Bexsero*	2D RSV ChAd	2D RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	FB	*Bexsero*	FB	*Bexsero*
1D RSV + *Nimenrix*	*1D RSV ChAd*	*FB*	*Nimenrix*	*Nimenrix*	*Nimenrix*
2D RSV + *Nimenrix*	*2D* RSV ChAd	*2D* RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	*FB*	*Nimenrix*	FB	*Nimenrix*
1D RSV + *Synflorix*	*1D RSV ChAd*	*FB*	*Synflorix*	*Synflorix*	*Synflorix*
2D RSV + *Synflorix*	*2D* RSV ChAd	*2D* RSV ChAd	*Synflorix*	*Synflorix*	*Synflorix*
Synflorix	*FB*	*Synflorix*	*Synflorix*	FB	*Synflorix*
1D RSV + *Menveo*	*1D RSV ChAd*	*FB*	*Menveo*		*Menveo*
2D RSV + *Menveo*	*2D RSV ChAd*	*2D RSV ChAd*	*Menveo*		*Menveo*
Menveo	*FB*	*Menveo*	FB		*Menveo*
1D RSV + Placebo	1D RSV ChAd	FB			
2D RSV + Placebo	2D RSV ChAd	2D RSV ChAd			
Placebo	FB	FB			

V: Visit; **D:** Day; **1D:** 1 Dose ($1.5x10^{10}$ vp/dose); **2D:** 2 Dose ($5x10^{10}$ vp/dose); **RSV ChAd**: ChAd155-RSV vaccine**; FB:** Formulation buffer S9b.

* Assumes enrolled at 6 and 7 months of age for the vaccine Dose 1 to be administered before the first RSV season (RSV seasons will be determined for each country based on local epidemiological data).

** In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7.

– For ~~the United Kingdom (UK)~~authorized sites only, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator **(Amended 21 March 2019).**

- Surveillance for spontaneous or excessive bleeding.

Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination ***(Visit 1 and Visit 3)***, in order to detect any thrombocytopenic petechiae or purpura. The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets **(Amended 21 March 2019)**.

Section 1.2.2.1, Study Population was amended as follows:

The immunogenicity, safety and reactogenicity of the pediatric candidate RSV vaccine (ChAd155-RSV vaccine) has been evaluated in healthy adults aged 18 to 45 years (study 201974 [RSV PED-001; NCT02491463]). A clinical study is currently being conducted in RSV-seropositive infants aged 12 to 23 months (study 204838 [RSV PED-002]). The safety profile of the ChAd155-RSV vaccine in adults (study 201974 [RSV PED-001; NCT02491463]) has been ~~evaluated~~ ***deemed*** satisfactory by ***GSK and*** an Independent Data Monitoring Committee (IDMC). Should there be a satisfactory safety profile of the ChAd155-RSV vaccine in RSV-seropositive infants, as evaluated by an IDMC on Day 60 data (i.e., 30 days post-Dose 2 of the highest dose level) of the study RSV PED-002, the present study will be performed. This study will be conducted on infants aged 6 and 7 months (having a low chance of natural exposure to RSV before inclusion in the study). ***Although potentially both RSV-exposed and RSV-unexposed subjects will be enrolled, T****he primary analysis for incidence of LRTI will be conducted in infants with a negative RSV exposure status (at screening based on in-stream serological testing). This study will support the decision to age de-escalate to the targeted population (infants as from 6 weeks of age) **(Amended 21 March 2019)**.

Section 1.2.4, Rationale for safety monitoring plan was amended as follows:

During this study, safety evaluations will be performed by an internal safety review committee (iSRC) (refer to Section 9.10.2) and an ***independent data monitoring committee (***IDMC***)*** (refer to Section 9.10.3), with specific holding rules. Data of LRTI associated with RSV infection will be received by the IDMC within 48 hours upon GSK becoming aware (refer to Section 9.10.3 for more detailed information). Any holding rules met during the study will be escalated to the Vaccine Safety Monitoring Board (VSMB; refer to Sections 9.10.4 and 9.10.5) **(Amended 21 March 2019)**.

Section 1.2.4.2, Rationale for monitoring for spontaneous or excessive bleeding was revised as follows:

During a study carried out in adult subjects (RSV001), a mild non-clinically significant drop in hemoglobin was noted following vaccination with another adenoviral vector (PanAd3-RSV) without clinical signs and with a reversal towards baseline values over time [RSV001 Interim Study Report, 2014]. In the repeat dose toxicology study in rabbits using the ChAd155-RSV vaccine, a transient non-clinically significant drop in platelets was noted post IM vaccination (maximal drop of platelet observed 24 hours after vaccination; refer to the current IB for further details). In light of these data, subjects' parent(s)/ legally acceptable representative(s) (LAR[s]) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination ***(Visit 1 and Visit 3)***, in order to detect any thrombocytopenic petechiae or purpura. The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets **(Amended 21 March 2019)**.

Section 1.2.7, Rationale for ChAd155 RSV vaccine recipients receiving active comparator vaccine was amended as follows:

To provide ***potential*** benefit to all trial participants and to maintain the study blind until the end of follow up, the ChAd155-RSV vaccine recipients will also receive immunization with the selected active comparator vaccine **(Amended 21 March 2019).**

Section 1.3.1, Risk Assessment was amended as follows:

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. In order to be able to treat infants with an immediate systemic allergic reaction to vaccination, all infants across all ~~steps~~***groups*** will need to remain under observation (visual follow-up as well as measurement of vital signs) at the study site for at least 60 minutes after vaccination ***for Visit 1 and Visit 3 and 30 minutes for all remaining vaccination visits*** **(Amended 21 March 2019)**.

Section 1.3.2, Benefit Assessment was amended as follows:

The choice of active comparator vaccine (*Bexsero*, *Nimenrix, Synflorix,* or *Menveo*) for each participating country ensures that the vaccine may be given according to the local label and provides ***potential*** medical benefit in the country that chose active comparator. Within a given participating country, all infants in both groups of this study will receive the full locally recommended vaccination course of active comparator vaccine where possible and may be immunized against either invasive meningococcal disease caused by *Neisseria meningitidis* (with the meningococcal vaccines *Bexsero*, *Nimenrix or Menveo*)*;* or against invasive pneumococcal disease, ***pneumonia,*** and acute otitis media caused by *Streptococcus pneumoniae* (with the pneumococcal vaccine *Synflorix)* **(Amended 21 March 2019)**.

Section 1.3.2, Overall Benefit: Risk Conclusion was amended as follows:

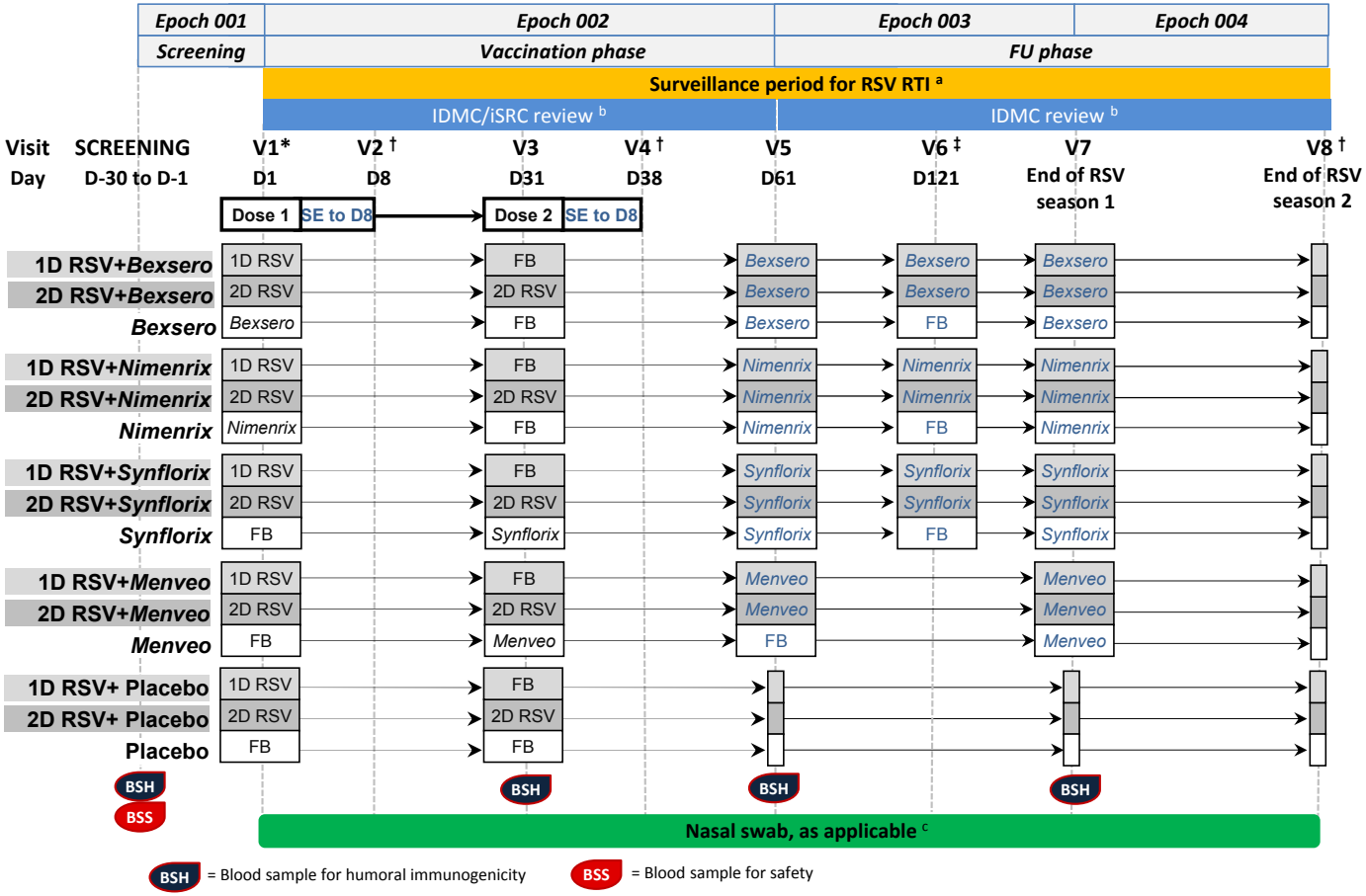
The investigational ChAd155-RSV vaccine is currently in Phase I/II stage of clinical development and no vaccine efficacy has been demonstrated. Taking into account the measures taken to minimize the risk to infants participating in this study, the potential risks to the subjects are justified by the potential benefits linked to the development of this pediatric RSV vaccine.

The four ***control*** vaccines administered to all participants in this study as active ***comparators***, are licensed for infants in the particular country where possible, and therefore have demonstrated medical benefit in the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* (for the *meningococcal vaccines Bexsero, Nimenrix, Menveo);* or against invasive *pneumococcal* disease, ***pneumonia,*** and acute otitis media caused by *Streptococcus pneumoniae* (for the *pneumococcal* vaccine *Synflorix)* **(Amended 21 March 2019)**.

Section 3 has been amended as follows:

STUDY DESIGN OVERVIEW (AMENDED 21 MARCH 2019)

Figure 7 Study design



D: Day; **FU**: follow-up; **IDMC**: Independent Data Monitoring Committee; **iSRC**: internal Safety Review Committee; **RSV**: respiratory syncytial virus; **RTI:** respiratory tract infection; **SE**: solicited events; **V**: Visit ***1D:*** 1 Dose ($1.5x10^{10}$ vp/dose)***; 2D:*** 2 Dose ($5x10^{10}$ vp/dose)***; FB:*** Formulation buffer S9b.

* Vaccine Dose 1 at Day 1 will be administered before the first RSV season (refer to Section 5.1 for definition of RSV season).

† Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator. *For ~~the United Kingdom (UK)~~**authorized sites** only, Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator* **(Amended 21 March 2019)**.

‡ In countries where *Menveo or Placebo* is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

[a] Surveillance for RSV-RTI comprises monthly nasal swab collected to detect asymptomatic RSV infections during RSV season and active and passive surveillance contacts for RSV symptomatic RTI. Of note the swab may be omitted if a nasal swab has been taken at a symptomatic visit in the same month (see Section 9.2). Data about RSV–RTI incidence will be reviewed monthly by an IDMC.

[b] An iSRC will review all accumulating safety data monthly until the IDMC reviews has reviewed all safety data up to 30 days after administration of Dose 2 (i.e., Day 61). The IDMC will review all accumulating safety data monthly throughout the period of vaccination and accumulating SAEs until the end of the second RSV transmission season. Refer to Sections 9.10.2 and 9.10.3.

[c] Refer to Section 6.6.12.3

Table 2 Vaccines administered and vaccination schedules (Amended 21 March 2019)

Groups	Age* (Months) / (Visit, Day)				
	6-7 / (V1, D1)	**7-8 / (V3, D31)**	**8-9 / (V5, D61)**	**10-11 / (V6, D121)****	**14-18 / ~~(V7, D365)~~**
1D RSV + *Bexsero*	1D RSV ChAd	FB	*Bexsero*	*Bexsero*	*Bexsero*
2D RSV + *Bexsero*	2D RSV ChAd	2D RSV ChAd	*Bexsero*	*Bexsero*	*Bexsero*
Bexsero	*Bexsero*	FB	*Bexsero*	FB	*Bexsero*
1D RSV + *Nimenrix*	1D RSV ChAd	FB	*Nimenrix*	*Nimenrix*	*Nimenrix*
2D RSV + *Nimenrix*	2D RSV ChAd	2D RSV ChAd	*Nimenrix*	*Nimenrix*	*Nimenrix*
Nimenrix	*Nimenrix*	FB	*Nimenrix*	FB	*Nimenrix*
1D RSV + *Synflorix*	1D RSV ChAd	FB	*Synflorix*	*Synflorix*	*Synflorix*
2D RSV + *Synflorix*	2D RSV ChAd	2D RSV ChAd	*Synflorix*	*Synflorix*	*Synflorix*
Synflorix	FB	*Synflorix*	*Synflorix*	FB	*Synflorix*
1D RSV + *Menveo*	1D RSV ChAd	FB	*Menveo*		*Menveo*
2D RSV + *Menveo*	2D RSV ChAd	2D RSV ChAd	*Menveo*		*Menveo*
Menveo	FB	*Menveo*	FB		*Menveo*
1D RSV + Placebo	1D RSV ChAd	FB			
2D RSV + Placebo	2D RSV ChAd	2D RSV ChAd			
Placebo	FB	FB			

V: Visit; **D:** Day; **1D:** 1 Dose ($1.5x10^{10}$ vp/dose**); 2D**: 2 Dose ($5x10^{10}$ vp/dose)**; RSV ChAd**: ChAd155-RSV vaccine**;** **FB:** Formulation buffer S9b.

* Assumes enrolled at 6 and 7 months of age for the vaccine Dose 1 to be administered before the first RSV season; the second dose will be given one month after the first dose. (RSV seasons will be determined for each country based on local epidemiological data [The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. Refer to the SPM for RSV seasons per *country*.])

** In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7.

Table 3 Study groups and epochs foreseen in the study (Amended 21 March 2019)

Study groups	*Target* Number of subjects	Age (Min/Max)	Epochs			
			Epoch 001	Epoch 002	Epoch 003	Epoch 004
1D RSV + Bexsero	50	6 – 7 months	N/A	x	x	x
1D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
1D RSV + Synflorix		6 – 7 months	N/A	x	x	x
1D RSV + Menveo		6 – 7 months	N/A	x	x	x
1D RSV + Placebo		6 – 7 months	N/A	x	x	x
2D RSV + Bexsero	50	6 – 7 months	N/A	x	x	x
2D RSV + Nimenrix		6 – 7 months	N/A	x	x	x
2D RSV + Synflorix		6 – 7 months	N/A	x	x	x
2D RSV + Menveo		6 – 7 months	N/A	x	x	x
2D RSV + Placebo		6– 7 months	N/A	x	x	x
Bexsero	50	6 – 7 months	N/A	x	x	x
Nimenrix		6 – 7 months	N/A	x	x	x
Synflorix		6 – 7 months	N/A	x	x	x
Menveo		6 – 7 months	N/A	x	x	x
Placebo		6 – 7 months	N/A	x	x	x

1D: 1 Dose (1.5x10[10] vp/dose); **RSV**: ChAd155-RSV vaccine; ***2D: 2 Dose (5x10[10] vp/dose); N/A: Not Applicable***.

- Vaccination schedules:

  RSV investigational vaccine:

  – In the 1 Dose (1D) groups, a single lower dose of 1.5x10***[10]*** vp will be administered IM at Day 1 (Visit 1). Formulation buffer will be administered in the 1D groups at Day 31 (Visit 3). In the 2 Dose (2D) groups, two doses of 5x10***[10]*** vp will be administered IM according to a 0, 1-month schedule, (i.e., at Day 1 [Visit 1] and Day 31 [Visit 3]) (see Figure 1 and Table 2). Dose 1 will be administered before the first RSV season and the second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the Study Procedures Manual [SPM]. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. **(Amended 21 March 2019)**.

  Comparator or Placebo:

  – In countries where *Bexsero or Nimenrix* is used as a control, two doses will be administered IM with at least a 2 month interval between these primary doses. A booster dose will be administered IM in the second year of life at ~~Day 365 (~~Visit 7~~)~~, with an interval of at least 2 months between the primary series and booster dose. The first *Bexsero or Nimenrix* dose will be administered at Day 1 (Visit 1) (in the groups receiving only *Bexsero* or *Nimenrix*, respectively). In the groups receiving only *Bexsero* or *Nimenrix,* the second dose will be at Day 61 (Visit 5). The first *Bexsero* or *Nimenrix* dose to be administered to the 1D and

2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of *Bexsero* or *Nimenrix* in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Figure 1 and Table 2). **(Amended 21 March 2019)**

- In countries where *Synflorix* is used as a control, two doses will be administered IM with at least a 1 month interval between these primary doses. A booster dose will be administered IM in the second year of life at ~~Day 365 (~~Visit 7~~)~~. The first *Synflorix* dose will be administered at Day 31 (Visit 3) (in the group receiving only *Synflorix).* In the group receiving only *Synflorix*, the second dose will be at Day 61 (Visit 5). The first *Synflorix* dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. The second dose of *Synflorix* in the 1D and 2D groups will be at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine nor comparator is scheduled, at the 5 vaccination visits (see Figure 1 and Table 2). **(Amended 21 March 2019)**
- In countries where *Menveo* is used as a control, two doses will be administered IM at least 3 months apart with the second dose in the second year of life *at* ~~Day 365 (~~Visit 7~~)~~. The first *Menveo* dose will be administered at Day 31 (Visit 3) (in the group receiving only Menveo). The first *Menveo* dose to be administered to the 1D and 2D RSV groups will be at Day 61 (Visit 5), following the 1 or 2 RSV vaccine doses, respectively. Since the second Menveo dose has to be administered in the second year of life at ~~Day 365 (~~Visit 7~~)~~, no administration will be performed at Day 121 (Visit 6). Formulation buffer will be administered, when neither RSV vaccine or comparator is scheduled, at the 4 vaccination visits (see Figure 1 and Table 2). **(Amended 21 March 2019)**

Section 5.3, Exclusion criteria for enrolment has been amended as follows:

- History of recurrent wheezing. ("Recurrent wheezing" is defined as ≥ 2 episodes of wheezing***in the subject's lifetime***~~in the past 12 months~~). Wheezing should have been verified on auscultation by doctor **(Amended 21 March 2019)**.
- Weight below the fifth percentile ***according to the World Health Organization (WHO) weight-for-age tables (https://www.who.int/childgrowth/standards/weight_for_age/en/)***
- ***(*Amended 21 March 2019**).
- ~~Concurrently p~~***P***articipating in another clinical study, at any time during the study period, in which the subject or mother ***(if breastfeeding)*** has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device) **(Amended 21 March 2019).**

Section 6.2.2.2.1, **Study group and treatment number allocation**

After obtaining the signed and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, the ***delegated*** study staff ~~in charge of the vaccine administration~~ will access SBIR. Upon providing the subject identification number and

the age, the randomization system will determine the study group and will provide the treatment number to be used for the first dose **(Amended 21 March 2019)**.

Section 6.2.2.2.2, **Treatment number allocation for subsequent doses**

For each dose subsequent to the first dose, the ***delegated*** study staff ~~in charge of the vaccine administration~~ will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group **(Amended 21 March 2019)**.

Section 6.6.5, Medical History was amended as follows:

6.6.5 Medical History

Obtain the subject's medical history by interview and/or review of the subject's medical records and record weight at birth and gestation in weeks at birth as well as any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF. ***For World Health Organization (WHO) weight percentile standards for girls and boys, refer to the following link:*** https://www.who.int/childgrowth/standards/weight_for_age/en/ **(Amended 21 March 2019)**.

Section 6.6.9 was revised as follows:

6.6.9 Assess pre-vaccination body temperature

The rectal (preferred route) body temperature of each subject needs to be measured prior to any study vaccines administration. If the subject has fever (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table ***24***) **(Amended 21 March 2019)**.

Section 6.6.15 was amended as follows:

6.6.15 Recording of AEs, AEs of special interest and SAEs

- Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination ***(Visit 1 and Visit 3)***, in order to detect any thrombocytopenic petechiae or purpura after each vaccination from Visit 1 [Day 1] to Visit 5 Day 61 **(Amended 21 March 2019)**.

Table 7 List of study procedures

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	~~D365~~ End of the 1st RSV season [d]	~~D730~~ End of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Informed consent	●												
Check inclusion/exclusion criteria	●	O											
Collect demographic data	● [i]												
Medical history [j]	●												
Physical examination [k]	●	O	O	O	O	O		O	O	O		O	●
Growth monitoring [l]	●			●		●		●	●				
Check contraindications and warnings and precautions		O		O		O	O	O					
(Pre-vaccination) body temperature		●		●		●	●	●					
Randomization		O											
Vaccine administration [m]		●		●		●	● [c]	●					
Recording of administered treatment number		●		●		●	●	●					
60 minutes post-vaccination observation [n]		O		O									
30 minutes post-vaccination observation for additional comparator/FB vaccinations						O	O	O					

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	~~D365~~ *E*nd of the 1st RSV season [d]	~~D730~~ *E*nd of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Blood sampling for assessment of mechanisms of illness (potential ERD; ~2.5 mL)													● [o]
Blood sampling for hematology and biochemistry (~2.3 mL)	● [p]									● [q]			
Blood sampling for humoral response (~2.5 mL)	● *[r]*			● *[s]*		●		●					
Surveillance for RSV-RTI, difficulty in breathing and wheezing		O	O	O	O	O	O	O	O		O	O	
Documentation of symptoms and signs of RTI *[t]*													●
Nasal swab for central testing (RSV and RVP)												● *[u]*	● *[v]*
Specimen for local testings (RSV and RVP)													● *[w]*
Distribution of RTI episode card *[x]*		O	O	O	O	O	O	O					
Collection of RTI episode card *[x]*			O	O	O	O	O	O	O	O		O	O
Transcription of RTI episode card			●	●	●	●	●	●	●	O		●	●
Record any concomitant medications/vaccinations		●	●	●	●	●	●	●	●	●		●	●
Distribution of the subject card	O												
Distribution of diary card		O	O	O	O								

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	~~D365~~ *E*nd of the 1st RSV season [d]	~~D730~~ *E*nd of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Return of diary card			O	O	O	O							
Diary card transcription by investigator			●	●	●	●							
Recording of solicited AEs (Day 1–7)		●	●	●	●					● *y*			
Recording of unsolicited AEs (Day 1-30)		●	●	●	●	●				● *y*			
Recording of AE leading to study withdrawal		●	●	●	●	●	●	●	●	●	●	●	●
Recording of AESI (RSV-LRTI)		●	●	●	●	●	●	●	●	●	●	●	●
Recording of AESI (spontaneous or excessive bleeding) [z]		●	●	●	●	●				●			
Reporting of easy bruising, or rash/petechiae monitored by parent(s)/LAR(s) [z]		O	O	O	O	O							
Recording of SAEs		●	●	●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	●	●
Screening conclusion	●												
Study conclusion									●				

Epoch	Epoch 001	Epoch 002					Epoch 003		Epoch 004				
Age	6-7 months	6-9 months											
Type of contact	Screening	Visit 1	Visit 2 [b]	Visit 3	Visit 4 [b]	Visit 5	Visit 6 [c]	Visit 7	Visit 8 [b]	Unscheduled visit for safety [e]	Contact for active/ passive surveillance [f]	Surveillance for asymptomatic RSV-RTI [g]	Assessment of potential RSV-RTI [h]
Timepoints	D -30 to D-1 [a]	D1	D8	D31	D38	D61	D121	~~D365~~ *E*nd of the 1st RSV season [d]	~~D730~~ *E*nd of the 2nd RSV season [d]		Monthly or Weekly	Monthly	
Signing of investigator signature form by investigator after Screening and before each analysis	●					●		●	●				

AE: adverse event; AESI: Adverse Events of Special Interest; FB: Formulation buffer S9b; LRTI: lower respiratory tract infection; RSV: respiratory syncytial virus; RTI: respiratory tract infection, RVP: respiratory viral panel SAE: serious adverse event.

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

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

Note: the double-bordered lines following Visit 5 (Day 61), Visit 7 (end of the first RSV transmission season) and Visit 8 (end of the second RSV transmission season) indicate the statistical analyses which will be performed. After Visit 5 (Day 61) the study will be conducted in a single blind manner, with patients remaining blinded up to the last study visit (end of the second RSV transmission season). The investigator will not have access to the treatment allocation up to the last study visit (end of the second RSV transmission season), except in case of emergency unblinding.

[a] For vaccination done on the same day as screening, it must be ensured that screening procedures only begin after signing consent and that all the screening procedures confirming eligibility, including the laboratory results, are made available prior to vaccination (see Section 6.6.2).

[b] Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (~~Day 730~~) (no blood sampling for immune response and no vaccine administration) may take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator. ~~For the UK only~~***For authorized sites only; screening,*** Visit 5 (Day 61) and Visit 7 (both with blood sampling) may also take place in the subject's home or at the investigators clinical facility as appropriate to the circumstances in the judgment of the investigator **(Amended 21 March 2019)**.

[c] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and it will be administered at the end of the first RSV season at Visit 7 (refer Figure 1 and Table 2).

[d] Refer to the SPM for RSV seasons per country.

[e] This visit is applicable for infants with hematological/biochemical values out of normal range or for further evaluation of clinical suspicion of low platelet count.

[f] Active contacts for surveillance of RSV-RTI will take place weekly during each RSV season and every month outside the RSV season. Passive phone contacts from the carers to the investigator will take place when symptoms occur.

[g] In order to detect asymptomatic RSV infection, monthly visits will be performed during the RSV season.

[h] This visit is only applicable for infants with potential RSV-RTI.

[i] Recording of demographic data includes date of birth, sex, race, ethnicity and comparator group.

[j] Medical history is collected by interview and/or review of the subject's medical records and includes recording the subject's weight at birth and gestation in weeks at birth as well as any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF.

[k] At screening, perform a complete physical examination, including assessment of vital signs (body temperature, heart rate [HR], and RR). At subsequent study visits, perform a physical examination only if the subject's parent(s)/LAR(s) indicate(s) during questioning that there might be some underlying pathology(ies) or if deemed necessary.

[l] Growth monitoring includes weight and length (for infants < 24 months of age) or height (for subjects ≥ 24 months of age).

[m] Refer to Table 2 and to the SPM for the comparator vaccine selection for each country.

[n] Infants will need to remain under observation (visual follow-up as well as measurement of resting vital signs) at the study site for at least 60 minutes after vaccination. Vital signs are body temperature, HR and RR. Vital signs are measured preferably when the infant is calm.

[o] Blood sample collected for subjects hospitalized for LRTI (only for RSV-positive subjects using a locally available RSV test). Refer to Section 6.7.3

[p] At Screening, for infants with hematological/biochemical values out of normal range which are expected to be temporary, a re-screening visit may be scheduled during which blood sample collection for hematology/biochemistry will be repeated (maximum one re-screening visit per infant is allowed).

[q] If any Grade 1 abnormality with potential clinical relevance (according to investigator judgment) or any ≥ Grade 2 abnormality is detected, or for further evaluation of clinical suspicion of low platelet count, refer to Section 6.6.12.2 and Figure 2 for re-test.

[r] If no blood sample was collected for humoral immunogenicity at the screening visit, an additional blood sample will be taken at Visit 1 that must be taken before vaccination.

[s] Samples ***must*** be taken before vaccination.

[t] Signs and symptoms to be recorded in the eCRF are listed in the SPM.

[u] Nasal swab collected at the monthly surveillance for asymptomatic RSV-RTI will be tested by quantitative RT-PCR. This swab may be omitted upon investigator discretion if a swab has been taken for a symptomatic episode in the previous 4 weeks (see Section 6.6.12.3).

[v] If during passive or active surveillance contact, the investigator/study staff assesses that an infant presents a potential RSV-RTI (refer to Table 6 for definition), the potential RSV infection will be assessed by quantitative RT-PCR.

[w] ***At a local routine laboratory*** **(Amended 21 March 2019)**.

[x] Subject's parent(s)/LAR(s) will be instructed to record on the RTI episode card symptoms the start date and the end date of the following symptoms (cough, runny nose, blocked nose, difficulty in breathing, or wheezing) and to return it to the investigator at the next visit or by mail (e-mail or postal mail).

[y] Only when the unscheduled visit occurs within the AE reporting time frame, i.e., from Day 1 to Day 7 for solicited AEs and from Day 1 to Day 30 for unsolicited AEs.

z Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination, in order to detect any thrombocytopenic petechiae or purpura (see Table 19).

Table 8 was amended as follows:

Table 8 Target intervals between study visits (Amended 21 March 2019)

Interval	Length of interval
Screening → Visit 1 (Day 1)	30 days [1]
Visit 1 (Day 1) → Visit 2 (Day 8)	7 days
Visit 1 (Day 1) → Visit 3 (Day 31)	30 days
Visit 1 (Day 1) → Visit 5 (Day 61)	60 days
Visit 3 (Day 31) → Visit 4 (Day 38)	7 days
Visit 3 (Day 31) → Visit 5 (Day 61)	30 days
Visit 5 (Day 61) → Visit 6 (Day 121) [2]	60 days
~~Visit 1 (Day 1) →~~ Visit 7 (end of the first RSV transmission season)	~~365 days~~ (~~From~~ vaccination to the defined end of the first RSV transmission season~~)~~
~~Visit 1 (Day 1) →~~ Visit 8 (end of the second RSV transmission season)	~~730 days~~ (~~From~~ vaccination to the defined end of the second RSV transmission season~~)~~

[1] Visit 1 should take place no longer than 30 days after the Screening visit. When applicable, a re-screening visit may be scheduled at any time (but only once to assess eligibility). All screening procedures need to be performed within 30 days of Visit 1.

[2] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and ***if applicable*** it will be administered at the end of the first RSV season at Visit 7 (refer to Figure 1 and Table 2).

Table 10 was amended as follows:

Table 10 Humoral Immunity (Antibody determination) (Amended 21 March 2019)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off*	Laboratory**
SERUM	Respiratory Syncytial Virus A Ab	NEUTRALIZATION	In-house	ED60	***18 ED60To*** ~~be defined~~	GSK Biologicals[1]
SERUM	Respiratory Syncytial Virus F protein Ab.IgG (Anti-RSV PreF antibody)	ELISA	In-house	EU/ml	To be defined	NÉOMED-LABS[1]

Ab: antibody; **ELISA**: enzyme-linked immunosorbent assay; **IgG**: immunoglobulin G; **RSV**: respiratory syncytial virus

* Assay cut-off and unit might be subject to change (e.g., in case of requalification, revalidation or standardization). In this case, this will be documented in the clinical report.

**Refer to APPENDIX B for the laboratory addresses.

[1] GSK Biologicals laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium

Section 9.1.5.1, Spontaneous or excessive bleeding was amended as follows:

9.1.5.1 Spontaneous or excessive bleeding

Subjects' parent(s)/ legally acceptable representative(s) (LAR[s]) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination ***(Visit 1 and Visit 3),*** in order to detect any thrombocytopenic petechiae or

purpura. The investigator will, based on his/her medical judgment, measure the total blood count and appropriately investigate infants with clinical suspicion of low platelets.

Any episode of spontaneous or excessive bleeding occurring within 30 days after each vaccination should be fully investigated with a full range of hematological tests to identify the underlying cause and reported as an AE of special interest **(Amended 21 March 2019)**.

Section 9.10.2, Internal safety review committee (iSRC) oversight was amended as follows:

9.10.2 Internal safety review committee (iSRC) oversight

This study will be overseen by an iSRC operating under a charter. An iSRC was already involved in study RSV PED-002 (204838). Core members of the iSRC will include a GSK Biologicals' safety physician, a CRDL, and a biostatistician who are not otherwise involved in the conduct of the project. The iSRC safety reviews will be conducted using unblinded data. The iSRC has access to the subject randomization and reviews unblinded data.

The iSRC will review all accumulating safety and reactogenicity data four weeks after the start of vaccination and then every 4 weeks until all dosing with ChAd155-RSV vaccine is complete on the study. The iSRC members will determine if a safety signal should be escalated to the ***VSMB***. The iSRC members will determine whether any of the predefined holding rules are met (refer to Section 9.10.4) or if there is any other safety signal. In this case, vaccination in the study will be immediately put on hold (refer to Section 9.10.5) **(Amended 21 March 2019)**.

Section 9.10.3, Independent Data Monitoring Committee (IDMC) oversight was amended as follows:

9.10.3 Independent Data Monitoring Committee (IDMC) oversight

This study will be overseen by an IDMC operating under a charter. The IDMC involved in the present study was already involved in study RSV PED-002 (204838). Overall, the role of the IDMC includes the review and protection of data integrity and rights and safety of study participants throughout the study period. It will provide initial, regular, and closing advice to GSK Biologicals on medical, ethical, scientific and safety-related issues. Its advice will be based on the interpretation of study data with reference to the study protocol.

The IDMC will review the protocol and statistical analysis plan. Meetings will be documented and minutes of open sessions of the IDMC meetings made available to the sponsor. The IDMC may, if deemed necessary, convene a meeting with, or request further information from the principal investigators and GSK Biologicals' designated project representatives at any stage of the study.

The IDMC may recommend to the sponsor to suspend the enrolment to the study and/or vaccination based on their review of safety data arising in this study (refer to Section 9.10.4)

The IDMC safety reviews will be conducted using unblinded data. The IDMC will review all available safety data while taking into account any other findings that could have an impact on the safety of the subjects.

The IDMC members will determine whether any of the predefined study holding rules are met (refer to Section 9.10.4) or if there is any other safety signal. If this is the case, vaccination in the study will be immediately put on hold. If no safety signal is observed, the favorable outcome of the safety evaluation authorizing the investigator to proceed with vaccination of infants as outlined in Figure 1 will be also documented and provided in writing.

- The IDMC will receive the following safety data within 48 hours upon GSK becoming aware of:
  - Fatal SAEs occurring from Day 1 to the end of the second RSV transmission season.
  - Life-threatening SAEs occurring from Day 1 to the end of the second RSV transmission season.
  - Related SAEs occurring from Day 1 to the end of the second RSV transmission season.
  - SAEs occurring within 30 days of vaccination.
  - LRTI associated with RSV infection (AE of special interest) occurring from Day 1 to the end of the second RSV transmission season.
  - Spontaneous or excessive bleeding (AE of special interest) occurring within 30 days after each vaccination.

  The IDMC will receive the following safety data monthly:
  - Summary reports of solicited and unsolicited AEs. (during the period of vaccination).
  - Cumulative reports of the incidence of RSV RTI, RSV-LRTI, severe RSV-LRTI, very severe RSV-LRTI and RSV-RTI leading to hospitalization based on Table 6 by using local test results until the quantitative PCR results are available.
  - Cumulative tables of incidence of all SAEs.

Additionally, an analysis on occurrence of the progression from infection to very severe RSV-LRTI from first vaccination (Day 1) up to the end of the first RSV transmission season will be conducted on all subjects who have completed Visit 7 (end of the first RSV transmission season) by independent Data Analysis Center if there are minimum of 5 infections among subjects with a negative RSV exposure status (at screening which will be assessed by in-stream serological testing of baseline samples) in each randomized group. **(Amended 21 March 2019)**

In addition, the IDMC will receive from GSK Biologicals:

- New information that may adversely affect the safety of the subjects or the conduct of the study.
- All subsequent protocol amendments, informed consent changes or revisions or other documents originally submitted for review.
- All subsequent protocol administrative changes (for information).

Table 22 was amended as follows:

Table 22 Holding rules assessed by the investigator (Amended 21 March 2019)

Holding Rule	Event	Number of infants/group
1a	Death or any life-threatening serious adverse event (SAE) that can be causally related to vaccination, according to investigator's assessment.	≥ 1
1b	Any withdrawal from the study (by investigator or parent(s)/LAR(s) of the subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination.	≥ 1
1c	Any local or general solicited AE leading to hospitalization that cannot reasonably be attributed to a cause other than vaccination.	≥ 1
1d	Within 30 days post-vaccination ***(Visit 1 and Visit 3),*** Any spontaneous local or general bleeding AND Thrombocytopenia < 50000/mm^3	≥ 1

If an investigator detects one of the holding rules mentioned above, he/she will immediately put the enrolment or the vaccination on hold (refer to Section 9.10.4) and he/she will immediately inform the sponsor and enter the data in the eCRF. It is sponsor's responsibility to put the enrolment or the vaccination on hold at all sites.

Section 9.10.5 was amended as follows:

9.10.5 Procedure if the trial is put on hold

If the trial is put on hold by the investigator ***or*** iSRC or IDMC because a pre-defined holding rule is met or because of a safety concern, then all enrolment in the study and all vaccination will cease immediately, but all other procedures relating to safety, immunology and disease monitoring will continue. The ***iSRC/***IDMC will review all available safety information and may ask for additional information to be provided by the investigators or the ~~sponsor~~***study team***. The ***iSRC/***IDMC will make a recommendation to the ~~sponsor~~***study team*** whether the study should be stopped permanently, modified or continued unchanged **(Amended 21 March 2019)**.

The ~~sponsor~~ ***VSMB*** will review all data and ***iSRC/***IDMC recommendation and will decide whether to stop permanently, modify or continue the conduct of the study. The decision of the VSMB regarding the further conduct of the study will be documented and provided in writing to the investigators **(Amended 21 March 2019)**.

Table 24 was amended as follows:

Table 24 Maximum allowed interval between study visits (Amended 21 March 2019)

Interval	Allowed length of interval[1]
Screening → Visit 1 (Day 1)	0 - 30 days
Visit 1 (Day 1) → Visit 2 (Day 8)	7 - 10 days
Visit 1 (Day 1) → Visit 3 (Day 31)	23 - 44 days
Visit 1 (Day 1) → Visit 5 (Day 61)	60 - 81 days
Visit 3 (Day 31) → Visit 4 (Day 38)	7 - 10 days
Visit 3 (Day 31) → Visit 5 (Day 61)	28 - 37 days [2]
Visit 5 (Day 61) → Visit 6 (Day 121) [3]	60 - 81 days
Visit 5 (Day 61) → Visit 7 (end of the first RSV transmission season)	90 days to the defined end of transmission season or up to 4 weeks after
Visit 6 (Day 121) [3] → Visit 7 (end of the first RSV transmission season)	60 days to the defined end of transmission season or up to 4 weeks after
~~Visit 1 (Day 1) →~~ Visit 7 (end of the first RSV transmission season)	~~180 days to the D~~defined end of ***first RSV*** transmission season ~~or up to 4 weeks after~~
~~Visit 1 (Day 1) →~~ Visit 8 (end of the second RSV transmission season)	~~from the d~~***D***defined end of ***second RSV*** transmission season ~~or up to 4 weeks after~~

[1] Subjects will not be eligible for inclusion in the PP cohort for analysis of immunogenicity if they make the study visit outside this interval.

[2] The interval between Visit 1 and Visit 5 must be a minimum of 60 days to be in line with the active comparator vaccination schedules as per the respective approved labels.

[3] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and Menveo will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7). ***For those countries where there is no Visit 6, should consider the interval from Visit 5 - Visit 7.***

Section 11.5.3 was amended as follows:

11.5.3 Per-protocol Set for analysis of immunogenicity (Amended 21 March 2019)

The per-protocol set (PPS) cohort for analysis of immunogenicity will be defined by timepoint and will consist of all subjects from the ES who complied with eligibility criteria, study procedures up to the end of the study and had immunogenicity results in the epoch as described below.

More specifically, the PPS cohort for analysis of immunogenicity up to Day 61 (Visit 5) /at Visit 7 (end of the first RSV transmission season) will include all evaluable subjects:

- Who met all eligibility criteria (i.e., no protocol violation linked to the inclusion/exclusion criteria, including age).
- Who received study vaccine as scheduled per protocol.
- For whom the administration route and site of the vaccine was as according to protocol.
- Who received the vaccine according to protocol procedures.
- Who complied with the vaccination schedule, as specified in Table 7.

- Who did not receive a concomitant medication/product/vaccine leading to exclusion from a PPS analysis, as described in Section 7.6.2 up to Day 61 (Visit 5) /at ~~Day 365 (~~Visit 7~~)~~ (end of the first RSV transmission season).
- Who complied with the timings of the post vaccination blood sampling for immune response evaluation, up to Day 61 (Visit 5) /at ~~Day 365 (~~Visit 7~~)~~ (end of the first RSV transmission season), as specified in Table 7.
- For whom post-vaccination immunogenicity results are available for at least one assay up to Day 61 (Visit 5) /at ~~Day 365 (~~Visit 7~~)~~ (end of the first RSV transmission season).

Section 11.8.1 was amended as follows:

11.8.1 Within groups assessment

The safety will be descriptively summarized based on the ES. The analysis of local AEs, general AEs and fever will be reported for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups. For the analysis of SAEs and AE of specific interest, the analysis will be performed only on the pooled RSV and pooled comparator groups.

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 will be tabulated with exact 95% confidence interval (CI) after each vaccine dose and overall. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE during the 7-day or 30-day follow-up period will be tabulated, overall vaccination course, with exact 95% CI. The same computations will be done for Grade 3 AEs, for any AEs considered related to vaccination for any Grade 3 AEs considered related to vaccination and AEs resulting in a medically attended visit.

The percentage of subjects reporting each individual solicited local AE (any grade, Grade 2, Grade 3, resulting in a medically attended visit) and 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 (Day 1-7) will be tabulated for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups after each vaccine dose and overall. Similarly, the percentage of doses followed by each individual solicited local and general AE and their sub-categories, will be tabulated, overall vaccination course, with exact 95% CI.

For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (Day 1-7) will be tabulated for each RSV + comparator vaccine group and each active control comparator group and also for the pooled RSV vaccine and pooled comparator groups after each vaccine dose and overall. Similar tabulations will be performed for any fever with a causal relationship to vaccination, Grade 3 (> 40.0°C) causally related fever and for any 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.

For ~~each group and for each hematology and biochemistry~~***clinical safety laboratory*** parameter***s***: ***a listing of laboratory value outside the normal range for the unscheduled visits will be provided as per the toxicity scale refered in the protocol.*** ~~The percentage of subjects having hematology and biochemistry results below or above the local laboratory normal ranges will be tabulated by timepoint.~~ The maximum grading during the study will be tabulated (Refer to APPENDIX C) ***Laboratory values will be classified according to toxicity criteria. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and assessment of clinical significance*** **(Amended 21 March 2019)**

Section 11.12.1 was amended as follows:

Section 11.12.1 Sequence of analyses

In preparation of the planned iSRC and IDMC evaluations, analyses of all available safety data (i.e., data that are as clean as possible) will be performed (see Section 9.10 for more information). These analyses will be done by an unblinded statistician outside GSK to maintain the blinding of the study, and will be documented in a statistical analysis report. Only the outcome of the iSRC and IDMC reviews will be communicated to the RSV study team (no safety signal or safety signal). No clinical study report will be written.

The statistical analyses will be performed in 3 steps:

- An analysis will be performed when all data up to Day 61 ~~(i.e., data that are as clean as possible)~~ are available. Additional safety data available at the time of this analysis will be described. At this point, the statistician will be unblinded (i.e., individual subject treatment assignments will be available) and the study will be conducted in a single blind manner, with patients remaining blinded up to the last study visit (end of the second RSV transmission season). Summary results may unblind some specific subjects but no individual listings will be provided and the investigator will not have access to the treatment allocation up to the last study visit (end of the second RSV transmission season), except in case of emergency unblinding (see Section 9.8). **(Amended 21 March 2019)**
- An analysis will be performed when all data up to Visit 7 (end of the first RSV transmission season) are available. No individual listings will be provided.
- The final analysis will be performed when all data up to study conclusion (end of the second RSV transmission season) are available. An integrated clinical study report containing all data will be written and made available to the investigators at that time.

If the 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.

GlaxoSmithKline Biologicals SA	
Vaccines R &D	
Protocol Amendment 4	
eTrack study number and Abbreviated Title	204894 (RSV PED-011)
IND number	16999
EudraCT number	2018-000431-27
Amendment number:	Amendment 4
Amendment date:	01 August 2019
Co-ordinating author:	• PPD (Scientific Writer)
Rationale/background for changes:	
• The per protocol set definition in the synopsis was updated. • Clarification was added on recruiting sufficient subjects with negative RSV exposure status. • Clarification was added to RTI and LRTI episode definitions. • Table 24 was updated to clarify the visit window intervals. • Additional wording was added to indicate that for countries where it is not acceptable to provide copies of medical records to the sponsors, the investigator will transcribe the required information in a manner that respects the subject's anonymization. • In addition, some typographical errors have been corrected throughout the protocol.	

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

On the protocol cover page, a **Contributing author** has been added.

Contributing authors **(Amended 1 August 2019)**	• PPD (Clinical Research and Development Lead) • PPD (Clinical Research and Development Lead) • PPD (Lead Statistician) • PPD ***(Project Statistician***

Number of subjects	The target will be to enroll approximately 150 infants likely to be previously unexposed to RSV with about 50 infants for each of three randomization groups. If necessary, the sample size ~~will~~ ***may*** be increased through additional recruitment in order to achieve ~~at least 5~~ ***a sufficient number of*** RSV infected infants, with a negative RSV exposure status (at screening based on in-stream baseline serological testing), in each RSV vaccine group. Dose 1 of the ChAd155-RSV vaccine should be administered before the first RSV season and second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the SPM. The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable.) **(Amended 1 August 2019)**.
Per Protocol Set	***Subset of subjects in the exposed set (ES) who have complied with eligibility criteria, study procedures up to the time point of analysis and who have availability of measurement(s) for the analysis variable(s) of interest*** **(Amended 1 August 2019)**. ~~All subjects who received at least 1 dose of the study treatment to which they are randomised and have post-vaccination data (Full Analysis Set) minus subjects with protocol deviations that lead to exclusion.~~

Section 1.2.2.3 was updated as follows:

1.2.2.3 In-stream serological testing of baseline samples to determine exposure status *(Amended 1 August 2019)*

Subjects will not be screened for serostatus as criterion for enrolment in the study, due to the potential presence and detection of residual maternal antibodies (Refer to Section 6.7.3 for more details on the determination of a negative RSV exposure status). The assumption is that the majority of infants are previously unexposed (see Section 1.2.2.2). Serological testing of baseline samples to determine exposure status will be performed in-stream to ensure at least 50% of infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) and the sample size ~~will~~ may be adjusted as needed through additional recruitment (Section 11.4).

Section 5.1 was updated as follows:

5.1 Number of subjects

The target will be to enroll approximately 150 infants likely to be previously unexposed to RSV with about 50 infants for each of three randomization groups. If necessary, the sample size ~~will~~ ***may*** be increased through additional recruitment in order to achieve ~~at least 5~~ ***a sufficient number of*** RSV infected infants, with a negative RSV exposure status (at screening based on in-stream serological testing), in each RSV vaccine group. Dose 1 administration should be completed before the first RSV season and second dose will be given one month after the first dose (RSV seasons will be determined for each country based on local epidemiological data and documented in the SPM). The RSV season is defined as the period of the year when 70% of the RSV cases have occurred in previous years. For the calculation, where available, data from up to the ten previous years should be applied. If the data permit calculation of the actual date of the beginning of the season, rather than approximation to the nearest month, this is desirable. Refer to the SPM for RSV seasons per country. Refer to Section 11.4 for the determination of sample size **(Amended 1 August 2019**).

Section 6.7.3 was updated for clarification as follows:

Section 6.7.3 Laboratory assays

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

Determination of a negative RSV exposure status in infants at 6 to 7 months of age will be based on RSV A and/or B neutralizing antibody titers present in serum at screening (before vaccination with the RSV vaccine) based on in-stream baseline serological testing. At birth, newborns do show positive for neutralizing antibodies due to maternal transfer during gestation. The titer of these antibodies declines over time. At the age of 6 to 7 months a cut-off can be defined below which infants are considered to have a negative RSV exposure status. Infants that show neutralizing antibody titers above this cut-off are suspected to have experienced a recent RSV infection. This cut-off will thus allow the discrimination between a negative RSV exposure status versus RSV infected infants before start of vaccination.

The following laboratory assays are planned:

- Functional (neutralizing) antibody titers against RSV-A will be measured by a neutralization assay on serum samples (Table 10).
- RTI will be assessed by:
  - Quantitative RT-PCR that is able to discriminate RSV-A and RSV-B subtypes (Table 11).
  - Qualitative multiplex PCR for detection of a panel of viruses (Table 11).
  - Local RSV assay, and***/or*** local RVP where available (Table 11) **(Amended 1 August 2019)**.

Table 19 was updated to slign the shading for “Unsolicited AEs” and “AE of special interest (spontaneous or excessive bleeding) so that both end around V5 D6.

Table 19 Reporting periods for collecting safety information (Amended 1 August 2019)

Visit	SCR	V1	V2		V3		V4		V5		V6	V7	V8
Days	-30 to -1	1	7	8	30	31	37	38	60	61	121	end of the 1st RSV season	end of the 2nd RSV season
Solicited local and general AEs													
Unsolicited AEs													
AEs/SAEs leading to withdrawal from the study													
AE of special interest (RSV-LRTI)													
AE of special interest (spontaneous or excessive bleeding)*													
SAEs**													
SAEs related to study participation (start at signature of informed consent form) or concurrent GSK medication/ vaccine													

AE: Adverse Event; **RSV-LRTI:** Respiratory Syncytial Virus-Lower Respiratory Tract Infection; **SAE**: Serious Adverse Event; **SCR**: Screening**; V**: Visit.

* Subjects' parent(s)/LAR(s) will be instructed to contact the investigator/study staff if their child presents symptoms of spontaneous bleeding or easy bruising or if their child develops a rash, within 30 days after either vaccination, in order to detect any thrombocytopenic petechiae or purpura.

** Each subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious

Section 3.3.1 was updated as follows:

Section 3.3.1 Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last 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. ***For countries where it is not acceptable to provide copies of medical records to the sponsor, the required information will be transcribed by the investigator and provided to GSK respecting the subject's anonymization*** **(Amended 1 August 2019)**.

Section 11.4 was revised as follows:

11.4 Determination of sample size

The sample size determination is based on the minimum number of subjects needed to allow detection of a serious ERD signal having a magnitude similar to that of the historic FI-RSV vaccine trials [Kim, 1969]. A total of 150 infants will be enrolled and randomized with 1:1:1 ratio to receive either 1 dose of the $1.5x10^{10}$ vp/dose ChAd-155 RSV vaccine [the 1D RSV + comparator group], 2 doses of the $5x10^{10}$ vp/dose ChAd-155 RSV vaccine [the 2D RSV + comparator group], or no ChAd-155 RSV vaccine [the comparator/Placebo control alone group].

An effect of vaccination on ERD will be monitored very closely. It is anticipated that at least 50% of subjects [Dunn, 2013] will have a negative RSV exposure status (at screening which will be assessed by in-stream serological testing of baseline samples). While the rate of RSV infection could be highly variable by season, a conservative rate of infection of 20% in the first season is assumed [Kutsaya, 2016]. Therefore, with 50 infants in each RSV vaccine group, it is anticipated to observe at least 5 infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in each RSV vaccine group [50×0.5×0.2=5].

With a one-sided type I error of 0.05, and the assumption of a 10% rate of infection progressing to very severe RSV-LRTI (which is a conservative assumption based on the rate in the natural history of disease), 5 infections can provide at least 90% statistical power to demonstrate the progression rate from infection to very severe RSV-LRTI is less than 80%. That is less extreme than that observed in the historic FI-RSV vaccine trial where 80% of RSV RTI cases progressed to hospitalization [Kim, 1969]. During the course of the study, since the actual negative RSV exposure status (at screening based on in-stream baseline serological testing) and infection rates may be lower than 50% and 20%, respectively, the sample size ~~will~~ ***may*** be adjusted as needed through additional recruitment in order to achieve ~~at least 5~~ ***a sufficient number of*** RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in each RSV vaccine group **(Amended 1 August 2019)**.

Tabe 24 was updated to clarify window intervals as follows:

Table 24 Maximum allowed interval between study visits (Amended 1 August 2019)

Interval	Allowed length of interval
Screening → Visit 1 (Day 1)	0 - 30 days
Visit 1 (Day 1) → Visit 2 (Day 8)	7 - 10 days
Visit 1 (Day 1) → Visit 3 (Day 31)	23 - 44 days[1]
Visit 1 (Day 1) → Visit 5 (Day 61)	60 - 81 ***days***[1]
Visit 3 (Day 31) → Visit 4 (Day 38)	7 - 10 days
Visit 3 (Day 31) → Visit 5 (Day 61) [2]	***30*** - 37 days [1,3]
Visit 5 (Day 61) → Visit 6 (Day 121)[4]	60 - 81 days
Visit 7 (end of the first RSV transmission season)	Defined end of first RSV transmission season[5]
Visit 8 (end of the second RSV transmission season)	Defined end of second RSV transmission season[5]

[1] Subjects will not be eligible for inclusion in the PP cohort for analysis of immunogenicity if they make the study visit outside this interval.

[2] ***Where Synflorix is used as the comparator, a minimum of 30 days between Visit 3 and Visit 5 must be maintained to align with the active comparator vaccination schedule.***

[3] The interval between Visit 1 and Visit 5 must be a minimum of 60 days to be in line with the active comparator vaccination schedules as per the respective approved labels.

[4] In countries where *Menveo* or Placebo is used as a comparator, no administration will be performed at Day 121 and therefore in those countries there will be no Visit 6 and Menveo will be administered at the end of the first RSV season at Visit 7 (refer to Table 2 and Table 7).

[5] ***As soon as possible after the end of the RSV season (approximately within 4 weeks) and in accordance with the active comparator vaccination schedule if applicable. If the active comparator dosing for V7 is later than 4 weeks after the end of the first RSV transmission season, then the recommended timing of the active comparator takes precedence.***

Section 11.6.3 was updated as follows:

11.6.3 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. Kinetics will be plotted on subjects with results available at all timepoints. The geometric mean titers/concentrations (GMTs/GMCs) will be computed by taking the anti-logarithm of the arithmetic mean of the log10 transformed titers/concentrations.

A seronegative subject will be defined as a subject whose antibody titer/concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody titer/concentration is greater than or equal to the cut-off value of the assay.

Determination of a negative RSV exposure status in infants at 6 to 7 months of age will be based on RSV A and/or B neutralizing antibody titers present in serum at screening (before vaccination with the RSV vaccine) based on in-stream baseline serological testing. At birth, newborns do show positive for neutralizing antibodies due to maternal transfer during gestation. The titer of these antibodies declines over time. At the age of 6 to 7 months a cut-off can be defined below which infants are considered to have a

negative RSV exposure status. Infants that show neutralizing antibody titers above this cut-off are suspected to have experienced a recent RSV infection. This cut-off will thus allow the discrimination between a negative RSV exposure status versus RSV infected infants before start of vaccination.

~~Vaccine response in terms of RSV neutralizing antibodies will be defined in the statistical analysis plan.~~

The description of the handling of data below the lower limit of quantification for GMC calculation and fold increase will be described in the statistical analysis plan.

Section 11.6.4 was updated as follows:

11.6.4 RTI and LRTI

For the analysis of RTI and LRTI, all cases will be definitively classified as either RSV-RTI, RSV-LRTI, severe RSV-LRTI or very severe RSV-LRTI according to the case definitions presented in Table 6, and the association to RSV infection will be assessed by quantitative PCR as primary analysis.

All confirmed LRTI will also be investigated for a panel of respiratory viruses (multiplex PCR; refer to Table 11, as a supplementary analysis of the occurrence of RSV-LRTI diagnosed upon the multiplex PCR.

For the analysis of RTI episode, a new RTI episode will be defined as any occurrence of cough, runny nose, blocked nose ~~wheezing or difficulty breathing~~ with an interval of at least 7 symptom free days since the last episode of RTI that was diagnosed. ***For the analysis of LRTI episode, a new LRTI episode will be defined as a history of cough or difficulty breathing and blood oxygen saturation < 95%, or respiratory rate increase and confirmed RSV infection with an interval of at least 7 symptom free days since the last episode of LRTI that was diagnosed*** **(Amended 1 August 2019)**.

Section 11.8.1 was updated as follows:

For clinical safety laboratory parameters: a listing of laboratory value outside the normal range for the unscheduled visits will be provided as per the toxicity scale ~~refered in the protocol~~. The maximum grading during the study will be tabulated (Refer to APPENDIX C) Laboratory values will be classified according to toxicity criteria. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and assessment of clinical significance **(Amended 1 August 2019)**.

Section 11.10 was updated as follows:

11.10. Analysis of RTI and LRTI

The primary analysis will be performed on the ES of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) in the pooled single dose RSV vaccine group, the pooled two dose RSV vaccine group, and the pooled comparator group separately for first and second RSV seasons and overall. A

similar analysis will be performed on the entire ES. As primary analysis, the assessment of RSV infection will be performed using the quantitative RT-PCR according to standardized case definitions (see Table 6) based on the available WHO case definitions.

The number of RSV infections within each group and the maximum disease severity of the event will be tabulated. The rate (with 95% CI) of RSV-RTI and RSV-LRTI and infections progressing to hospitalization will be evaluated for each of the three pooled groups.

The ***incidence*** rate of very severe RSV-LRTI among RSV infected infants with a negative RSV exposure status (at screening based on in-stream baseline serological testing) from first vaccination (Day 1) up to the end of the first RSV transmission season will be estimated as well as 95% one-sided lower CI.

The ~~proportion~~ ***incidence rate*** and the relative risk of subjects with ~~at least one~~ RSV-associated RTI (with 95% CI) between each of two pooled RSV vaccine groups and the pooled control group will be calculated for both the cohort of subjects with a negative RSV exposure status (at screening based on in-stream baseline serological testing) on the ES and on the entire ES. The same descriptive analysis will be performed for ~~subjects with at least one~~ RSV-associated LRTI and ~~those with at least one~~ RSV-associated severe LRTI **(Amended 1 August 2019)**.

Section 11.12.1 was updated as follows:

11.12.1 Sequence of analyses

In preparation of the planned iSRC and IDMC evaluations, analyses of all available safety data (i.e., data that are as clean as possible) will be performed (see Section 9.10 for more information). These analyses will be done by an ~~unblinded statistician outside GSK~~ ***independent data analysis center*** to maintain the blinding of the study, and will be documented in a statistical analysis report. Only the outcome of the iSRC and IDMC reviews will be communicated to the RSV study team (no safety signal or safety signal). No clinical study report will be written **(Amended 1 August 2019)**.