Amsterdam, 21 July 2022
EMA/32440/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

MENVEO

meningococcal group A, C, W-135 and Y conjugate vaccine

Procedure no.: EMEA/H/C/001095/P46/045

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Introduction

On 5th of May 2022, the MAH submitted a completed paediatric study for Bexsero, Menveo and Synflorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The current indications for these vaccines in EU are following:

Bexsero is indicated for active immunisation of individuals from 2 months of age and older against invasive meningococcal disease caused by Neisseria meningitidis group B.

Menveo is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to Neisseria meningitidis groups A, C, W-135 and Y, to prevent invasive disease.

Synflorix is indicated for active immunisation against invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 5 years of age.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that RSV PED-011: 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 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Study intervention, dose, mode of administration and lot number:

Treatment name	Vaccine name	Volume to be administered	Mode of administration	Number of doses	Lot numbers
1D RSV ChAd	1D ChAd155-RSV	0.5 mL	Intramuscular injection	1	DRSAA003A
2D RSV ChAd	2D ChAd155-RSV	0.5 mL		2	DRSAA007A; DRSAA008A

Other interventions, dose, mode of administration and lot number:

Treatment name	Vaccine name	Volume to be administered	Mode of administration	Number of doses	Lot numbers
Formulation buffer (FB)	Formulation buffer S9b	0.5 mL	Intramuscular injection	0, 1 or 2 ‡	PFLSA007A; PFLSA010A
Placebo	Formulation buffer S9b	0.5 mL		2	PFLSA007A; PFLSA010A
Bexsero	Bexsero	0.5 mL		3	176521; ABXA48B
	Nimenrix § MenACWY-TT				X62080

Nimenrix	Nimenrix § NaCl	0.5 mL		3	AD02A025A
Menveo	Menveo ¥ MenA lyo	0.5 mL		2	US: AMAA045A; AMAA193AZ NON-US: AMAA145AZ
	Menveo ¥ MenCWY liquid				US: AMXA045A; AMXA193AZ NON-US: AMXA06B
Synflorix	Synflorix 10Pn-PD-DiT	0.5 mL		3	ASPNB065D ; ASPNB203C

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

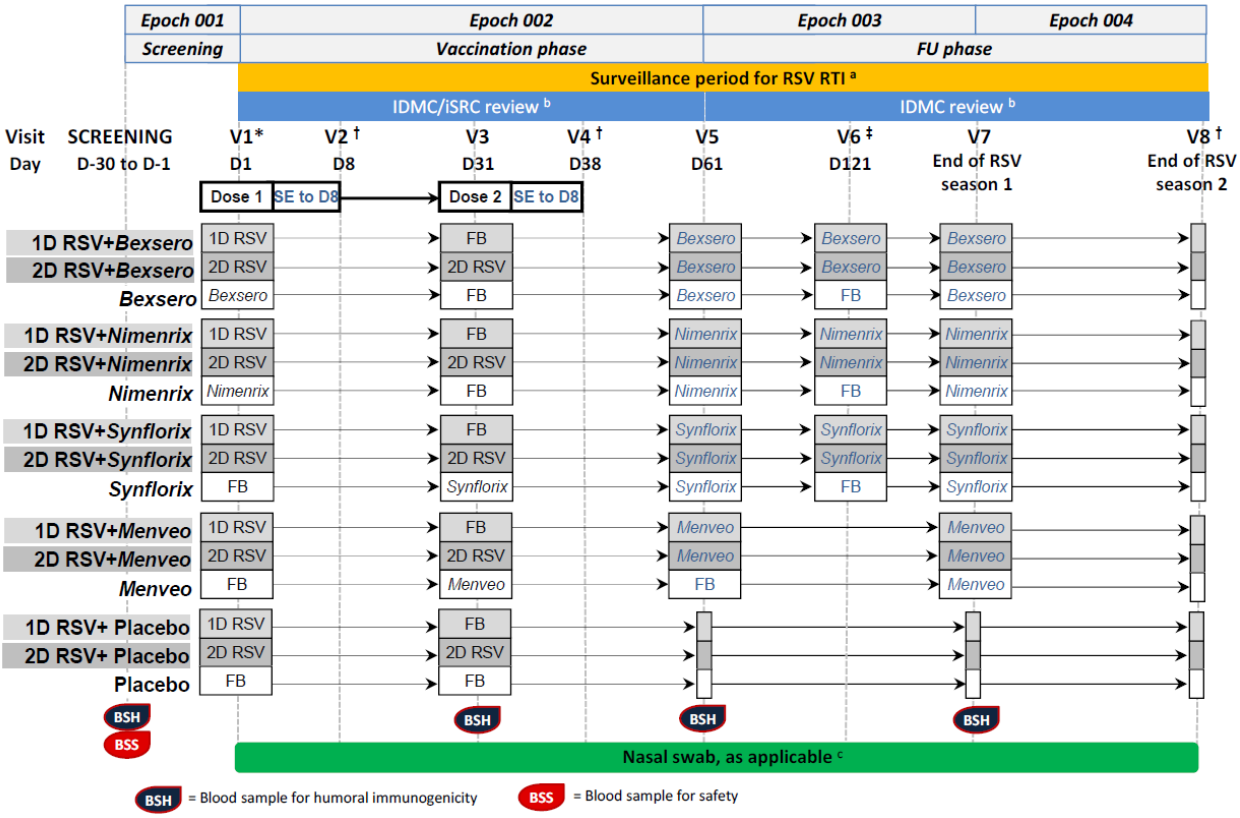
- PED-011: A Phase 1/2, randomized, observer-blind, controlled, multi-center study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' respiratory syncytial virus (RSV) investigational vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (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

2.3.2. Clinical study

PED-011

Description

A Phase I/II, observer-blind, randomized, controlled, multi-centric study with 3 parallel groups for approximately 24 months per study participant. The study was conducted with 4 Epochs and active comparators (*Bexsero*, or *Nimenrix*, or *Synflorix,* or *Menveo*, or placebo (formulation buffer)) with choice of active comparator or placebo done at country level. Active comparators administration was scheduled at different time points according to group allocation ensuring that all participants were vaccinated according to their recommended schedule during the study.



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 was administered before the first RSV season.

† Visit 2 (Day 8), Visit 4 (Day 38), and Visit 8 (no blood sampling for immune response and no vaccine administration) was to take place in the participant'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) was to take place in the participant'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* was used as a comparator, no administration was performed at Day 121 and therefore in those countries there was no Visit 6 and it was administered at the end of the first RSV season at Visit 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 was to be omitted if a nasal swab was taken at a symptomatic visit in the same month. Data about RSV-RTI incidence was reviewed monthly by an IDMC.

[b] An iSRC reviewed all accumulating safety data monthly until the IDMC reviews had reviewed all safety data up to 30 days after administration of Dose 2 (i.e., Day 61). The IDMC reviewed all accumulating safety data monthly
throughout the period of vaccination and accumulating serious adverse events (SAEs) until the end of the second RSV transmission season.

Methods

Study participants

Healthy, full-term born, 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 and whose parent(s)/legally acceptable representative (LAR(s)) who could provide written informed consent and in the opinion of the investigator, could and would

comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits) were included in the study.

Study participant considered as child in care and with any other applicable exclusion criteria was excluded from the study.

Assessor´s comment: Menveo is not indicated in the group included in the current study (infants 6/7 months of age) in EU as it is authorized from 2 years and older individuals. Bexsero is indicated in EU from 2 months of age and therefore the study subjects were also 1-2 weeks younger than indication in EU would allow. As the study was conducted also out of EU, it is not clear if these vaccines were used in EU out of the indicated age.

Treatments

The participants received either 1 or 2 doses of study vaccine ChAd155-RSV sequentially with another vaccine belonging to national child vaccination program (Bexsero, Menveo, Nimenrix, Synflorix) or placebo.

Objectives

Primary:

To evaluate the safety and reactogenicity of the RSV investigational vaccine when administered intramuscular (IM) as one ($1.5x\ 10^{10}$ vp) dose or as two ($5x\ 10^{10}$ 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-lower respiratory tract infection (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.

Outcomes/endpoints

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.

Secondary endpoints:

- Occurrence of RSV-respiratory tract infections (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 PreF3 Immunoglobulin G (IgG) antibody concentrations.

Assessor´s comment: the study objectives and endpoints focus on immunogenicity and safety of the new experimental RSV vaccine for infants. None of the objectives or endpoints would give information about co-administration of RSV vaccine along with Bexsero, Menveo, Nimenrix or Synflorix. Therefore we conclude that no new information can be expected from this study for already authorized vaccines Bexsero, Menveo, Nimenrix and Synflorix.

Sample size

A total of 248 study participants were planned to be enrolled in the study.

The target enrollment was met with the enrollment of a total of 159 infants previously exposed to RSV, of which 151 infants completed the study.

Overall, of the 201 study participants who were enrolled in the study, 192 study participants completed the study.

Assessor´s comment: the study sample size is small, suitable for phase 1 and 2, but as it will be including sub-groups receiving simultaneously some of the other 4 vaccines (Bexsero, Menveo, Nimenrix and Synflorix), the sub-groups are expected to be too small to give adequate information about safety and immunogenicity.

Randomisation and blinding (masking)

Randomisation

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.

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	

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

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.

Assessor´s comment: The use of minimization may be understood given the relatively small numbers, however, possible implications of dynamic allocation methods on potential bias and type I error inflation are expected to be justified (EMA/CHMP/295050/2013). Considering the scope of the current procedure this is not further pursued.

Blinding (masking)

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.

Assessor´s comment: Blinding is considered acceptable. The double blind will be achieved by vaccine preparation and administration being performed by authorized medical personnel who do not participate in any of the clinical evaluation assays. This is an acceptable method.

Statistical Methods

Analysis of demographics

The analysis of demographics was performed on the Exposed Set (ES) and on the ES with negative RSV exposure at baseline for the pooled RSV 1 dose, pooled RSV 2 doses and pooled comparator groups.

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

- Frequency tables were generated for categorical variables such as race.
- Mean, median, standard deviation and range were provided for continuous data such as age.

The distribution of participants was tabulated as a whole and per group. Withdrawal status

was summarized by group using descriptive statistics:

- The number of participants enrolled into the study as well as the number of participants excluded from per-protocol analyses were tabulated.
- The number of withdrawn participants was tabulated according to the reason for withdrawal.

Analysis of safety

Within groups assessment

The safety was descriptively summarized based on the ES. The analysis of local AEs, general AEs and fever was reported for the pooled RSV 1 dose, pooled RSV 2 doses and **pooled comparator groups**. The analysis of SAEs and AE of specific interest was performed on the same pooled groups.

The number and percentage of participants 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 was 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 were tabulated, overall vaccination course, with exact 95% CI. The same computations were performed 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 number and percentage of participants 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) were tabulated for each RSV vaccine group and each comparator group and also for the pooled comparator group after each vaccine dose and overall. Similarly, the percentage of doses followed by each individual solicited local and general AE and their sub categories, were tabulated, overall vaccination course, with exact 95% CI.

For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (Day 1-7) were tabulated for each RSV vaccine group and each comparator group and also for the pooled comparator group after each vaccine dose and overall. Similar tabulations were 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 was presented graphically over time after vaccination.

For clinical safety laboratory parameters: a listing of laboratory value outside the normal range for the unscheduled visits was provided as per the toxicity scale.

The number and percentage of participants with unsolicited AEs within 30 days (Day 1- 30) after each vaccine dose (overall doses) with its exact 95% CI was tabulated for each RSV vaccine group and the pooled comparator group and by MedDRA Preferred Term. Similar tabulation was 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 number and percentage of participants 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 was tabulated according to associated Preferred Term code presented in the statistical analysis plan.

The number and percentage of participants with SAE within 30 days (Day 1-30) after each vaccine dose with its exact 95% CI was tabulated and by MedDRA Preferred Term. Similar tables were generated for SAEs from Dose 1 to end of first RSV season and from Dose 1 to end of the second RSV season.

Serious Adverse Events reported throughout the study and AE of special interest were described in detail.

The number and percentage of participants 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) was summarized by each RSV vaccine and pooled comparator groups after each vaccine dose and overall.

Assessor´s comment: it is noticed that comparator group consists of both placebo and active comparators (the other infant vaccines Bexsero, Menveo, Nimenrix and Synflorix). The safety profile for these 4 vaccines is not the same and observing the reactogenicity to these as one group gives

unclear information. The active comparators and placebo is lumped together, diluting the reactogenicity for this control arm (in tables COMP_PLB).

Analysis of immunogenicity

The analysis was performed on the per protocol set (PPS) for immunogenicity and on the PPS for immunogenicity with negative RSV exposure at baseline. The results from immunogenicity analysis were reported for each RSV vaccine group and the pooled comparator group.

For the final analysis, the adapted PPS for immunogenicity analysis was used which allows the summary of immunogenicity results by time point. In summary table by time point, the immunogenicity data from a participant is included as much as possible (e.g. data from participants who missed dose 2 are still included in the Pre and Day 31 summary).

Within groups assessment

For 3 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 PreF3 IgG antibody concentrations).

- Geometric mean titers/concentrations (GMTs/GMCs) were tabulated with 95% CI and represented graphically.
- Percentage of participants above the seropositivity threshold was tabulated with exact 95% CI.
- The distributions of neutralizing antibody titers/concentrations were tabulated.
- Percentage of responders in terms of neutralizing antibody titers were tabulated with exact 95% CI.
- Individual post-vaccination versus pre-vaccination results were plotted using scatter plots. Results of the comparator group were used as a reference.
- Geometric mean of ratios of antibody titers/concentrations at each post-vaccination timepoint over pre-vaccination were tabulated with 95% CI.

Analysis of RTI and LRTI

The number of RSV infections within each group and the maximum disease severity of the event were tabulated. The rate (with 95% CI) of RSV-RTI and RSV-LRTI and infections progressing to hospitalization were evaluated for each of the 3 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 was estimated as well as the corresponding exact 95% CI.

The incidence rate and the relative risk of participants with RSV-associated RTI (with 95% CI) between each of 2 pooled RSV vaccine groups and the pooled control group were calculated for both the cohort of participants 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 was performed for RSV-associated LRTI and RSV- associated severe LRTI.

The incidence rate of asymptomatic RSV infections (with 95% CI) detected by the quantitative polymerase chain reaction (PCR) (RSV-A/B), was tabulated by the 3 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 were also to be done on the 3 pooled groups.

Assessor´s comment: antibody response to antigens incorporated into Bexsero, Menveo, Nimenrix and Synflorix was not studied. The responses to RSV vaccine is not an interest of current application and are therefore not assessed.

Results

Participant flow

Overall, 201 study participants were vaccinated, of which, 192 completed the study. 9 study participants withdrew from the study for multiple reasons.

Table Subjects disposition

Category Sub category	RSV1D N=65		RSV2D N=71		COMP_PLB N=65		Total N=201	
	n	%	n	%	n	%	n	%
Withdrawals	4	6.2	0	0	5	7.7	9	4.5
Consent withdrawal, not due to an adverse event and/or a serious adverse event	2	3.1	0	0	1	1.5	3	1.5
Not willing to participate this visit	1	1.5	0	0	2	3.1	3	1.5
Lost to follow-up	1	1.5	0	0	0	0	1	0.5
Other	0	0	0	0	1	1.5	1	0.5
Unsolicited non-serious adverse event	0	0	0	0	1	1.5	1	0.5
Number of subjects who completed the study	61	93.8	71	100	60	92.3	192	95.5

RSV1D= 1 dose ChAd155-RSV (1.5 x 10^{10} vp); RSV2D= 2 doses ChAd155-RSV (5 x 10^{10} vp); COMP_PLB= Pooled group of active comparators and placebo
N = Number of subjects
n/% = number / percentage of participants in a given category
Source: Table 14.1.1.6 (22FEB2022 14:23 GMT)

Assessor´s comment: no information, how many subjects received each concomitant vaccine has been given.

Recruitment

The study was conducted at 41 centers in 13 countries: 9 in Spain, 8 in the United States (US), 5 in Poland, 4 in Panama, 3 each in Turkey, United Kingdom (UK) and Finland, 2 Brazil, 3 in Canada, and 1 each in Columbia, Mexico and Thailand. Study period was between 8.04.2019 until 22.07.2021.

Baseline data

Negative RSV exposure status:

Determination of a negative RSV exposure status at screening in infants at 6 to 7 months of age was 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 were suspected to have experienced a recent RSV infection. This cut-off thus allowed the discrimination between a negative RSV exposure status versus RSV infected infants before start of vaccination.

Demographics

- The mean age of the study participants was 6.5 months (standard deviation (SD)= 0.5 months).
- The study population was well representative for both the genders (57% male to 43% female in Exposed Set with negative RSV exposure at baseline and 52% male to 48% female in the Exposed Set). Most of the study participants were of white race followed by another race.

Table. Demographics of the study population

	Exposed Set with negative RSV exposure at baseline				Exposed Set			
	RSV1D N=49	RSV2D N=58	COMP_PLB N=52	Total N=159	RSV1D N=65	RSV2D N=71	COMP_PLB N=65	Total N=201
Age (month) at first vaccination								
Mean	6.4	6.5	6.6	6.5	6.4	6.5	6.5	6.5
Standard Deviation	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sex								
Male	26 (53.1%)	35 (60.3%)	29 (55.8%)	90 (56.6%)	33 (50.8%)	38 (53.5%)	34 (52.3%)	105 (52.2%)
Female	23 (46.9%)	23 (39.7%)	23 (44.2%)	69 (43.4%)	32 (49.2%)	33 (46.5%)	31 (47.7%)	96 (47.8%)
Geographic Ancestry								
American Indian Or Alaska Native	-	1 (1.7%)	1 (1.9%)	2 (1.3%)	1 (1.5%)	1 (1.4%)	2 (3.1%)	4 (2%)
Asian	1 (2%)	1 (1.7%)	1 (1.9%)	3 (1.9%)	1 (1.5%)	1 (1.4%)	1 (1.5%)	3 (1.5%)
Black Or African American	-	-	-	-	-	1 (1.4%)	-	1 (0.5%)
Native Hawaiian Or Other Pacific Islander	-	-	-	-	-	-	-	-
White	28 (57.1%)	33 (56.9%)	30 (57.7%)	91 (57.2%)	38 (58.5%)	39 (54.9%)	37 (56.9%)	114 (56.7%)
Other	20 (40.8%)	23 (39.7%)	20 (38.5%)	63 (39.6%)	25 (38.5%)	29 (40.8%)	25 (38.5%)	79 (39.3%)

Source: Table 14.1.3.1, Table 14.1.3.3

Number analysed

	Exposed Set with negative RSV exposure at baseline				Exposed Set			
	RSV1D	RSV2D	COMP_PLB	Total	RSV1D	RSV2D	COMP_PLB	Total
Exposed Set								
Number of subjects who received Dose 1	49	58	52	159	65	71	65	201
Number of subjects who received Dose 2	47	58	49	154	63	71	61	195
PPS for immunogenicity at EOS1	45	58	49	152	60	70	61	191

Source: Table 14.1.5.1, Table 14.1.5.3, Table 14.2.2.2, Table 14.2.2.7

Assessor´s comment: the comparison group (COMP_PLB) consists of both active comparators (any of the 4 vaccines Bexsero, Menveo, Nimenrix or Synflorix) or placebo. No separate demographics description for each comparator neither exact number of each separate comparator has been given.

Efficacy results

The analysis of immunogenicity evaluated the humoral responses to the RSV vaccine at screening, post-Dose 1 at Day 31 (D31), post-Dose 2 at D61 and at end of first RSV transmission season (EOS1) in the PPS across the RSV1D, RSV2D and pooled comparators (COMP_PLB) groups.

Analysis of anti-RSV-A NAb titers

The anti-RSV-A NAb titers were evaluated at each timepoint by calculating the geometric mean titers (GMTs) and the geometric mean ratios (GMRs) expressed in ED_{60} as unit with an assay cut-off (i.e., lower limit of quantification [LLOQ]) at 18 ED_{60}.

In the RSV seronaïve PPS (N=152 at EOS1), the GMTs of anti-RSV-A NAb were higher at D31 and D61 in the vaccinated groups compared to the COMPL_PLB group. GMTs at SCR, D31, D61 and EOS1 in the RSV seronaïve PPS were as follows:

- **Anti-RSV-A NAb GMTs for the RSV1D group:** 17.1 (95% confidence interval [CI]: 13.8-21.3), 49.4 (95% CI: 35.0-69.7), 54.3 (95% CI: 34.4-85.7) and 170.6 (95% CI: 89.3-326.0) ED_{60};
- **Anti-RSV-A NAb GMTs for the RSV2D group:** 21.2 (95% CI: 17.7-25.4), 93.9 (95% CI: 74.6-118.3), 246.0 (95% CI: 200.9-301.2) and 225.1 (95% CI: 149.3- 339.2) ED_{60}; and
- **Anti-RSV-A NAb GMTs for the COMP_PLB group:** 21.9 (95% CI: 18.3-26.3), 13.9 (95% CI: 11.3-17.3), 10.7 (95% CI: 9.5-12.0) and 58.5 (95% CI: 33.1-103.3), respectively.

The GMRs at D31, D61 and EOS1 in the RSV seronaïve PPS were as follows:

- **Anti-RSV-A NAb GMRs for the RSV1D group:** 2.88 (95% CI: 1.89-4.39), 3.12 (95% CI: 1.90-5.13), 10.25 (95% CI: 5.16-20.36);
- **Anti-RSV-A NAb GMRs for the RSV2D group:** 4.44 (95% CI: 3.32-5.92), 11.80 (95% CI: 8.80-15.82), 10.61 (95% CI: 6.89-16.36); and
- **Anti-RSV-A NAb GMRs for the COMP_PLB group:** 0.64 (95% CI: 0.51-0.79), 0.50 (95% CI: 0.41-0.60), 2.67 (95% CI: 1.46-4.88), respectively.

In addition, these results show that the GMTs were higher at D31 and D61 in the RSV2D group compared to the RSV1D and COMP_PLB groups. In contrast to the RSV1D and COMP_PLB groups, GMTs in the RSV2D group increased between D31 and D61 but were similar between D61 and EOS1. These results suggest that Dose 2 in the RSV2D group provides a substantial boost in the RSV-A NAb titers (see Table 2.1).

In the RSV total PPS (N=191 at EOS1), the anti-RSV-A NAb titers were similar as those observed in the RSV seronaïve PPS. Although no significant differences were observed, GMTs tended to be slightly higher at baseline and at D31 in both vaccinated groups in the total PPS compared to the RSV seronaïve PPS. More specifically, GMTs at SCR, D31, D61 and EOS1 in the total PPS were as follows:

- **Anti-RSV-A NAb GMTs for the RSV1D group:** 26.8 (95% CI: 20.7-34.6), 60.2 (95% CI: 44.2-81.9), 54.3 (95% CI: 37.7-78.0) and 165.0 (95% CI: 95.0-286.6) ED_{60};
- **Anti-RSV-A NAb GMTs for the RSV2D group:** 29.6 (95% CI: 23.6-37.3), 116.2 (95% CI: 87.6-153.9), 259.4 (95% CI: 211.6-318.1) and 223.7 (95% CI: 154.7- 323.4) ED_{60};
- **Anti-RSV-A NAb GMTs for the COMP_PLB group:** 32.2 (95% CI: 24.9-41.6), 18.9 (95% CI: 14.8-24.1), 14.4 (95% CI: 11.8-17.7) and 66.3 (95% CI: 40.2-109.5) ED_{60}.

The GMRs at D31, D61 and EOS1 in the RSV total PPS were as follows:

- **Anti-RSV-A NAb GMRs for the RSV1D group:** 2.29 (95% CI: 1.58-3.31), 1.99 (95% CI: 1.28-3.10), 6.28 (95% CI: 3.40-11.60);
- **Anti-RSV-A NAb GMRs for the RSV2D group:** 3.95 (95% CI: 2.94-5.32), 8.83 (95% CI: 6.54-11.93), 7.83 (95% CI: 5.19-11.81); and
- **Anti-RSV-A NAb GMRs for the COMP_PLB group:** 0.59 (95% CI: 0.49-0.70), 0.44 (95% CI: 0.37-0.52), 2.06 (95% CI: 1.19-3.56), respectively (see Table 2.2).

In the RSV seropositive PPS (N=39 at EOS1), the baseline GMTs were higher in each group as expected in infants previously exposed to RSV. The confidence intervals were wide, which might reflect the smaller proportion of participants included in the seropositive PPS. Of note, GMTs in the RSV2D group were still significantly higher than in the COMP_PLB group at D31 and D61. In the RSV1D and COMP_PLB, GMTs were the lowest at D61 and the highest at EOS1. More specifically, GMTs at SCR, D31, D61 and EOS1 in the seropositive PPS were as follows:

- **Anti-RSV-A NAb GMTs for the RSV1D group:** 102 (95% CI: 82.8-125.6), 113.0 (95% CI: 59.2-215.6), 54.3 (95% CI: 30.6-96.1), 149 (95% CI: 45.1-492.2) ED_{60} ;
- **Anti-RSV-A NAb GMTs for the RSV2D group:** 131.9 (95% CI: 93.1-186.8), 318.7 (95% CI: 100.4-1011.5), 327.6 (95% CI: 159.7-671.9), 217.0 (95% CI: 81.2- 579.8) ED_{60}; and
- **Anti-RSV-A NAb GMTs for the COMP_PLB group:** 154.8 (95% CI: 105.9- 226.1), 64.8 (95% CI: 42.4-99.1), 43.6 (95% CI: 25.5-74.6), 110.7 (95% CI: 34.1- 358.8) ED_{60}, respectively.

The GMRs at D31, D61 and EOS1 in the RSV seropositive PPS were as follows:

- **Anti-RSV-A NAb GMRs for the RSV1D group:** 1.10 (95% CI: 0.54-2.24), 0.53 (95% CI: 0.28-1.01), 1.45 (95% CI: 0.46-4.56);
- **Anti-RSV-A NAb GMRs for the RSV2D group:** 2.29 (95% CI: 0.76-6.92), 2.48 (95% CI: 1.24-4.96), 1.80 (95% CI: 0.78-4.18); and
- **Anti-RSV-A NAb GMRs for the COMP_PLB group:** 0.42 (95% CI: 0.35-0.50), 0.28 (95%

CI: 0.21-0.38), 0.72 (95% CI: 0.20-2.58), respectively (see Table 2.3).

In each PPS group (i.e., total, RSV seronegative, RSV seropositive), the anti-RSV-A NAb titers evolution over time per individual were highly variable, which might be associated with differences in RSV exposure during the RSV season and follow-up.

A re-run analysis of RSV-A NAb GMTs using international unit (IU)/ mL as unit (assay cut-off: 56 IU/ mL) showed similar trends across the different timepoints and study groups for each PPS group.

Analysis of anti-RSV-PreF3 IgG concentrations

The concentrations of anti-RSV-F Ab (i.e., total IgG) were evaluated at each timepoint by calculating the geometric mean concentrations (GMCs) expressed in EU/ mL with an assay cut-off (i.e., LLOQ) at 25 EU/ mL

In the RSV seronaïve PPS (N=151 at EOS1), the GMCs of anti-RSV-F IgG increased between SCR and D31 in both vaccinated groups (RSV1D and RSV2D), in contrast to the COMP_PLB group, which decreased. In the RSV2D group, GMCs also increased between the D31 and D61 timepoints. At EOS1 (versus D61), GMCs increased in the COMP_PLB group, although the vaccinated groups had higher GMCs than the COMPL_PLB group. More specifically, the GMCs at SCR, D31, D61 and EOS1 in the RSV seronaïve PPS were as follows:

- **Anti-RSV-F IgG GMCs for the RSV1D group:** 68.5 (95% CI: 53.6-87.7), 2106.1 (95% CI: 1460.9-3036.2), 2300.0 (95% CI: 1441.2-3670.4) and 5460.6 (95% CI: 3023.2-9863.4) EU/ mL;
- **Anti-RSV-F IgG GMCs for the RSV2D group:** 60.9 (95% CI: 48.2-76.9), 4176.6 (95% CI: 3066.9-5687.9), 9082.3 (95% CI: 7635.2-10803.6) and 5191.2 (95% CI: 3719.1-7246.1) EU/ mL; and
- **Anti-RSV-F IgG GMCs for the COMP_PLB group:** 64.3 (95% CI: 49.7-83.0), 33.2 (95% CI: 22.8-48.3), 17.4 (95% CI: 14.7-20.6) and 251.6 (95% CI: 111.1- 569.9) EU/ mL, respectively.

The GMRs at D31, D61 and EOS1 in the RSV seronaïve PPS were as follows:

- **Anti-RSV-F IgG GMRs for the RSV1D group:** 30.72 (95% CI: 19.41-48.64), 32.90 (95% CI: 19.11-56.64), 83.58 (95% CI: 42.02-166.25);
- **Anti-RSV-F IgG GMRs for the RSV2D group:** 68.62 (95% CI: 45.53-103.41), 150.00 (95% CI: 107.17-209.95), 85.29 (95% CI: 58.97-123.35); and
- **Anti-RSV-F IgG GMRs for the COMP_PLB group:** 0.51 (95% CI: 0.39-0.67), 0.27 (95% CI: 0.22-0.33), 3.94 (95% CI: 1.69-9.21), respectively (see Table 2.4).

In the RSV total PPS (N=189 at EOS1), the trends in anti-RSV-F IgG concentrations were relatively similar to those observed in the RSV seronaïve PPS. Of note, the CIs were substantially narrower in this full cohort analysis, with clearer differences observed between groups. More specifically, GMCs at SCR, D31, D61 and EOS1 in the total PPS were as follows:

- **Anti-RSV-F IgG GMCs for the RSV1D group:** 93.1 (95% CI: 72.7-119.1), 2035.2 (95% CI: 1490.0-2779.9), 1976.5 (95% CI: 1346.2-2901.8) and 5108.7 (95% CI: 3096.7-8428.0) EU/ mL;
- **Anti-RSV-F IgG GMCs for the RSV2D group:** 81.9 (95% CI: 61.8-108.6), 4550.8 (95% CI: 3354.6-6173.7), 9287.9 (95% CI: 7885.5-10939.7) and 4935.5 (95% CI: 3639.8-6692.4) EU/ mL; and
- **Anti-RSV-F IgG GMCs for the COMP_PLB group:** 86.0 (95% CI: 65.5-112.7), 46.2 (95%

CI: 31.6-67.6), 24.6 (95% CI: 18.3-33.0) and 345.1 (95% CI: 165.9- 717.7) EU/ mL, respectively.

The GMRs at D31, D61 and EOS1 in the RSV total PPS were as follows:

- **Anti- RSV-F IgG GMRs for the RSV1D group:** 22.34 (95% CI: 15.06-33.15); 21.76 (95% CI: 13.62-34.77), 55.58 (95% CI: 29.84-103.52);
- **Anti-RSV-F IgG GMRs for the RSV2D group:** 55.53 (95% CI: 38.02-81.12), 113.38 (95% CI: 82.32-156.15), 61.54 (95% CI: 42.00-90.17); and
- **Anti-RSV-F IgG GMRs for the COMP_PLB group:** 0.53 (95% CI: 0.41-0.69), 0.27 (95% CI: 0.22-0.35), 4.02 (95% CI: 1.93-8.35), respectively (see Table 2.5).

In the RSV seropositive PPS (N=38 at EOS1), the anti-RSV-F IgG baseline GMCs were higher in each group and the CIs were wider compared to the larger RSV seronaïve PPS group. GMCs in both vaccinated groups increased between SCR and D31, whereas the variations in GMCs between D31 and D61 were not significant. In the COMP_PLB group only, GMCs were increased at EOS1 (versus D61), but this difference was not significant. At EOS1, the highest GMC across groups was observed in the RSV1D group. More specifically, GMCs at SCR, D31, D61 and EOS1 were as follows:

- **Anti-RSV-F IgG GMCs for the RSV1D group:** 247.6 (95% CI: 168.2-364.4), 1836.5 (95% CI: 944.5-3571.1), 1241.6 (95% CI: 650.0-2371.7) and 4183.3 (95% CI: 1463.6-11957.1) EU/ mL;
- **Anti-RSV-F IgG GMCs for the RSV2D group:** 308.3 (95% CI: 125.7-756.2), 6889.7 (95% CI: 2340.7-20 279.9), 10 245.7 (95% CI: 6179.1-16 988.7) and 3781.3 (95% CI: 1589.5-8995.8) EU/ mL; and
- **Anti-RSV-F IgG GMCs for the COMP_PLB group:** 281.8 (95% CI: 163.5- 485.7), 173.6 (95% CI: 69.5-434.0), 85.2 (95% CI: 31.2-233.0) and 1220.6 (95% CI: 226.0-6591.9) EU/ mL, respectively.

The GMRs at D31, D61 and EOS1 in the RSV seropositive PPS were as follows:

- **Anti-RSV-F IgG GMRs for the RSV1D group:** 8.06 (95% CI: 4.63-14.02), 5.60 (95% CI: 3.38-9.26), 14.97 (95% CI: 3.98-56.24);
- **Anti-RSV-F IgG GMRs for the RSV2D group:** 19.97 (95% CI: 8.39-47.51), 33.23 (95% CI: 18.94-58.31), 11.01 (95% CI: 4.16-29.14); and
- **Anti-RSV-F IgG GMRs for the COMP_PLB group:** 0.62 (95% CI: 0.27-1.40), 0.30 (95% CI: 0.12-0.75), 4.33 (95% CI: 0.85-22.19), respectively

Assessor´s comment: the study objective was to study immune response to RSV after vaccination and therefore immune responses to other concomitant vaccines (Bexsero, Menveo, Nimenrix and Synflorix) were not studied. The comparison group (COMP_PLB) consisted of any of the 4 comparison vaccines or placebo and immune response to RSV different antigens was studied to this control group. As expected, much lower immune responses to RSV proteins were measured in this control group in comparison to the groups receiving RSV vaccine.

Safety results

The incidence and nature of solicited and unsolicited AEs, during the 7-day were similar across study groups and between doses.

Table 2.7 Summary of adverse events (solicited and unsolicited) within 7 days following first and second vaccination and overall - Exposed Set

		RSV1D				RSV2D				COMP_PLB				Total			
				95% CI				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Dose 1	N	65				71				65				201			
	Any adverse event	42	64.6	51.8	76.1	53	74.6	62.9	84.2	51	78.5	66.5	87.7	146	72.6	65.9	78.7
	General adverse event	34	52.3	39.5	64.9	50	70.4	58.4	80.7	45	69.2	56.6	80.1	129	64.2	57.1	70.8
	Local adverse event	16	24.6	14.8	36.9	15	21.1	12.3	32.4	30	46.2	33.7	59.0	61	30.3	24.1	37.2
Dose 2	N	63				71				61				195			
	Any adverse event	34	54.0	40.9	66.6	46	64.8	52.5	75.8	33	54.1	40.8	66.9	113	57.9	50.7	65.0
	General adverse event	31	49.2	36.4	62.1	45	63.4	51.1	74.5	29	47.5	34.6	60.7	105	53.8	46.6	61.0
	Local adverse event	11	17.5	9.1	29.1	14	19.7	11.2	30.9	14	23.0	13.2	35.5	39	20.0	14.6	26.3
Per subject	N	65				71				65				201			
	Any adverse event	53	81.5	70.0	90.1	59	83.1	72.3	91.0	55	84.6	73.5	92.4	167	83.1	77.2	88.0
	General adverse event	51	78.5	66.5	87.7	58	81.7	70.7	89.9	52	80.0	68.2	88.9	161	80.1	73.9	85.4
	Local adverse event	19	29.2	18.6	41.8	20	28.2	18.1	40.1	32	49.2	36.6	61.9	71	35.3	28.7	42.4
Per dose	N	128				142				126				396			
	Any adverse event	76	59.4	50.3	68.0	99	69.7	61.5	77.1	84	66.7	57.7	74.8	259	65.4	60.5	70.1
	General adverse event	65	50.8	41.8	59.7	95	66.9	58.5	74.6	74	58.7	49.6	67.4	234	59.1	54.1	64.0
	Local adverse event	27	21.1	14.4	29.2	29	20.4	14.1	28.0	44	34.9	26.6	43.9	100	25.3	21.0	29.8

RSV1D= 1 dose ChAd155-RSV (1.5 x 10^{10} vp); RSV2D= 2 doses ChAd155-RSV (5 x 10^{10} vp); COMP_PLB= Pooled group of active comparators and placebo
For each dose and per subject:
N = number of participants
n/%= number/percentage of participants presenting at least one type of symptom whatever the dose administered
For per dose:
N = number of doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the dose administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Solicited administration site events

- The solicited administration site events (any local symptom) were similar across all study groups and ranged between 14.9% to 23.0%. The most frequently reported solicited local AEs (per participant) across groups were pain and erythema.
- The overall per subject incidence of solicited administration site events were comparatively high in active control group reported for 26 participants (61.9%) followed by RSV2D group with 11 participants (15.5%).
- The overall per dose incidence of solicited administration site events were comparatively high in active control group reported for 33 participants (39.8%) followed by RSV1D group with 13 participants (10.2%).
- The solicited administration site event with medically attended visit was reported by only 1 study participant in RSV1D group (1.5%).
- Reported rates of grade 2 or 3 solicited administration site AEs in the RSV groups appear similar to those in the Placebo and Active comparator groups. There are no concerns about the frequency or severity of the solicited local AEs in the RSV groups.

Solicited systemic events

The results of analysis of solicited general AEs in the total ES were similar to those reported in the RSV seronaïve ES.

- Of note, fever (overall per participant, any grade) in the total ES was reported in 23.1 % (15 out of 65) participants in the RSV1D group, 52.1% (37 out of 71) in the RSV2D group, 22.7% (5 out of 22) in the placebo group and 38.1% (16 out of 42, including 28 participants who received *Bexsero*) in the active comparator group. After Dose 1 (any grade), reported rates appear higher in the RSV2D group (33.8%) than in the RSV1D group (13.8%) and Placebo group (22.7%) but similar to the active comparator group (31.0%). After Dose 2 (any grade), the reported rate is higher in the RSV2D group (39.4%) than both in the Placebo group

(0.0%) and in the active comparator group (9.8%). However, many participants in the comparator group received a vaccine as first dose (43.8% *Bexsero*, 1.6% *Nimenrix*, 54.7% placebo) and a majority of these participants received a placebo as second dose (78.7% placebo, 21.3% vaccine [*Menveo*, *Synflorix*]).Table 2.9 shows that reports of fever observed after Dose 1 (33.8%) and Dose 2 (39.4%) of the study product in RSV2D group are similar when compared to Bexsero sub-group where participants received this active comparator vaccine as Dose 1 (39.3%) and placebo was administered as Dose 2.

- Grade 3 fever (>40°C) was observed in 1 out of 71 participants in the RSV2D group (1.4%) and in 1 out of 42 participants in the active comparator group who received *Bexsero* (2.4%).
- More frequent reports of fever have been observed after Dose 2 versus administration of Dose 1 of the study intervention in RSV2D group and in participants vaccinated with only one dose of *Bexsero* (39.4% and 39.3%, respectively).

Table Percentage of subjects with solicited general adverse events by maximum intensity within the 7-day (Days 1-7) following first and second vaccination with overall and separate active comparators - Exposed Set

	Drowsiness	**RSV1D**		**RSV2D**		**Placebo**		**Active**		**Bexsero**		**Menveo**		**Nimenrix**		**Synflorix**		**Total**	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Dose 1	**N**	**65**		**71**		**22**		**42**		**28**		**12**		**1**		**1**		**200**	
	Any	12	18.5	19	26.8	7	31.8	14	33.3	11	39.3	2	16.7	0	0	1	100	52	26.0
	Grade 2	1	1.5	4	5.6	3	13.6	3	7.1	2	7.1	1	8.3	0	0	0	0	11	5.5
	Grade 3	1	1.5	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	2	1.0
	Any related	8	12.3	15	21.1	5	22.7	12	28.6	10	35.7	1	8.3	0	0	1	100	40	20.0
	Grade 2 related	0	0	4	5.6	2	9.1	2	4.8	2	7.1	0	0	0	0	0	0	8	4.0
	Grade 3 related	1	1.5	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	2	1.0
	Medically attended visits	1	1.5	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	2	1.0
Dose 2	**N**	**63**		**71**		**20**		**41**		**27**		**12**		**1**		**1**		**195**	
	Any	10	15.9	18	25.4	3	15.0	9	22.0	5	18.5	4	33.3	0	0	0	0	40	20.5
	Grade 2	2	3.2	4	5.6	0	0	0	0	0	0	0	0	0	0	0	0	6	3.1
	Grade 3	1	1.6	3	4.2	0	0	3	7.3	0	0	3	25.0	0	0	0	0	7	3.6
	Any related	7	11.1	15	21.1	3	15.0	3	7.3	2	7.4	1	8.3	0	0	0	0	28	14.4
	Grade 2 related	2	3.2	3	4.2	0	0	0	0	0	0	0	0	0	0	0	0	5	2.6
	Grade 3 related	0	0	3	4.2	0	0	1	2.4	0	0	1	8.3	0	0	0	0	4	2.1
	Medically attended visits	1	1.6	2	2.8	0	0	0	0	0	0	0	0	0	0	0	0	3	1.5
Per subject	**N**	**65**		**71**		**22**		**42**		**28**		**12**		**1**		**1**		**200**	
	Any	18	27.7	29	40.8	8	36.4	18	42.9	13	46.4	4	33.3	0	0	1	100	73	36.5
	Grade 2	2	3.1	7	9.9	3	13.6	2	4.8	2	7.1	0	0	0	0	0	0	14	7.0
	Grade 3	2	3.1	4	5.6	0	0	3	7.1	0	0	3	25.0	0	0	0	0	9	4.5
	Any related	12	18.5	24	33.8	6	27.3	12	28.6	10	35.7	1	8.3	0	0	1	100	54	27.0
	Grade 2 related	1	1.5	6	8.5	2	9.1	2	4.8	2	7.1	0	0	0	0	0	0	11	5.5
	Grade 3 related	1	1.5	4	5.6	0	0	1	2.4	0	0	1	8.3	0	0	0	0	6	3.0
	Medically attended visits	2	3.1	3	4.2	0	0	0	0	0	0	0	0	0	0	0	0	5	2.5
Per dose	**N**	**128**		**142**		**42**		**83**		**55**		**24**		**2**		**2**		**395**	
	Any	22	17.2	37	26.1	10	23.8	23	27.7	16	29.1	6	25.0	0	0	1	50.0	92	23.3
	Grade 2	3	2.3	8	5.6	3	7.1	3	3.6	2	3.6	1	4.2	0	0	0	0	17	4.3

	Grade 3	2	1.6	4	2.8	0	0	3	3.6	0	0	3	12.5	0	0	0	0	9	2.3
	Any related	15	11.7	30	21.1	8	19.0	15	18.1	12	21.8	2	8.3	0	0	1	50.0	68	17.2
	Grade 2 related	2	1.6	7	4.9	2	4.8	2	2.4	2	3.6	0	0	0	0	0	0	13	3.3
	Grade 3 related	1	0.8	4	2.8	0	0	1	1.2	0	0	1	4.2	0	0	0	0	6	1.5
	Medically attended visits	2	1.6	3	2.1	0	0	0	0	0	0	0	0	0	0	0	0	5	1.3

Assessor´s comment: From the data presented for each vaccine separately, one can see, that the number in each active comparator sub-group is very low (Bexsero N=28; Menveo N=12; Nimenrix N=1, Synflorix N=1). Therefore, it is not considered possible to draw immunogenicity conclusions regarding these vaccine from these data, but do provide a possibility for safety comparison to the new RSV vaccine.

	Fever (°C)	**RSV1D**		**RSV2D**		**Placebo**		**Active**		**Bexsero**		**Menveo**		**Nimenrix**		**Synflorix**		**Total**	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Dose 1	**N**	**65**		**71**		**22**		**42**		**28**		**12**		**1**		**1**		**200**	
	Any	9	13.8	24	33.8	5	22.7	13	31.0	11	39.3	2	16.7	0	0	0	0	51	25.5
	≥38.0	9	13.8	24	33.8	5	22.7	13	31.0	11	39.3	2	16.7	0	0	0	0	51	25.5
	>38.5	1	1.5	11	15.5	0	0	9	21.4	8	28.6	1	8.3	0	0	0	0	21	10.5
	>39.0	1	1.5	3	4.2	0	0	2	4.8	2	7.1	0	0	0	0	0	0	6	3.0
	>39.5	0	0	1	1.4	0	0	1	2.4	1	3.6	0	0	0	0	0	0	2	1.0
	>40.0	0	0	0	0	0	0	1	2.4	1	3.6	0	0	0	0	0	0	1	0.5
	>39.0 - ≤40.0	1	1.5	3	4.2	0	0	1	2.4	1	3.6	0	0	0	0	0	0	5	2.5
	Any related	7	10.8	20	28.2	2	9.1	12	28.6	10	35.7	2	16.7	0	0	0	0	41	20.5
	>39.0 - ≤40.0 Related	0	0	2	2.8	0	0	1	2.4	1	3.6	0	0	0	0	0	0	3	1.5
	>40.0 Related	0	0	0	0	0	0	1	2.4	1	3.6	0	0	0	0	0	0	1	0.5
	Medically attended visits	2	3.1	1	1.4	3	13.6	3	7.1	2	7.1	1	8.3	0	0	0	0	9	4.5
Dose 2	**N**	**63**		**71**		**20**		**41**		**27**		**12**		**1**		**1**		**195**	
	Any	6	9.5	28	39.4	0	0	4	9.8	1	3.7	3	25.0	0	0	0	0	38	19.5
	≥38.0	6	9.5	28	39.4	0	0	4	9.8	1	3.7	3	25.0	0	0	0	0	38	19.5
	>38.5	2	3.2	14	19.7	0	0	3	7.3	1	3.7	2	16.7	0	0	0	0	19	9.7
	>39.0	1	1.6	7	9.9	0	0	3	7.3	1	3.7	2	16.7	0	0	0	0	11	5.6
	>39.5	1	1.6	3	4.2	0	0	2	4.9	1	3.7	1	8.3	0	0	0	0	6	3.1
	>40.0	0	0	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	1	0.5
	>39.0 - ≤40.0	1	1.6	6	8.5	0	0	3	7.3	1	3.7	2	16.7	0	0	0	0	10	5.1
	Any related	0	0	24	33.8	0	0	4	9.8	1	3.7	3	25.0	0	0	0	0	28	14.4
	>39.0 - ≤40.0 Related	0	0	6	8.5	0	0	3	7.3	1	3.7	2	16.7	0	0	0	0	9	4.6

	>40.0 Related	0	0	1	1.4	0	0	0	0	0	0	0	0	0	0	0	0	1	0.5
	Medically attended visits	4	6.3	3	4.2	0	0	2	4.9	0	0	2	16.7	0	0	0	0	9	4.6

	Fever (°C)	RSV1D		RSV2D		Placebo		Active		Bexsero		Menveo		Nimenrix		Synflorix		Total
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Per subject	**N**	**65**		**71**		**22**		**42**		**28**		**12**		**1**		**1**		**200**
	Any	15	23.1	37	52.1	5	22.7	16	38.1	12	42.9	4	33.3	0	0	0	0	73
	≥38.0	15	23.1	37	52.1	5	22.7	16	38.1	12	42.9	4	33.3	0	0	0	0	73
	>38.5	3	4.6	19	26.8	0	0	12	28.6	9	32.1	3	25.0	0	0	0	0	34
	>39.0	2	3.1	9	12.7	0	0	5	11.9	3	10.7	2	16.7	0	0	0	0	16
	>39.5	1	1.5	4	5.6	0	0	3	7.1	2	7.1	1	8.3	0	0	0	0	8
	>40.0	0	0	1	1.4	0	0	1	2.4	1	3.6	0	0	0	0	0	0	2
	>39.0 - ≤40.0	2	3.1	8	11.3	0	0	4	9.5	2	7.1	2	16.7	0	0	0	0	14
	Any related	7	10.8	31	43.7	2	9.1	15	35.7	11	39.3	4	33.3	0	0	0	0	55
	>39.0 - ≤40.0 Related	0	0	7	9.9	0	0	4	9.5	2	7.1	2	16.7	0	0	0	0	11
	>40.0 Related	0	0	1	1.4	0	0	1	2.4	1	3.6	0	0	0	0	0	0	2
	Medically attended visits	6	9.2	4	5.6	3	13.6	5	11.9	2	7.1	3	25.0	0	0	0	0	18
Per dose	**N**	**128**		**142**		**42**		**83**		**55**		**24**		**2**		**2**		**395**
	Any	15	11.7	52	36.6	5	11.9	17	20.5	12	21.8	5	20.8	0	0	0	0	89
	≥38.0	15	11.7	52	36.6	5	11.9	17	20.5	12	21.8	5	20.8	0	0	0	0	89
	>38.5	3	2.3	25	17.6	0	0	12	14.5	9	16.4	3	12.5	0	0	0	0	40
	>39.0	2	1.6	10	7.0	0	0	5	6.0	3	5.5	2	8.3	0	0	0	0	17
	>39.5	1	0.8	4	2.8	0	0	3	3.6	2	3.6	1	4.2	0	0	0	0	8
	>40.0	0	0	1	0.7	0	0	1	1.2	1	1.8	0	0	0	0	0	0	2
	>39.0 - ≤40.0	2	1.6	9	6.3	0	0	4	4.8	2	3.6	2	8.3	0	0	0	0	15
	Any related	7	5.5	44	31.0	2	4.8	16	19.3	11	20.0	5	20.8	0	0	0	0	69
	>39.0 - ≤40.0 Related	0	0	8	5.6	0	0	4	4.8	2	3.6	2	8.3	0	0	0	0	12
	>40.0 Related	0	0	1	0.7	0	0	1	1.2	1	1.8	0	0	0	0	0	0	2
	Medically attended visits	6	4.7	4	2.8	3	7.1	5	6.0	2	3.6	3	12.5	0	0	0	0	18

Unsolicited adverse events

- Overall, at least one unsolicited AE was reported for 115 study participants (57.2%).
- The percentage of study participants who reported at least one unsolicited AE was comparatively high in the RSV2D group reported for 45 participants (63.4%).
- Nasopharyngitis (SOC: Infections and infestations) was the most frequently reported unsolicited AE across all study groups.
- Unsolicited AEs of grade 3 intensity were reported for 7 study participants (3.5%) (4 is RSV1D group, 1 in RSV2D group and 2 in comparators group).
- Related unsolicited AEs were reported for 17 study participants (8.5%) (4 is RSV1D group, 8 in RSV2D group and 5 in comparators group).

Serious adverse events

In the total ES, a higher proportion of SAEs was observed in the ChAd155 RSV vaccinated groups than in the pooled comparator group.

Overall at least one SAE was reported for 21 study participant (10.4%).

The percentages of participant with at least one SAE reported during the entire study period were as follows:

- **SAEs in the RSV1D group:** 7 study participants (10.8%)
- **SAEs in the RSV2D group:** 11 study participants (15.5%)
- **SAEs in the comparators group:** 3 study participants (4.6%)

Table. Summary of subjects with at least one serious adverse event classified by MedDRA Primary System Organ Class and Preferred Term from vaccination dose 1 up to end of second RSV season - Exposed Set

	RSV1D N=65		RSV2D N=71		COMP_ PLB N=65		Total N= 201	
Primary System Organ Class (CODE) Preferred Term (CODE)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
At least one serious symptom	7	10.8	11	15.5	3	4.6	21	10.4
Gastrointestinal disorders (10017947)	1	1.5	0	0	0	0	1	0.5
Gastrointestinal hemorrhage (10017955)	1	1.5	0	0	0	0	1	0.5
Infections and infestations (10021881)	5	7.7	9	12.7	3	4.6	17	8.5
Abscess neck (10053576)	1	1.5	0	0	0	0	1	0.5
Bronchiolitis (10006448)	0	0	1	1.4	0	0	1	0.5
Gastroenteritis (10017888)	2	3.1	0	0	0	0	2	1.0
Gastroenteritis viral (10017918)	0	0	1	1.4	0	0	1	0.5
H1N1 influenza (10069767)	1	1.5	1	1.4	0	0	2	1.0
Infectious mononucleosis (10021914)	0	0	0	0	1	1.5	1	0.5
Lower respiratory tract infection viral (10065188)	0	0	1	1.4	0	0	1	0.5
Mastoiditis (10026900)	0	0	1	1.4	0	0	1	0.5
Parvovirus infection (10057343)	0	0	1	1.4	0	0	1	0.5
Periorbital cellulitis (10057182)	0	0	1	1.4	0	0	1	0.5
Pneumonia (10035664)	1	1.5	2	2.8	0	0	3	1.5
Pneumonia respiratory syncytial viral (10035732)	1	1.5	0	0	0	0	1	0.5
Respiratory syncytial virus bronchiolitis (10038718)	0	0	1	1.4	1	1.5	2	1.0
Urinary tract infection (10046571)	0	0	0	0	1	1.5	1	0.5
Injury, poisoning and procedural complications (10022117)	0	0	1	1.4	0	0	1	0.5

Foreign body in respiratory tract (10079847)	0	0	1	1.4	0	0	1	0.5
Metabolism and nutrition disorders (10027433)	0	0	1	1.4	0	0	1	0.5
Diabetic ketoacidosis (10012671)	0	0	1	1.4	0	0	1	0.5
Psychiatric disorders (10037175)	0	0	1	1.4	0	0	1	0.5
Insomnia (10022437)	0	0	1	1.4	0	0	1	0.5
Respiratory, thoracic and mediastinal disorders (10038738)	1	1.5	0	0	0	0	1	0.5
Asthma (10003553)	1	1.5	0	0	0	0	1	0.5

RSV1D= 1 dose ChAd155-RSV (1.5×10^{10} vp); RSV2D= 2 doses ChAd155-RSV (5×10^{10} vp); COMP_PLB= Pooled group of active comparators and placebo Any adverse event=at least one adverse event experienced (regardless of the MedDRA Preferred Term)

N=number of subjects with at least one administered vaccination; n/%=number/percentage of subjects reporting the adverse event at least once

Assessor´s comment: the 3 SAEs observed in COMP_PLB arm were all infections and not related to the any of the comparator vaccines.

RSC-LRTI surveillance

- Lower rate of RSV infection, RSV-RTI, as well as RSV-severe LRTI was reported for study participants in the RSV2D group in comparison to other study groups, among both RSV seronaïve participants and the ES.
- Up to EOS2, among the seronaïve study participants,
  - 15 study participants from RSV1D, 13 from RSV2D and 20 from pooled comparators reported RSV-RTI (excluding RSV-LRTI, RSV-severe or very severe LRTI).
  - 2 study participants from RSV1D, 2 from RSV2D and 1 from pooled comparators reported RSV-LRTI (excluding RSV-severe or very severe LRTI).
  - 1 study participants from RSV1D, 1 from RSV2D and 3 from pooled comparators reported RSV-severe LRTI (excluding RSV-very severe LRTI).
  - 13 study participants from RSV1D, 11 from RSV2D and 8 from pooled comparators reported all-cause LRTI.
- Up to EOS2, among all vaccinated study participants
  - 21 study participants from RSV1D, 16 from RSV2D and 28 from pooled comparators reported RSV-RTI (excluding RSV-LRTI, RSV-severe or very severe LRTI).
  - 2 study participants from RSV1D, 2 from RSV2D and 1 from pooled comparators reported RSV-LRTI (excluding RSV-severe or very severe LRTI).
  - 1 study participants from RSV1D, 1 from RSV2D and 3 from pooled comparators reported RSV-severe LRTI (excluding RSV-very severe LRTI).
  - 14 study participants from RSV1D, 14 from RSV2D and 11 from pooled comparators reported all-cause LRTI.

Among all the reported RSV infection cases, more number of the cases were asymptomatic in the RSV vaccine groups than in the pooled comparators group, in both seronaïve participants and the ES.

Conclusions

- Results for this study suggest no concerns with regards to the reactogenicity or safety data.
- Anti-RSV-A NAb titers and anti-RSV-F IgG concentrations at D31, D61 and EOS1 were the highest in the ChAd155 RSV2D (i.e., high-dose) vaccinated group compared to the levels observed in the RSV1D (i.e., low-dose) and COMP_PLB groups. This suggests that the 2-Dose high-dose regimen is more immunogenic compared to the 1-Dose low-dose regimen, the active comparators and the placebo and that there may be long-term antibody persistence together with further boosting of antibody levels through natural RSV exposure in RSV vaccinated participants.
- In the RSV seropositive PPS, the baseline anti-RSV-A titers and anti-RSV-F IgG concentrations were higher than in the RSV seronaïve and total PPS, as expected in infants previously exposed to RSV. Of note, the values in the RSV2D group were increased at D31 and D61, suggesting that the 2-Dose regimen may have boosted the anti-RSV-Ab levels even in participants previously exposed to RSV.
- The percentages of participants with anti-RSV-A NAbs and anti-RSV-F IgG values above the assay cut-offs at EOS1 were the highest in the RSV2D group as compared to the RSV1D group. This observation suggests that the persistence in the anti-RSV Ab levels is higher after vaccination with the 2-Dose regimen and/or is experienced by more participants in the RSV2D group.
- The anti-RSV-F IgG fold change to anti-RSV-A NAbs fold change ratio showed a high level of variability, making difficult the interpretation of the results. However, it could be observed that all ratios were above 1 in the vaccinated group in the RSV seronaïve and total ES, which may suggest a larger increase in total anti-RSV-F IgG compared to the increase in anti-RSV-A NAb.

2.3.3. Discussion on clinical aspects

A Phase I/II, observer-blind, randomized, controlled, multi-centric study with 3 parallel groups evaluated safety, reactogenicity and immunogenicity of RSV investigational vaccine. The study was conducted with 4 Epochs and active comparators (*Bexsero*, or *Nimenrix*, or *Synflorix,* or *Menveo*, or placebo (formulation buffer)) with choice of active comparator or placebo done at country level. Active comparators administration was scheduled at different time points according to group allocation ensuring that all participants were vaccinated according to their recommended schedule during the study.

Immunogenicity of active comparators was not studied and the influence to RSV vaccine immunogenicity of these comparator vaccines was not studied. In most immunogenicity and safety analyses active comparator and placebo together formed a comparison group (COMP_PLB) to the active arm with RSV vaccine. The safety data presented for each vaccine separately revealed, that the number in each active comparator sub-group was very low (Bexsero N=28; Menveo N=12; Nimenrix N=1, Synflorix N=1). Therefore the observed safety data for comparator vaccines is not seen as robust, but as providing some comparison moment to the new RSV vaccine. No new safety concern was observed for authorized comparator vaccines. The study sample size was too low to allow any conclusions for active comparator vaccines.

3. CHMP overall conclusion and recommendation

The results from RSV PED-011: 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

do not change the benefit-risk profile of Bexsero, Menveo and Synflorix. The results of this study indicate no new efficacy or safety concern.

☒ **Fulfilled:**

No regulatory action required.