14 November 2024
EMA/CHMP/486812/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Abrysvo

Respiratory syncytial virus vaccine (bivalent, recombinant)

Procedure no: EMEA/H/C/006027/P46/006

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	29 Aug 2024	29 Aug 2024	☐
☐	CHMP Rapporteur Assessment Report	21 Oct 2024	17 Oct 2024	☐
☐	CHMP members comments	04 Nov 2024	04 Nov 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Nov 2024	07 Nov 2024	☐
☒	CHMP adoption of conclusions:	14 Nov 2024	14 Nov 2024	☐

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1. Introduction

On 29 August 2024, the MAH submitted a completed paediatric study C3671016 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The CSR is dated 9 July 2024. A short critical expert overview was also provided.

2. Scientific discussion

2.1. Information on the development programme

The MAH conducted C3671016 in accordance with the approved PIP for Abrysvo (P/0058/2023). The PIP required that Abrysvo should be investigated for the prevention of RSV disease in 2 to <5-year-old children and in 5 to <18-year-old children with high-risk chronic medical conditions. Due to the nature of RSVpreF, being a non-live vaccine, it was not required that it should be evaluated in children aged <2 years who are most likely to be RSV-naïve.

2.2. Information on the pharmaceutical formulation used in the study

The approved formulation contains RSVpreF 120 µg per 0.5 mL dose. There is no adjuvant.

C3671016 was a Phase 1 study of the safety and immunogenicity of RSVpreF in children from 2 to <18 years of age. In C3671016, all vaccinated participants received 1 dose of RSVpreF, either the adult dose (120 µg) or half the adult dose (60 µg). See further below on the dose groups.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for C3671016 dated 09 July 2024. The study was initiated (FPFV) 22 June 2023 and the LPLV was on 29 February 2024. The CSR contains a statement on GCP compliance.

2.3.2. Clinical study C3671016

Description

This was a Phase 1, open label age descending dose-finding study to evaluate the and safety and immunogenicity of RSVpreF vaccine in children aged from 2-<18 years. The study was conducted at 16 sites in the US, one of which closed early for financial reasons.

Methods

- *Study participants*

Children were eligible as follows:

1. Age 2 to <18 years of age at enrolment (Visit 1).

2. Healthy or considered by the investigator to be at high risk of RSV disease based on the presence of at least one of the following chronic medical conditions:
☐ Cystic fibrosis
☐ Medically treated asthma
☐ Other chronic respiratory diseases and malformations of the lung

☐ Down syndrome
☐ Neuromuscular disease
☐ Cerebral palsy
☐ Hemodynamically significant or symptomatic congenital heart disease

3. Children aged 2 to <5 years of age were to be confirmed seropositive for RSV (see below). Children older than 5 years were assumed to be seropositive and were not tested before vaccination.

Exclusions included the following:

1. Known or suspected immunodeficiency
2. Autoimmune disease (stable type 1 diabetes and hypothyroidism permitted)
3. Other medical or psychiatric condition that may make the participant inappropriate for the study.
4. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention(s).
5. Bleeding diathesis
6. Seizure disorders or neurological complications following vaccination
7. Previous vaccination with any licensed or investigational RSV vaccine
8. Receipt of monoclonal antibodies against RSV within 6 months
9. Receipt of blood/plasma products or immunoglobulins within 28 days
10. Chronic systemic treatment with known immunosuppressant medications or radiotherapy within 60 days

Vaccination was delayed in case of i) a febrile illness (body temperature ≥38°C); ii) other acute illness within 48 hours; iii)receipt of short-term (<14 days) corticosteroids within 28 days; or iv) receipt of inactivated vaccine within 14 days or live vaccine within 28 days. Non-study vaccines were not given concomitantly or within 14-days of study intervention.

- *Treatments*

Age Stratum (Years)	Number of Participants
2 to <5	~20/~20[a]
5 to <18	~40/~40[a,b]
Total	~60-120

a. Up to 2 dose levels of RSVpreF (120 µg and 60 µg) will be tested in participants.
b. Approximately 40 participants 5 to <18 years old will be enrolled, with ~20 healthy participants and ~20 participants with high-risk chronic medical conditions receiving each dose level.

A single dose of RSVpreF 120 µg (0.5 mL) was to be given to ~40 participants in the 5 to <18-year age stratum first, equally divided between healthy children and those with high-risk chronic medical conditions.

Upon IRC approval, a dose of 60 µg (0.25 mL) was to be given to 20 participants in the 2 to <5-year age stratum. If the IRC was of the opinion that 60 µg was safe, another 20 participants in the 2 to <5-year age stratum were to receive a 120 µg dose. The IRC could also request that a single dose of RSVpreF 60 µg be given to approximately 40 participants in the 5 to <18-year age stratum.

IM injections were into the non-dominant deltoid muscle.

- *Objectives*

The primary objective was to describe the safety of adult and half adult doses. Description of humoral and cell-mediated immunity were secondary objectives.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To describe the safety and tolerability of RSVpreF at each dose level in children 5 to <18 years of age and children 2 to <5 years of age.	Prompted local reactions (pain at the injection site, redness, and swelling). Prompted systemic events (fever, vomiting, diarrhea, headache, fatigue/tiredness, muscle pain, and joint pain). AEs. SAEs. NDCMCs.	In participants receiving 1 dose of study intervention at each dose level, for each age stratum: • The percentage of participants reporting local reactions within 7 days after vaccination. • The percentage of participants reporting systemic events within 7 days after vaccination. • The percentage of participants reporting AEs from vaccination through 1 month after vaccination. • The percentage of participants reporting SAEs throughout the study. • The percentage of participants reporting NDCMCs throughout the study.
Secondary:	**Secondary:**	**Secondary:**
To describe the immune responses elicited by RSVpreF at each dose level in children 5 to <18 years of age and children 2 to <5 years of age.	RSV A and RSV B NTs.	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • GMTs of NT for RSV A and RSV B 1 month after vaccination. • GMTs of NT for RSV A and RSV B before vaccination. • GMFRs of NT for RSV A and RSV B from before vaccination to 1 month after vaccination.
To describe the cell-mediated immune response in children 5 to <18 years of age and children 2 to <5 years of age.	RSV F antigen–specific CD4+ T cells secreting IFNγ. RSV F antigen–specific CD4+ T cells secreting IL-4.	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • Median frequencies of RSV F antigen–specific CD4+ T cells expressing IFNγ before vaccination and 1 month after vaccination. • Median frequencies of RSV F antigen–specific CD4+ T cells expressing IL-4 before vaccination and 1 month after vaccination.

- *Outcomes/endpoints*

The participant or their parent(s)/legal guardian completed a reactogenicity e-diary after each vaccination. Information was collected for 7 days on local reactions, systemic events and temperature. At Visit 2 (a telephone contact on day 7) the content and completion of the diaries was discussed.

Blood samples (approximately 5 mL per sample if <10 years and 10 mL if 10-17 years) were collected at both Visit 1 (day of vaccination) and Visit 3 (1 month post-vaccination) to determine neutralizing antibody using assays conducted at the sponsor's laboratories as documented in the initial MAA. RSV A– and RSV B–neutralizing antibody titres were reported as neutralizing titres (NTs).

Assessor comment

For children aged 2-<5 years, serostatus testing was conducted at Visit 1 or, if a delay in results was expected, at a screening visit that was followed by Visit 1. This testing was conducted by sites using a test kit developed and provided by Pfizer. In the discussion section of the Clinical Overview it is mentioned that this was a lateral flow assay. The assessor is unable to find information in the dossier on this kit and how the results might correlate with NTs.

As described and discussed further below, baseline RSV A and RSV B 50% NT GMTs were lower in the 2 to <5-year group compared to the 5 to <18-year group. In the lower age group there were 6/44 children (13.6%) with baseline NTs for both RSV A and RSV B at the RSV neutralization assay LOD despite being enrolled as seropositive based on the lateral flow test kit. See further below.

Additionally, participants provided blood samples for PBMCs (approximately 1 mL per year of age up to 10 mL maximum) at Visits 1 and 3 to evaluate cell-mediated immunity (CMI) elicited by the vaccine by measuring RSV F antigen–specific CD4+ T cells secreting IFN gamma and F antigen–specific CD4+ T cells secreting IL-4. A description of the methods used to determine CMI is provided.

- *Sample size*

This was an open label study in which groups defined by age were enrolled to receive adult or half adult doses according to the IRC recommendations. As shown above, it was anticipated that between 60 and 120 children would be enrolled to support descriptive analyses.

- *Randomisation and blinding (masking)*

This was a non-randomised and fully open-label study as described above.

- *Statistical methods*

There was no formal hypothesis testing. Immunogenicity results were reported in a descriptive manner. For purposes of descriptive analyses, the populations were defined as shown in the table.

The immunogenicity analyses were conducted for the evaluable immunogenicity population and for the MITT immunogenicity population.

Population	Description
Enrolled	All participants who had a signed ICD.
Randomized population	All enrolled participants who were assigned a randomization number in the IRT system.
Safety population	All enrolled participants who received the study intervention.
Evaluable immunogenicity population	This population was defined for all participants who met the following criteria: • Were eligible for the study; • Received the intervention; • Had the 1-month postvaccination blood collection 27 through 42 days after vaccination; • Had at least 1 valid and determinate assay result 1 month after vaccination; • Had no major protocol violations from vaccination through the 1-month postvaccination blood draw.
mITT immunogenicity population	All participants who were randomized and had at least 1 valid and determinate assay result at any time point after receiving the study intervention.

The SAP (V 3.0) was dated 6 March 2024.

C3671016 - Results Immunogenicity

- *Participant flow*

Of 136 children consented, 127 were vaccinated and 121 (95.3%) completed the 6-month follow-up visit. Among the 2- to <5-year age group, 3 out of 47 tested for serostatus were RSV seronegative and were among the 8 counted as screening failures. One child was consented but not vaccinated.

Table 4. Disposition of All Participants

	Vaccine Group (as Administered)								
	5 to <18 Years				5 to <18 Years				
	Healthy RSVpreF 120 µg n[a] (%)	High Risk RSVpreF 120 µg n[a] (%)	Total RSVpreF 120 µg n[a] (%)	2 to <5 Years RSVpreF 120 µg n[a] (%)	Healthy RSVpreF 60 µg n[a] (%)	High Risk RSVpreF 60 µg n[a] (%)	Total RSVpreF 60 µg n[a] (%)	2 to <5 Years RSVpreF 60 µg n[a] (%)	Total n[a] (%)
Enrolled[b]									136
Vaccinated[c]	25	23	48	24	17	18	35	20	127
Completed	24 (96.0)	21 (91.3)	45 (93.8)	23 (95.8)	17 (100.0)	17 (94.4)	34 (97.1)	19 (95.0)	121 (95.3)
Withdrawn after vaccination	1 (4.0)	2 (8.7)	3 (6.3)	1 (4.2)	0	1 (5.6)	1 (2.9)	1 (5.0)	6 (4.7)
Reason for withdrawal									
Lost to follow-up	1 (4.0)	2 (8.7)	3 (6.3)	1 (4.2)	0	1 (5.6)	1 (2.9)	1 (5.0)	6 (4.7)
Completed 6-month follow-up visit	24 (96.0)	21 (91.3)	45 (93.8)	23 (95.8)	17 (100.0)	17 (94.4)	34 (97.1)	19 (95.0)	121 (95.3)

a. n = Number of participants with the specified characteristic. Each participant was counted once.
b. Enrolled participants are all who signed an informed consent document.
c. The values in this row are the denominators for the percentage calculations.

There were 14 participants considered to have had important protocol deviations (PDs). Dosing error was the most common important PD, occurring in 10 (7.9%) who were given a 120 µg dose of RSVpreF instead of 60 µg (see below). The others had missing samples for determination of immunogenicity.

Table 5. Important Protocol Deviations – Safety Population

	Vaccine Group (as Administered)								
	5 to <18 Years				5 to <18 Years				
Protocol Deviation Category/ Subcategory	Healthy RSVpreF 120 µg (N[a]=25) n[b] (%)	High Risk RSVpreF 120 µg (N[a]=23) n[b] (%)	Total RSVpreF 120 µg (N[a]=48) n[b] (%)	2 to <5 Years RSVpreF 120 µg (N[a]=24) n[b] (%)	Healthy RSVpreF 60 µg (N[a]=17) n[b] (%)	High Risk RSVpreF 60 µg (N[a]=18) n[b] (%)	Total RSVpreF 60 µg (N[a]=35) n[b] (%)	2 to <5 Years RSVpreF 60 µg (N[a]=20) n[b] (%)	Total (N[a]=127) n[b] (%)
Participants with any protocol deviation	5 (20.0)	5 (21.7)	10 (20.8)	2 (8.3)	0	0	0	2 (10.0)	14 (11.0)
Investigational Product	4 (16.0)	4 (17.4)	8 (16.7)	2 (8.3)	0	0	0	0	10 (7.9)
Dosing/Administration error	4 (16.0)	4 (17.4)	8 (16.7)	2 (8.3)	0	0	0	0	10 (7.9)
Laboratory	1 (4.0)	2 (8.7)	3 (6.3)	0	0	0	0	2 (10.0)	5 (3.9)
PBMC samples not collected	1 (4.0)	1 (4.3)	2 (4.2)	0	0	0	0	0	2 (1.6)
Serology sample not collected	0	2 (8.7)	2 (4.2)	0	0	0	0	0	2 (1.6)
Whole blood samples for PBMC processed incorrectly, e.g. expired/incorrect lab supplies used	0	0	0	0	0	0	0	1 (5.0)	1 (0.8)
incorrect whole blood sample volume collected for PBMC	0	0	0	0	0	0	0	1 (5.0)	1 (0.8)

a. N = number of participants in the specified group, or the total sample who received vaccine. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic. A participant with multiple deviations is counted only once in each of the specified categories and subcategories.

From vaccination through the end of the study, 18.9% received non-study vaccines, the most common being influenza (16.5%) and COVID-19 (15.0%) vaccines. All vaccinated participants had blood samples obtained prior to Visit 1 (vaccination) and at Visit 3 99.2% had blood samples drawn.

- *Baseline data*

The table summarises baseline demographics for the safety population by age and dose group. Data were similar for the immunogenicity populations.

Table 7. Demographic and Baseline Characteristics – Safety Population

	Vaccine Group (as Administered)								
	5 to <18 Years				5 to <18 Years				
	Healthy RSVpreF 120 µg (N[a]=25) n[b] (%)	High Risk RSVpreF 120 µg (N[a]=23) n[b] (%)	Total RSVpreF 120 µg (N[a]=48) n[b] (%)	2 to <5 Years RSVpreF 120 µg (N[a]=24) n[b] (%)	Healthy RSVpreF 60 µg (N[a]=17) n[b] (%)	High Risk RSVpreF 60 µg (N[a]=18) n[b] (%)	Total RSVpreF 60 µg (N[a]=35) n[b] (%)	2 to <5 Years RSVpreF 60 µg (N[a]=20) n[b] (%)	Total (N[a]=127) n[b] (%)
Sex									
Male	10 (40.0)	12 (52.2)	22 (45.8)	11 (45.8)	12 (70.6)	11 (61.1)	23 (65.7)	13 (65.0)	69 (54.3)
Female	15 (60.0)	11 (47.8)	26 (54.2)	13 (54.2)	5 (29.4)	7 (38.9)	12 (34.3)	7 (35.0)	58 (45.7)
Race									
White	16 (64.0)	17 (73.9)	33 (68.8)	17 (70.8)	13 (76.5)	9 (50.0)	22 (62.9)	15 (75.0)	87 (68.5)
Black or African American	7 (28.0)	6 (26.1)	13 (27.1)	3 (12.5)	2 (11.8)	6 (33.3)	8 (22.9)	4 (20.0)	28 (22.0)
Asian	2 (8.0)	0	2 (4.2)	0	0	0	0	0	2 (1.6)
American Indian or Alaska Native	0	0	0	1 (4.2)	0	0	0	0	1 (0.8)
Multiracial	0	0	0	3 (12.5)	2 (11.8)	3 (16.7)	5 (14.3)	1 (5.0)	9 (7.1)
Ethnicity									
Hispanic/Latino	5 (20.0)	0	5 (10.4)	1 (4.2)	3 (17.6)	4 (22.2)	7 (20.0)	5 (25.0)	18 (14.2)
Non-Hispanic/non-Latino	20 (80.0)	23 (100.0)	43 (89.6)	22 (91.7)	14 (82.4)	13 (72.2)	27 (77.1)	15 (75.0)	107 (84.3)
Not reported	0	0	0	1 (4.2)	0	1 (5.6)	1 (2.9)	0	2 (1.6)
Age at vaccination (years)									
Mean (SD)	12.6 (4.55)	11.0 (3.50)	11.8 (4.11)	3.0 (0.78)	9.5 (3.57)	9.6 (3.40)	9.6 (3.43)	3.2 (0.77)	8.2 (4.93)
Median	14.0	12.0	12.5	3.0	8.0	9.5	9.0	3.0	7.0
Min, max	(5, 17)	(5, 17)	(5, 17)	(2, 4)	(5, 16)	(5, 16)	(5, 16)	(2, 4)	(2, 17)

- *Numbers analysed*

Table 6. Immunogenicity Populations

	Vaccine Group (as Administered)								
	5 to <18 Years				5 to <18 Years				
	Healthy RSVpreF 120 µg n[a] (%)	High Risk RSVpreF 120 µg n[a] (%)	Total RSVpreF 120 µg n[a] (%)	2 to <5 Years RSVpreF 120 µg n[a] (%)	Healthy RSVpreF 60 µg n[a] (%)	High Risk RSVpreF 60 µg n[a] (%)	Total RSVpreF 60 µg n[a] (%)	2 to <5 Years RSVpreF 60 µg n[a] (%)	Total n[a] (%)
Vaccinated [b]	25	23	48	24	17	18	35	20	127
mITT immunogenicity population	25 (100.0)	22 (95.7)	47 (97.9)	24 (100.0)	17 (100.0)	18 (100.0)	35 (100.0)	20 (100.0)	126 (99.2)
Participants excluded from mITT immunogenicity population	0	1 (4.3)	1 (2.1)	0	0	0	0	0	1 (0.8)
Reason for exclusion									
Had no valid and determinate assay results at 1-month follow-up visit	0	1 (4.3)	1 (2.1)	0	0	0	0	0	1 (0.8)
Evaluable immunogenicity population	24 (96.0)	21 (91.3)	45 (93.8)	24 (100.0)	15 (88.2)	18 (100.0)	33 (94.3)	20 (100.0)	122 (96.1)
Participants excluded from evaluable immunogenicity population	1 (4.0)	2 (8.7)	3 (6.3)	0	2 (11.8)	0	2 (5.7)	0	5 (3.9)
Reason for exclusion[c]									
Not eligible for the study	0	0	0	0	0	0	0	0	0
Did not have 1-month follow-up blood draw visit	0	1 (4.3)	1 (2.1)	0	0	0	0	0	1 (0.8)
Had 1-month follow-up visit but with blood draw outside 27 to 42 days window after vaccination	1 (4.0)	1 (4.3)	2 (4.2)	0	2 (11.8)	0	2 (5.7)	0	4 (3.1)
Had no valid and determinate assay results at 1-month follow-up	0	1 (4.3)	1 (2.1)	0	0	0	0	0	1 (0.8)

- *Outcomes and estimation*

Neutralizing antibody titres

Before vaccination

GMTs were higher in the older age group (5-<18 years) vs. the younger age group (2-<5 years). Additionally, in the older subgroup, baseline GMTs were higher in the high-risk vs. healthy children.

After vaccination (Visit 3 and month 1)

- The response to RSVpreF 120 µg in the 5 to <18-years group was higher than that in the 2 to <5-years group, especially for RSV-B.
- The response to RSVpreF 60 µg in the 5 to <18-years group was higher than that in the 2 to <5-years group.
- In the 5 to <18-years group, the RSV A and RSV B 50% NT GMTs were 31199 and 29670, respectively, after 120 µg doses and 24630 and 32146, respectively, after 60 µg doses. The RSV A and RSV B 50% NT GMFRs were both 20.3 in the 120 µg dose group compared to 19.0 and 23.5, respectively, in the
- 60 µg dose group.
- In the 2- to <5-years group, the RSV A and RSV B 50% NT GMTs were 26146 and 16504, respectively, after 120 µg doses and 11004 and 10659, respectively, after 60 µg doses. The RSV A and RSV B 50% NT GMFRs were 42.8 and 39.8 in the 120 µg dose group compared to 17.7 and 20.6, respectively, in the 60 µg dose group.

Similar results were obtained for the mITT immunogenicity population

Table 8. RSV A and RSV B 50% Neutralizing Titer GMTs and GMFRs – Evaluable Immunogenicity Population

		Before Vaccination			1 Month After Vaccination			Fold Rise (1 Month After Vaccination/Before Vaccination)		
RSV Subgroup	Vaccine Group (as Administered)	n[a]	GMT[b]	(95% CI)[b]	n[a]	GMT[b]	(95% CI)[b]	n[a]	GMFR[c]	(95% CI)[c]
A	5 to <18 Years Healthy RSVpreF 120 µg	24	1168	(706, 1932)	24	27862	(21493, 36119)	24	21.9	(14.46, 33.08)
	5 to <18 Years High Risk RSVpreF 120 µg	20	2003	(1421, 2823)	21	35503	(26876, 46900)	20	18.6	(13.03, 26.55)
	5 to <18 Years Total RSVpreF 120 µg	44	1493	(1090, 2044)	45	31199	(25909, 37569)	44	20.3	(15.55, 26.56)
	2 to <5 Years RSVpreF 120 µg	24	529	(335, 835)	24	26146	(13301, 51396)	24	42.8	(23.41, 78.16)
	5 to <18 Years Healthy RSVpreF 60 µg	15	916	(653, 1285)	15	25341	(15394, 41715)	15	27.7	(17.81, 42.93)
	5 to <18 Years High Risk RSVpreF 60 µg	18	1667	(1035, 2684)	18	24053	(17440, 33173)	18	13.9	(8.75, 22.03)
	5 to <18 Years Total RSVpreF 60 µg	33	1270	(936, 1724)	33	24630	(18814, 32244)	33	19.0	(13.68, 26.36)
	2 to <5 Years RSVpreF 60 µg	20	561	(309, 1016)	20	11004	(4287, 28245)	20	17.7	(9.02, 34.67)
B	5 to <18 Years Healthy RSVpreF 120 µg	24	1206	(717, 2027)	24	30251	(21607, 42355)	24	24.4	(15.53, 38.26)
	5 to <18 Years High Risk RSVpreF 120 µg	20	1905	(1238, 2930)	21	29019	(18786, 44827)	20	16.3	(9.91, 26.83)
	5 to <18 Years Total RSVpreF 120 µg	44	1484	(1058, 2082)	45	29670	(22884, 38469)	44	20.3	(14.65, 28.14)
	2 to <5 Years RSVpreF 120 µg	24	391	(231, 661)	24	16504	(8267, 32948)	24	39.8	(22.96, 69.08)
	5 to <18 Years Healthy RSVpreF 60 µg	15	965	(668, 1393)	15	33351	(23565, 47202)	15	34.6	(21.63, 55.23)
	5 to <18 Years High Risk RSVpreF 60 µg	18	1760	(947, 3272)	18	31174	(21756, 44668)	18	17.0	(9.25, 31.40)
	5 to <18 Years Total RSVpreF 60 µg	33	1339	(922, 1946)	33	32146	(25333, 40791)	33	23.5	(15.83, 34.90)
	2 to <5 Years RSVpreF 60 µg	20	499	(258, 967)	20	10659	(3526, 32228)	20	20.6	(10.00, 42.50)
A/B	5 to <18 Years Healthy RSVpreF 120 µg	24	1187	(741, 1900)	24	29032	(22267, 37853)	24	23.1	(15.17, 35.16)
	5 to <18 Years High Risk RSVpreF 120 µg	20	1953	(1353, 2820)	21	32098	(23148, 44509)	20	17.4	(11.73, 25.85)
	5 to <18 Years Total RSVpreF 120 µg	44	1488	(1098, 2017)	45	30425	(24909, 37162)	44	20.3	(15.31, 26.95)
	2 to <5 Years RSVpreF 120 µg	24	455	(285, 727)	24	20773	(10644, 40543)	24	41.3	(23.49, 72.51)
	5 to <18 Years Healthy RSVpreF 60 µg	15	940	(698, 1268)	15	29071	(19691, 42920)	15	30.9	(19.99, 47.81)
	5 to <18 Years High Risk RSVpreF 60 µg	18	1713	(1017, 2884)	18	27383	(20364, 36820)	18	15.4	(9.12, 25.94)
	5 to <18 Years Total RSVpreF 60 µg	33	1304	(949, 1792)	33	28138	(22449, 35269)	33	21.1	(14.87, 30.03)
	2 to <5 Years RSVpreF 60 µg	20	529	(295, 950)	20	10830	(3928, 29860)	20	19.1	(9.61, 37.96)

Abbreviations: GM = geometric mean; GMT = geometric mean titer; GMFR = geometric mean fold rise; LLOQ = lower limit of quantitation.
Note: For each individual, the combined A/B RSV subgroup is the GM of titer or fold rise of RSV A and RSV B at the specified time point.
Note: The LLOQ for each neutralization titer was: RSV A 50% = 242, RSV B 50% = 99. Assay results below the LLOQ were set to 0.5 x LLOQ for analysis, with the exception of calculating the fold-rise when a before vaccination assay value was below the LLOQ but a corresponding after vaccination assay value was at the LLOQ or above, where the LLOQ was set for before vaccination.
a. n = Number of participants with valid and determinate assay results at the specified visit; for GMFR, only participants with valid and determinate assay results before vaccination and 1 month after vaccination were counted.
b. GMTs and 2-sided 95% confidence intervals (CIs) were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution).
c. GMFRs and the corresponding 2-sided 95% confidence intervals (CIs) were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution).

The seroresponse rate was defined as achieving a ≥4-fold rise from baseline if the baseline value was above the LLOQ. If the baseline measurement was below the LLOQ, a postvaccination assay result ≥4 times the LLOQ was considered a seroresponse.

At 1 month after vaccination in the 5- to <18-years group, the proportions with seroresponse against both RSV A and RSV B were ≥93.2% and 93.9% in the 120 µg and 60 µg groups, respectively.

At 1 month after vaccination in the 2- to <5-year age group, the proportions with seroresponse against both RSV A and RSV B were ≥91.7% and 85.0% in the 120 µg and 60 µg dose groups, respectively.

Table 10. RSV A and RSV B 50% Neutralizing Titer Seroresponse Rate 1 Month After Vaccination – Evaluable Immunogenicity Population

	RSV A Neutralizing Titer			RSV B Neutralizing Titer		
Vaccine Group (as Administered)	N[a]	n[b] (%)	95% CI[c]	N[a]	n[b] (%)	95% CI[c]
5 to <18 Years Healthy RSVpreF 120 µg	24	23 (95.8)	(78.9, 99.9)	24	23 (95.8)	(78.9, 99.9)
5 to <18 Years High Risk RSVpreF 120 µg	20	19 (95.0)	(75.1, 99.9)	20	18 (90.0)	(68.3, 98.8)
5 to <18 Years Total RSVpreF 120 µg	44	42 (95.5)	(84.5, 99.4)	44	41 (93.2)	(81.3, 98.6)
2 to <5 Years RSVpreF 120 µg	24	22 (91.7)	(73.0, 99.0)	24	23 (95.8)	(78.9, 99.9)
5 to <18 Years Healthy RSVpreF 60 µg	15	15 (100.0)	(78.2, 100.0)	15	15 (100.0)	(78.2, 100.0)
5 to <18 Years High Risk RSVpreF 60 µg	18	16 (88.9)	(65.3, 98.6)	18	16 (88.9)	(65.3, 98.6)
5 to <18 Years Total RSVpreF 60 µg	33	31 (93.9)	(79.8, 99.3)	33	31 (93.9)	(79.8, 99.3)
2 to <5 Years RSVpreF 60 µg	20	17 (85.0)	(62.1, 96.8)	20	17 (85.0)	(62.1, 96.8)

CMI

Before vaccination

Based on IFN-gamma, evidence of pre-existing CMI was much less apparent in the 2-<5 years vs. 5-<18 years group.

Table 9. RSV F Antigen–Specific CD4+ T Cells Expressing IFN Gamma and IL-4 – Evaluable Immunogenicity Population

		Before Vaccination				1 Month After Vaccination				Fold Rise (1 Month After Vaccination/Before Vaccination)		
Vaccine Group (as Administered)	RSV F Antigen-Specific Response	n[a]	Mean(SD)	Median(Q1, Q3)	(Min, Max)	n[a]	Mean(SD)	Median(Q1, Q3)	(Min, Max)	n[a]	Median FR	(Q1, Q3)
5 to <18 Years Healthy RSVpreF 120 µg	IFNγ	23	77.5 (64.34)	47 (39, 135)	(10, 241)	22	316.4 (242.57)	255 (109, 517)	(10, 829)	21	4.1	(1.8, 5.5)
	IL-4	23	2.0 (0.00)	2 (2, 2)	(2, 2)	22	4.6 (4.09)	2 (2, 5)	(2, 16)	21	1.0	(1.0, 1.3)
5 to <18 Years High Risk RSVpreF 120 µg	IFNγ	19	67.3 (47.74)	60 (31, 85)	(10, 193)	21	415.5 (389.42)	293 (111, 479)	(10, 1339)	19	6.9	(2.5, 12.0)
	IL-4	19	2.5 (2.06)	2 (2, 2)	(2, 11)	21	7.8 (7.47)	4 (2, 12)	(2, 28)	19	1.0	(1.0, 3.0)
5 to <18 Years Total RSVpreF 120 µg	IFNγ	42	72.9 (56.99)	56 (35, 101)	(10, 241)	43	364.8 (322.71)	292 (109, 511)	(10, 1339)	40	4.8	(2.0, 7.7)
	IL-4	42	2.2 (1.39)	2 (2, 2)	(2, 11)	43	6.1 (6.12)	2 (2, 9)	(2, 28)	40	1.0	(1.0, 2.0)
2 to <5 Years RSVpreF 120 µg	IFNγ	22	18.1 (14.17)	10 (10, 23)	(10, 67)	21	63.4 (54.55)	61 (31, 79)	(10, 257)	20	2.1	(1.2, 3.3)
	IL-4	22	2.0 (0.00)	2 (2, 2)	(2, 2)	21	2.6 (1.33)	2 (2, 2)	(2, 7)	20	1.0	(1.0, 1.0)
5 to <18 Years Healthy RSVpreF 60 µg	IFNγ	14	71.3 (74.10)	53 (10, 95)	(10, 277)	15	323.9 (302.86)	244 (63, 532)	(23, 1027)	14	3.7	(2.0, 8.5)
	IL-4	14	2.1 (0.53)	2 (2, 2)	(2, 4)	15	5.8 (6.30)	2 (2, 7)	(2, 24)	14	1.0	(1.0, 1.8)
5 to <18 Years High Risk RSVpreF 60 µg	IFNγ	17	81.1 (87.43)	41 (27, 129)	(10, 336)	18	261.9 (213.58)	187 (133, 359)	(10, 780)	17	3.2	(1.8, 7.7)
	IL-4	17	2.3 (0.85)	2 (2, 2)	(2, 5)	18	5.6 (4.98)	2 (2, 9)	(2, 15)	17	1.0	(1.0, 2.3)
5 to <18 Years Total RSVpreF 60 µg	IFNγ	31	76.6 (80.50)	45 (20, 99)	(10, 336)	33	290.1 (255.63)	200 (104, 393)	(10, 1027)	31	3.2	(1.8, 8.4)
	IL-4	31	2.2 (0.72)	2 (2, 2)	(2, 5)	33	5.7 (5.53)	2 (2, 8)	(2, 24)	31	1.0	(1.0, 2.3)
2 to <5 Years RSVpreF 60 µg	IFNγ	17	20.8 (18.10)	10 (10, 25)	(10, 79)	17	68.6 (60.89)	45 (10, 127)	(10, 184)	15	2.2	(1.0, 3.4)
	IL-4	17	2.1 (0.49)	2 (2, 2)	(2, 4)	17	3.8 (3.72)	2 (2, 2)	(2, 13)	15	1.0	(1.0, 1.0)

Abbreviations: ELISpot = enzyme-linked immune absorbent spot assay; F = F-specific peptides; FR = fold rise; IFNγ = interferon γ; LOD = limit of detection; PBMC = peripheral blood mononuclear cell; Q1 = the first quartile; Q3 = the third quartile; SFC = spot forming cell.
Note: The RSV F ELISpot LOD values were: IFNγ = 20 SFC/million PBMCs, IL-4 = 4 SFC/million PBMCs. Assay results below the LOD were set to 0.5 x LOD for analysis, with the exception of calculating the fold-rise when a before vaccination assay value was below the LOD but a corresponding after vaccination assay value was at the LOD or above, where the LOD was set for before vaccination.
a. n = Number of participants with valid and determinate assay results at the specified visit; for median FR, only participants with valid and determinate assay results before vaccination and 1 month after vaccination were counted.

At Visit 3 (I month after vaccination)

- The median IFN-gamma fold rise in the 5- to <18-year age group was higher than that in the 2- to <5-year age group.
- At 1 month after vaccination in the 5- to <18-year age group, the median fold rises in IFN-gamma were 4.8 (Q1, Q3: 2.0, 7.7) and 3.2 (Q1, Q3: 1.8, 8.4) in the 120 µg and 60 µg dose groups,
- respectively.
- At 1 month after vaccination in the 2- to <5-year age group, the median fold rises in IFN-gamma were 2.1 (Q1, Q3: 1.2, 3.3) and 2.2 (Q1, Q3: 1.0, 3.4) in the 120 µg and 60 µg dose groups,
- respectively.
- No notable increases in IL-4 were observed in both age groups at either dose levels at 1 month after vaccination. IL-4 secretion was low, before and after vaccination.
- Similar results were obtained for the mITT immunogenicity population

MAH's conclusions on immunogenicity (summarised from the Clinical Overview)

Based on NTs in the 5- to <18-year-olds, the 120 µg dose was selected, i.e. the same dose as in adults was considered appropriate for use from 5 years of age.

For the 2 to <5-year-olds, the 120 µg dose elicited significantly higher GMTs and GMFRs than the 60 µg dose but immune responses in this age group were variable, suggesting that even 120 µg may not be the appropriate dose.

In this regard, the MAH notes that baseline RSV A and RSV B 50% NT GMTs were lower in the 2 to <5-year group compared to the 5 to <18-year group, including 6/44 children (13.6%) with baseline NTs for both RSV A and RSV B at the RSV neutralization assay LOD (despite being enrolled as seropositive based on the lateral flow test kit). Also, the seroresponse data showed that 3 in the 120 µg group and 6 in the 60 µg group showed no response after vaccination for either RSV A or RSV B. Therefore, although the 120 µg dose elicited significantly higher GMTs and GMFRs in the 2 to <5-year-olds compared to the 60 µg dose in this age stratum, it is stated that further dose finding is warranted for this age group before proceeding to Phase 3.

C3671016 - Results Safety

Patient exposure

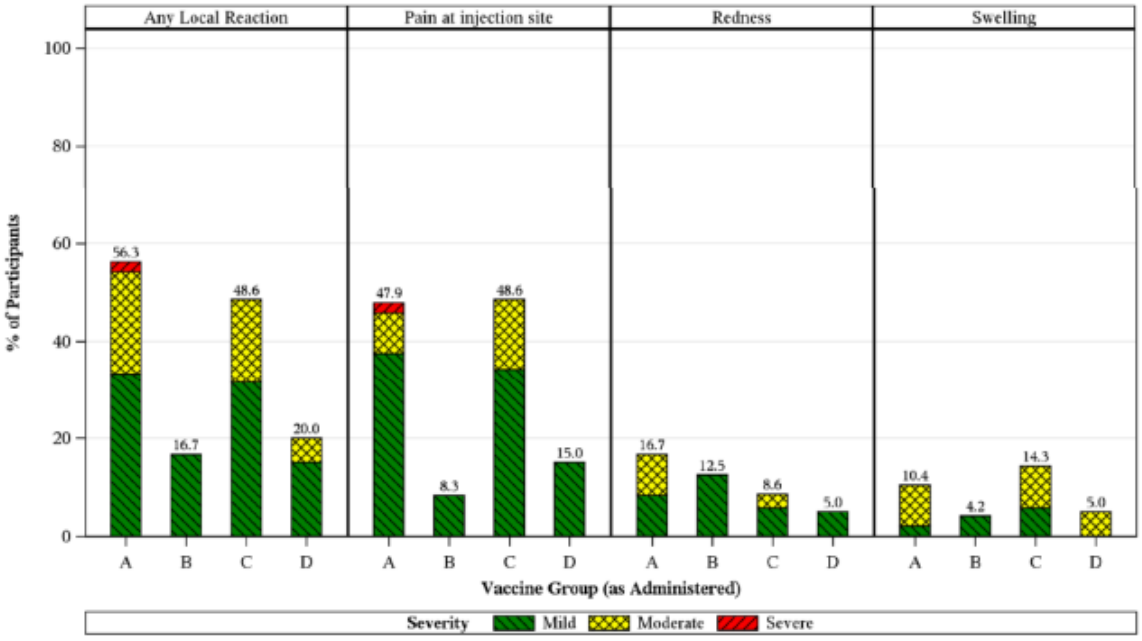
As shown in Table 4 above, there were 127 children vaccinated, of which 44 were aged 2-<5 years. In this age group, 24 received the adult dose and 20 the half adult dose.

In the older age group 5-<18 years, 42 healthy children received RSVpreF (25 received the adult dose and 17 the half adult dose) while 41 children considered high risk received RSVpreF (21 received the adult dose and 18 the half adult dose).

Adverse events

Local reactions

Figure 1. Participants Reporting Local Reactions, By Maximum Severity, Within 7 Days After Vaccination - Safety Population



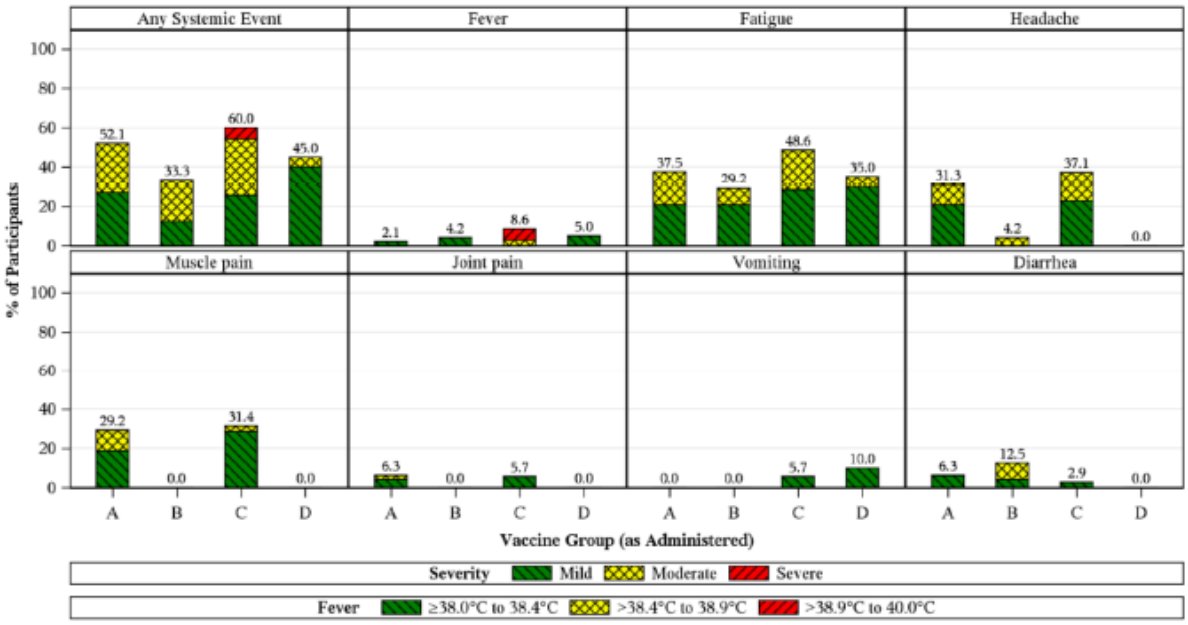
Note: A = 5 to <18 Years RSVpreF 120 µg; B = 2 to <5 Years RSVpreF 120 µg; C = 5 to <18 Years RSVpreF 60 µg; D = 2 to <5 Years RSVpreF 60 µg.
Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
Note: Local reactions were collected in the electronic diary (e-diary) from Day 1 through Day 7 after vaccination. Any local reactions reported as related or not related adverse events during the e-diary collection period were included.

In the 5 to <18-year age group, 56.3% and 48.6% in the 120 µg and 60 µg dose groups, respectively, reported any local reactions within 7 days after vaccination. Most were mild or moderate with a single report of severe injection site pain after 120 µg which resolved in 4 days. The median onset of local reactions was 2-3 days after vaccination and lasted for 1-3 days.

In the 2 to <5-year age group, 16.7% and 20.0% in the 120 µg and 60 µg groups, respectively, reported local reactions within 7 days after vaccination and none was severe. The median onset of local reactions was 1-3 days after vaccination and lasted for 1-3 days.

Systemic reactions

Figure 2. Participants Reporting Systemic Events, By Maximum Severity, Within 7 Days After Vaccination - Safety Population



Note: A = 5 to <18 Years RSVpreF 120 µg; B = 2 to <5 Years RSVpreF 120 µg; C = 5 to <18 Years RSVpreF 60 µg; D = 2 to <5 Years RSVpreF 60 µg.
Note: Number above each bar denotes percentage of participants reporting the event with any severity.
Note: Systemic events were collected in the electronic diary (e-diary) from Day 1 through Day 7 after vaccination. Any systemic events reported as related or not related adverse events during the e-diary collection period were included.

In the 5 to <18-year age group, 52.1% and 60.0% in the 120 µg and 60 µg dose groups, respectively, reported any systemic events within 7 days after vaccination. Most of the systemic events were mild or moderate with severe fever in two in the 60 µg group. The median onset was at 1-6 days after vaccination and lasted for 1-2.5 days.

In the 2 to <5-year age group, 33.3% and 45.0% of participants in the 120 µg and 60 µg dose groups, respectively, reported any systemic events within 7 days after vaccination and none was severe. The median onset of systemic events was at 1-3 days after vaccination and lasted for 1-7 days.

Other AEs reported up to 1 month post-vaccination

In the 5 to <18 years group, 8.3% and 14.3% in the 120 µg and 60 µg dose groups, respectively, reported AEs. Two in the 60 µg group were considered by the investigator to be vaccine-related (once case of axillary pain on the day of vaccination and one case of abdominal pain on day 2). One in the 120 µg group reported a severe AE within 1 month (food allergy) and another in the 60 µg group reported a severe AE after the 1-month follow-up visit (asthma) but neither was considered vaccine-related (see SAEs below). The most common AEs were reported in the infections and infestations SOC (6.3% and 8.6% per group).

In the 2 to <5 years group, 12.5% and 15.0% in the 120-µg and 60 µg dose groups, respectively, reported AEs but none was considered by the investigator to be vaccine-related. The most common AEs were reported in under the infections and infestations SOC (8.3% and 15.0% per group).

Table 11. Adverse Events (Excluding Prespecified Reactogenicity Events Reported in CRF), by Analysis Interval and Category – Safety Population

	Vaccine Group (as Administered)															
	5 to <18 Years								5 to <18 Years							
	Healthy RSVpreF 120 µg (N[a]=25)		High Risk RSVpreF 120 µg (N[a]=23)		Total RSVpreF 120 µg (N[a]=48)		2 to <5 Years RSVpreF 120 µg (N[a]=24)		Healthy RSVpreF 60 µg (N[a]=17)		High Risk RSVpreF 60 µg (N[a]=18)		Total RSVpreF 60 µg (N[a]=35)		2 to <5 Years RSVpreF 60 µg (N[a]=20)	
Reporting Interval Adverse Event Category	n[b](%)	(95% CI[c])	n[b](%)	(95% CI[c])	n[b](%)	(95% CI[c])	n[b](%)	(95% CI[c])	n[b](%)	(95% CI[c])	n[b](%)	(95% CI[c])	n[b](%)	(95% CI[c])	n[b](%)	(95% CI[c])
From vaccination through the 1-month follow-up visit																
Any adverse event	0	(0.0, 13.7)	4 (17.4)	(5.0, 38.8)	4 (8.3)	(2.3, 20.0)	3 (12.5)	(2.7, 32.4)	0	(0.0, 19.5)	5 (27.8)	(9.7, 53.5)	5 (14.3)	(4.8, 30.3)	3 (15.0)	(3.2, 37.9)
Related	0	(0.0, 13.7)	0	(0.0, 14.8)	0	(0.0, 7.4)	0	(0.0, 14.2)	0	(0.0, 19.5)	2 (11.1)	(1.4, 34.7)	2 (5.7)	(0.7, 19.2)	0	(0.0, 16.8)
Immediate[d]	0	(0.0, 13.7)	0	(0.0, 14.8)	0	(0.0, 7.4)	0	(0.0, 14.2)	0	(0.0, 19.5)	0	(0.0, 18.5)	0	(0.0, 10.0)	0	(0.0, 16.8)
Severe	0	(0.0, 13.7)	1 (4.3)	(0.1, 21.9)	1 (2.1)	(0.1, 11.1)	0	(0.0, 14.2)	0	(0.0, 19.5)	0	(0.0, 18.5)	0	(0.0, 10.0)	0	(0.0, 16.8)
Life-threatening	0	(0.0, 13.7)	0	(0.0, 14.8)	0	(0.0, 7.4)	0	(0.0, 14.2)	0	(0.0, 19.5)	0	(0.0, 18.5)	0	(0.0, 10.0)	0	(0.0, 16.8)
From vaccination throughout the study																
AE leading to withdrawal	0	(0.0, 13.7)	0	(0.0, 14.8)	0	(0.0, 7.4)	0	(0.0, 14.2)	0	(0.0, 19.5)	0	(0.0, 18.5)	0	(0.0, 10.0)	0	(0.0, 16.8)
Serious	0	(0.0, 13.7)	1 (4.3)	(0.1, 21.9)	1 (2.1)	(0.1, 11.1)	0	(0.0, 14.2)	0	(0.0, 19.5)	1 (5.6)	(0.1, 27.3)	1 (2.9)	(0.1, 14.9)	0	(0.0, 16.8)
NDCMC	0	(0.0, 13.7)	0	(0.0, 14.8)	0	(0.0, 7.4)	0	(0.0, 14.2)	0	(0.0, 19.5)	0	(0.0, 18.5)	0	(0.0, 10.0)	0	(0.0, 16.8)
AE of special interest	0	(0.0, 13.7)	0	(0.0, 14.8)	0	(0.0, 7.4)	0	(0.0, 14.2)	0	(0.0, 19.5)	0	(0.0, 18.5)	0	(0.0, 10.0)	0	(0.0, 16.8)

a. N = number of participants in the specified vaccine group. These values are the denominators for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any event", n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product.

Other safety data

There were no deaths, NDMCs, AESIs or withdrawals due to AEs. There were two SAEs reported. One was the case of food (nut) allergy (see severe AEs above) in a 12 year-old who had a history of food allergy (tree nuts) and asthma. Onset was the day of vaccination with resolution on day 2 and the SAE was considered unrelated to vaccination. The other SAE was the case of asthma in a 6 year-old with a history of asthma and atopic dermatitis. Onset was on day 39 and this SAE was considered unrelated to vaccination.

2.3.3. Discussion on clinical aspects

Immunogenicity

At 1 month after vaccination of 5-<18 year-olds, the RSV A and RSV B 50% NT GMTs were 31199 and 29670, respectively, in the 120 µg group and 24630 and 32146, respectively, in the 60 µg group, in the 5- to <18-year age group. These values overlap with those described in healthy young adults in prior studies. The corresponding GMTs in the 2-<5 year-olds were lower, at 26146 and 16504 in the 120 µg group and 11004 and 10659 in the 60 µg group.

The GMFRs reflected similar responses to both doses in older children but a greater response to the higher dose in the younger children. Similarly, the seroresponse rates were ~ 93-94% for both doses in older children but ~92% and 85% in the younger children.

The median fold rises in IFN-gamma were 4.8 and 3.2 for the 120 µg and 60 µg dose groups, respectively, in the 5 to <18-years age group whereas corresponding values were 2.1 and 2.2 in the 2 to <5-years age group.

From these humoral and cell-mediated immunogenicity data, noting that there were no additional safety concerns with the higher dose, the MAH has concluded that the 120 µg dose (i.e. the adult dose) may be given to children aged from 5-<18 years. It is agreed that it would be reasonable to take forward this dose into further studies in this age range.

In the younger age range of 2-<5 years, the humoral immunogenicity data suggested an advantage for the higher dose although the CMI data did not point to a difference. However, the MAH also noted that immune responses in this age group were more variable, suggesting that even 120 µg may not be the appropriate dose for children who have had no or few RSV exposures before vaccination. This is supported by the observation that baseline RSV A and RSV B 50% NT GMTs were lower in the younger age group, in which 6/44 (13.6%) had baseline NTs for both RSV A and RSV B at the assay LOD. Also, 3 in the 120 µg group and 6 in the 60 µg group did not have a seroresponse for either RSV A or RSV B. Therefore, although the 120 µg dose elicited significantly higher GMTs and GMFRs in the 2 to <5-year-olds compared to the 60 µg dose in this age stratum, The MAH concludes and the assessor agrees that further dose finding is warranted for this age group before proceeding to Phase 3.

In addition to dose selection considerations, the CMI data suggest that RSVpreF elicits a greater IFN-γ (Th1) than IL-4 (Th2) response in both age groups and at both dose levels. This finding supports a conclusion that Abrysvo does not elicit a Th2-skewed response.

Safety

There are no new issues raised by the safety data reported with either dose in either age sub-group.

Conclusions

C2671016 was a first dose-finding study in paediatric subjects aged from 2 years, by which age the majority of children in the US (where the study was conducted) are usually RSV non-naïve. Although the children aged 2-<5 years had to have a positive lateral flow test for RSV for study entry, not all were later found to have NA titres above the assay LOD for RSV-A or RSV-B.

Before proceeding to evaluate vaccine efficacy in children, it is agreed that further dose-finding is warranted in the younger age group. Meanwhile, it appears that with comparable immune responses to the higher and lower doses in children aged from 5 years, and supported by the CMI data, the adult dose is likely suitable for further testing in older children.

At this time, since no posology can be recommended in the SmPC and with no new safety information of importance, it is agreed with the MAH that no change to the SmPC is applicable at this time.

3. CHMP’s overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.