20 July 2023
EMA/351226/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abrysvo

International non-proprietary name: respiratory syncytial virus vaccine (bivalent, recombinant)

Procedure No. EMEA/H/C/006027/0000

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. Background information on the procedure 6
1.1. Submission of the dossier 6
1.2. Legal basis, dossier content 6
1.3. Information on paediatric requirements 6
1.4. Information relating to orphan market exclusivity 6
1.4.1. Similarity 6
1.4.2. Derogations from market exclusivity 6
1.5. Applicant's request for consideration 7
1.5.1. Accelerated assessment 7
1.5.2. Additional data exclusivity /Marketing protection 7
1.5.3. New active substance status 7
1.6. PRIME 7
1.7. Scientific advice 7
1.8. Steps taken for the assessment of the product 8

2. Scientific discussion 9
2.1. Problem statement 9
2.1.1. Disease or condition 9
2.1.2. Epidemiology 9
2.1.3. Aetiology and pathogenesis 10
2.1.4. Clinical presentation, diagnosis 10
2.1.5. Management 11
2.2. About the product 11
2.3. Type of application and aspects on development 12
2.4. Quality aspects 13
2.4.1. Introduction 13
2.4.2. Active substance 13
2.4.3. Finished medicinal product 20
2.4.4. Discussion on chemical, pharmaceutical and biological aspects 27
2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects 28
2.4.6. Recommendation(s) for future quality development 28
2.5. Non-clinical aspects 28
2.5.1. Pharmacology 28
2.5.2. Pharmacokinetics 32
2.5.3. Toxicology 32
2.5.4. Ecotoxicity/environmental risk assessment 33
2.5.5. Discussion on non-clinical aspects 34
2.5.6. Conclusion on the non-clinical aspects 36
2.6. Clinical aspects 36
2.6.1. Introduction 36
2.6.2. Clinical pharmacology 38
2.6.3. Discussion on clinical pharmacology 39
2.6.4. Conclusions on clinical pharmacology 39
2.6.5. Clinical efficacy 39

2.6.6. Discussion on clinical efficacy 102
2.6.7. Conclusions on the clinical efficacy 116
2.6.8. Clinical safety 116
2.6.9. Discussion on clinical safety 130
2.6.10. Conclusions on the clinical safety 132
2.7. Risk Management Plan 133
2.7.1. Safety concerns 133
2.7.2. Pharmacovigilance plan 133
2.7.3. Risk minimisation measures 136
2.7.4. Conclusion 137
2.8. Pharmacovigilance 137
2.8.1. Pharmacovigilance system 137
2.8.2. Periodic safety update reports submission requirements 137
2.9. Product information 137
2.9.1. User consultation 137
2.9.2. Labelling exemptions 137
2.9.3. Quick response (QR) code 137
2.9.4. Additional monitoring 138

3. Benefit-Risk Balance 138

3.1. Therapeutic Context 138
3.1.1. Disease or condition 138
3.1.2. Available therapies and unmet medical need 139
3.1.3. Main clinical studies 139
3.2. Favourable effects 140
3.3. Uncertainties and limitations about favourable effects 143
3.4. Unfavourable effects 145
3.5. Uncertainties and limitations about unfavourable effects 145
3.6. Effects Table 147
3.7. Benefit-risk assessment and discussion 148
3.7.1. Importance of favourable and unfavourable effects 148
3.7.2. Balance of benefits and risks 149
3.7.3. Additional considerations on the benefit-risk balance 150
3.8. Conclusions 150

4. Recommendations 150

List of abbreviations

Abbreviations	Term
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
$Al(OH)_3$	Aluminium hydroxide
ALRI	Acute lower respiratory infection
ARI	Acute respiratory illness
ARI-RSV	Respiratory syncytial virus-associated acute respiratory illness
AS	Active substance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BTD	Breakthrough therapy designation
CBER	Center for Biologics Evaluation and Research
CD	Circular dichroism
CD4+	Cluster of differentiation 4 positive
CGE	Capillary gel electrophoresis
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical laboratory improvement amendments
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CpG	Cytosine-guanine nucleotides
CSR	Clinical study report
DART	Developmental and reproductive toxicology
DMC	Data monitoring committee
DS-Cav 1	Incompletely stabilised RSV F
DTd	Diphteria toxoid
EAC	External Adjudication Committee
eAF	Electronic application form
E-DMC	External Data Monitoring Committee
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-human
FI-RSV	Formalin inactivated respiratory syncytial virus
GA	Gestational age
GBS	Guillain-Barré syndrome
GCP	Good clinical practice
GLP	Good laboratory practice
GMFR	Geometric mean fold rise
GMP	Good manufacturing practice
GMR	Geometric mean ratio
GMT	Geometric mean titer
HC	Host cell
HCP	Host cell proteins
IA	Interim analysis
ICU	Intensive care unit
IgG	Immunoglobulin G
IM	Intramuscular
LBCI	Lower bound confidence interval
LIVCA EOPs	Limit of in vitro cell age
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LMIC	Low- and middle-income countries
LRTI	Lower respiratory tract illness

Abbreviations	Term
MAA	Marketing authorisation application
mAb	Monoclonal antibody
MAH	Marketing authorisation holder
MA-LRTI	Medically attended lower respiratory tract illness
MA-RTI	Medically attended respiratory tract illness
MCB	Master cell bank
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NAAT	Nucleic acid amplification test
NDCMC	Newly diagnosed chronic medical condition
OOS	Out of apecification
OTC	Over the counter
PAR	Proven acceptable range
PASS	Post-authorisation safety study
PCR	Polymerase chain reaction
Ph. Eur.	European Pharmacopeia
PIP	Paediatric investigation plan
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
PVP	Pharmacovigilance plan
QC	Quality control
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
RMP	Risk management plan
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RSV A	Respiratory syncytial virus subgroup A
RSV B	Respiratory syncytial virus subgroup B
RSV F	Respiratory syncytial virus fusion glycoprotein
RSV-LRTI	Respiratory syncytial virus associated lower respiratory tract illness
RSVpreF	Respiratory syncytial virus stabilised prefusion F subunit vaccine
RT-PCR	Reverse transcription polymerase chain reaction
RTI	Respiratory tract illness
RVLP	Retrovirus-like particles
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIIV	Seasonal inactivated influenza vaccine
sLRTI	Severe lower respiratory tract illness
sLRTI-RSV	Severe respiratory syncytial virus associated lower respiratory tract illness
SOC	System organ class
SpO2	Oxygen saturation
T4	Bacteriophage T4
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
Th1	T-cell helper type 1
Th2	T-cell helper type 2
VE	Vaccine efficacy
VRF	Viral retaining filtration
WCB	Working cell bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 22 December 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Abrysvo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

- the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunisation of pregnant individuals.
- the prevention of acute respiratory disease and lower respiratory tract disease caused by RSV in individuals 60 years of age and older by active immunisation.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0058/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Derogations from market exclusivity

Not applicable.

1.5. Applicant's request for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. Additional data exclusivity /Marketing protection

1.5.3. New active substance status

The applicant requested the active substance RSV subgroup A glycoprotein F and RSV subgroup B glycoprotein F, stabilised in prefusion conformation and produced in Chinese Hamster Ovary cells by recombinant DNA technology contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Not applicable

1.7. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 April 2018	EMEA/H/SA/3794/1/2018/III	Mair Powell, Jens Reinhardt
26 March 2020	EMEA/H/SA/3794/2/2020/II	Minne Casteels, Mair Powell
16 December 2021	EMA/SA/0000069400	Mair Powell, Ingrid Schellens
22 April 2022	EMA/SA/0000080028	Ingrid Schellens, Bruno Delafont

The scientific advice pertained to the following non-clinical, and clinical aspects:

- Adequacy of nonclinical toxicology data and clinical safety data in healthy, non-pregnant adults to support use in healthy pregnant adults.
- Clinical development in the prevention of RSV-associated lower respiratory tract illness (MA-LRTI) in neonates and infant following active maternal immunisation during pregnancy:
  - Case definitions for RSV-associated MA-LRTI and severe MA-LRTI, adjudication process for RSV-associated MA-LRTI events, use of local laboratory diagnostics to detect RSV infection, primary and secondary study objectives and statistical analysis plan in the proposed phase 3 protocol.
  - Adequacy of high efficacy (≥70%, with LBCI >20%) at the interim analysis for either of the primary endpoints (RSV-associated MA-LRTI or RSV-associated severe MA-LRTI) to support authorisation.

- Size of the safety database and the length of the safety follow-up.
- Additional interim analysis implemented in the phase 3 trial to support filling of a MAA.

- Clinical development in the prevention of RSV-associated moderate to severe lower respiratory tract illness in adults 60 years of age and older by active immunisation:
  - Adequacy of Phase 1 and 2 clinical studies evidence to support progression into Phase 3.
  - Appropriateness of the proposed Phase 3 primary efficacy endpoint success criteria to support the intended indication.
  - Design of Phase 3 efficacy study including case definition, study population, and evaluation of reactogenicity.

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Daniela Philadelphy

The application was received by the EMA on	22 December 2022
Accelerated Assessment procedure was agreed upon by CHMP on	25 January 2023
The procedure started on	25 January 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 April 2023
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	14 July 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 April 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	08 June 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	20 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	08 July 2023

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Abrysvo on	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Respiratory syncytial virus (RSV) is a negative sense, single stranded RNA orthopneumovirus that causes infections of the human respiratory tract. RSV cases follow a seasonal pattern in many countries that is in line with that of influenza, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall. RSV can affect any age group and almost all children have serological evidence of exposure to the virus by the age of 2 years. Although first infections are likely to be symptomatic, repeated infections occur throughout life and it seems they are often asymptomatic. However, first and repeated infections may result in anything from mild upper respiratory tract symptoms to severe and life-threatening lower respiratory tract involvement, with a significant mortality rate in some at-risk subgroups.

2.1.2. Epidemiology

RSV disease in adults

RSV disease burden reported in 2015 demonstrated there were approximately 1.5 million episodes of acute respiratory infections (ARIs) due to RSV (RSV-ARI) in adults ≥65 years of age in industrialised countries. Approximately 15% of RSV-ARI cases led to hospitalisation. The burden of adult RSV disease could be underestimated since testing for RSV is less common in older adults than in children and some types of tests did not/do not detect low levels of virus shedding in older adults.

In Europe, RSV infection can also be serious for adults aged 50 years and older as it can cause acute respiratory infection, influenza-like illness or community-acquired pneumonia. Annual RSV attack rates of 4.2% and 7.2% were observed in community-living adults aged ≥60 years in successive seasons. In UK adults aged from 18 years, some authors have estimated of 487,247 outpatient episodes, 17,799 hospitalisations and 8482 attributable deaths per season. Of these, 36% of GP episodes, 79% of hospitalisations and 93% of deaths were in ≥65-year-olds.

RSV infection has been associated with up to 22% of acute COPD exacerbations in prospective cohort studies and 11% of wintertime hospitalisations for COPD exacerbations. In industrialised countries, the case fatality rate of RSV-ARI was 11.7% for adults with comorbidity but 1.6% for the general population.

There are some recognised risk factors for severe RSV disease in older adults, including the elderly.

Immunosenescence can result in a weakened immune response to pathogens and suboptimal response to vaccines. In addition, there may be reduced lung expansion in older adults because of decreased strength of the respiratory muscles and the diaphragm. Older adults may also have decreased protective mucus levels, lung compliance and elastin.

RSV disease in infants

RSV is the leading viral cause of lower respiratory tract infection in children. It may cause bronchiolitis and pneumonia and can lead to fatal respiratory distress. Globally, there are an estimated 33 million episodes of RSV-associated ALRI each year in children aged <5 years resulting in an estimated 3.6 million hospitalisations. Among children <6 months there are an estimated 6.6 million RSV-associated ALRI episodes and 1.4 million hospitalisations.

RSV is a leading cause of paediatric hospitalisation in Europe. In a recent study of the aetiology of severe ARI requiring hospitalisation conducted in 7 countries, RSV was identified as the most common cause of ARI hospitalisations in young children, causing one third of ARI admissions. In a separate European study, rates of RSV hospitalisation varied by country from 8.6 to 22.3 per 1,000 children <1 year of age but patterns across age were remarkably similar. In all countries, RSV-associated hospitalisation rates were significantly higher in children <1 year of age compared to those 1-4 years of age and decreased with increasing age. RSV admissions peaked among infants <1 month.

While virtually all children experience RSV in the first 2 years of life, rates of RSV hospitalisation in infancy are greater among those with medical (e.g. prematurity, low levels of maternal neutralising antibodies) and socioeconomic risk factors.

2.1.3. Aetiology and pathogenesis

RSV infects humans via the upper respiratory tract, where viral replication commences. If unchecked, the virus may spread to the lower airways where local pathological changes in response to active viral replication may result in impaired oxygenation of the blood.

During RSV entry into host cells, the trimeric viral fusion protein (RSV F) rearranges from a prefusion to a post-fusion conformation. As it rearranges, F fuses the viral and host cell membranes. Structural data show that the post-fusion F conformation targeted by many prior failed vaccine approaches is very different from the predominant prefusion conformation that is present on virions. The structural difference between conformations results in antigenic differences. In contrast to post-fusion F, prefusion F is in a metastable conformation that needs to be stabilised to be useful as an improved vaccine antigen.

Furthermore, RSV has two subgroups – RSV A and RSV B. The RSV F of A and B subgroups is ~90% identical and it is the primary target of neutralising antibodies that also show some degree of cross-neutralisation. Most of the sequence differences between the mature F glycoproteins of the subgroups are concentrated in the prefusion-specific epitopes that elicit the majority of RSV-neutralising and protective antibody responses.

2.1.4. Clinical presentation, diagnosis

The clinical presentation is very variable, as described above. The manifestations of the disease vary according to primary or repeated infection (and thereby by age), size of airways and underlying host conditions that predispose to progression to severe LRTI.

The diagnosis of RSV infection may involve detection of the virus or viral antigens or virus specific nucleic acid sequences in respiratory secretions. The kind and quality of the clinical specimen

influences the sensitivity and specificity of viral detection methods. A nasal wash or a nasopharyngeal aspirate is more sensitive for the detection of RSV than a nasopharyngeal swab. However, flocked nasopharyngeal-swabs effectively dislodge and collect virus-infected cells lining the nasopharynx, which significantly increases the diagnostic yield.

Laboratory methods currently available for the detection of RSV include virus isolation in tissue culture, detection of viral antigens (e.g. using Direct Fluorescent Assays/Indirect fluorescent Assays or Enzyme Immunoassays) and nucleic acid amplification tests (NAAT), predominantly reverse transcription polymerase chain reaction (RT-PCR). Viral culture really requires direct and rapid transfer to a laboratory since shipping samples reduces viral yield. Antigen detection kits are widely used. In specimens from infants and toddlers, their sensitivity ranges from 72 to 94% although specificity is 95 to 100% compared to cell culture. However, in RSV-experienced older children and adults, detection rates for EIA are extremely low with sensitivities of 0 to 20%, reflecting lower and shorter viral shedding vs. primary infections.

Nucleic acid assays are the most sensitive and specific methods for the detection of RSV, regardless of the patient population tested. Of the different nucleic acid amplification techniques, RT-PCR was the first of these and it remains the most frequently used NAAT. Commercial kits are available.

New PCR techniques, such as real-time PCR methods, enable the simultaneous performance of amplification and detection and result in a turnaround time of a few hours. Multiplex PCR tests may also allow simultaneous amplification of RSV together with various other respiratory viruses that cause similar clinical symptoms. Highly sensitive monoplex or multiplex PCR assays indicate that up to 10-30% of respiratory illness cases and up to 50% of RSV infections in infants represent mixed infections. Some authors reported an increased risk of more severe disease or of admission to a paediatric ICU for dual respiratory virus infections. Real-time PCR also allows quantification of viral nucleic acids present in a sample. As far as RSV is concerned, higher viral loads seem to correspond with a more severe clinical course of the disease and an increased likelihood of recurrence of wheezing.

2.1.5. Management

Currently, there is no authorised vaccine to prevent RSV disease. Treatment of RSV disease consists primarily of supportive care (e.g. oxygen, hydration and suctioning of secretions). The use of aerosolised ribavirin is usually limited to immunosuppressed persons due to inconvenient administration, questionable benefit, teratogenicity concerns and high cost.

Palivizumab is authorised for immunoprophylaxis, given as monthly injections during RSV seasons. In Europe, it is commonly used in infants aged <6 months who were born before 35 weeks of gestation and children aged <2 years of age who have been treated for bronchopulmonary dysplasia within the last 6 months or have a serious heart condition.

The effectiveness of palivizumab highlighted the importance of neutralising antibodies in protection against RSV disease. Subsequently, nirsevimab was developed as a single dose, extended half-life prefusion F-specific mAb. It demonstrated efficacy against RSV LRTI in Phase 3 studies and was given EU marketing authorisation in October 2022.

2.2. About the product

The applicant's RSVpreF vaccine contains 120 µg of stabilised prefusion RSV F glycoprotein from RSV A and RSV B (60 µg of each) in a lyophilised dosage form for reconstitution. There is no adjuvant. The stabilised prefusion F glycoproteins are engineered F glycoprotein ectodomains (one from the subgroup A Ontario genotype and one from the subgroup B Buenos Aires genotype, representing wild-type

contemporary strains). They lack the transmembrane regions and cytoplasmic tails. They are fused to fibritin foldon trimerisation domains at the C-termini of the remaining native sequences. The vaccine is prepared for injection by reconstituting the lyophilised drug product with sterile water for injection. The vaccine (0.5 mL/dose) is given intramuscularly into the deltoid muscle of adults.

The nature of this protein-based vaccine is such that the prevailing scientific opinion is that it might not be suitable for primary immunisation of RSV-naïve infants. The concerns rest on the prior experience with an inactivated whole virion RSV vaccine in RSV-naive children where the vaccine not only failed to protect against RSV disease, but it was associated with enhanced severity of disease. Evidence suggests that vaccine-associated disease enhancement was due to elicitation of non-neutralising antibodies that facilitated RSV spread between host cells. The applicant has directed development of RSVpreF to use in RSV-experienced persons, with a focus on two groups.

Older adults
Reinfection following a primary RSV exposure occurs throughout life due to short-lived natural immunity. RSV-infected older adults have significantly lower serum RSV-neutralising antibody titres and RSV-specific IgG levels than uninfected age-matched controls. The evidence supports an important role for serum neutralising titres in reducing the risk of RSV disease in older adults. In these naturally primed individuals, the administration of RSVpreF should act as a booster. The unanswered question is whether further doses could be required before each RSV season or, perhaps, at longer intervals.

Maternal immunisation to prevent RSV disease in infants
There is an early peak of RSV disease at around 1 to 2 months after birth. Post-natal active immunisation of infants with a suitable vaccine (to be identified) is not likely to address these early and often very severe cases. Moreover, maximum protection of infants via active immunisation of infants may require several priming doses.

Pregnant women are universally RSV experienced so they are not at risk for vaccine-associated RSV disease enhancement. Furthermore, only maternal IgG reaches the unborn infant and administration of palivizumab to neonates has not been associated with RSV disease enhancement. Therefore, augmentation of anti-RSV neutralizing antibodies in pregnant women has potential to result in passive protection of their infants, as long as sufficient maternal antibody persists in infant serum. This strategy is effective for short-term post-natal prevention of pertussis and tetanus in infants born to mothers vaccinated during pregnancy.

2.3. Type of application and aspects on development

The CHMP agreed to the applicant’s request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the therapeutic innovation of the candidate vaccine, in the context of an identified unmet medical need for the treatment of RSV disease in both infants up to 6 months of age and older adults.

The protection against lower respiratory tract disease caused by RSV in infants from birth through 6 months of age, following maternal immunisation during pregnancy was considered a major public interest.

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is a presented as a powder and solvent for solution for injection containing equal amounts of the active substances (AS), two RSV F antigens stabilised in the prefusion conformation, denoted 847A and 847B, representing the two major RSV subgroups A and B, respectively. The vaccine is designed to deliver a 60 µg dose of each prefusion protein antigen, equivalent to 120 µg dose of total protein in a 0.5 mL injection.

The other ingredients are trometamol, trometamol hydrochloride, sucrose, mannitol, polysorbate 80, sodium chloride, hydrochloric acid (for pH adjustment) and water for injections (solvent).

The finished product powder is supplied in a 2 mL clear glass vial. Prior to use, the lyophilised FP is reconstituted with solvent (water for injections) in a single-use prefilled syringe using a vial adapter and the entire contents are withdrawn to enable a dose of 0.5 mL for administration as an intramuscular injection. The product may be supplied with a co-packaged syringe needle. CE certificates for the vial adapters and needle are provided. The applicant provided evidence of compliance of the pre-filled syringe with the relevant General Safety and Performance Requirements (GSPRs) of the Medical Device Regulation ((EU 2017/745).

2.4.2. Active substance

2.4.2.1. General information

847A and 847B antigens are trimeric, recombinant glycoprotein ectodomain antigens from RSV produced in Chinese Hamster Ovary (CHO) cells.

The sequence used for the 847A AS is derived from the Ontario RSV strain while the 847B sequence has been derived from the Buenos Aires RSV strain. Both recombinant proteins have been engineered to trimerise through the inclusion of a bacteriophage T4 foldon domain. Both proteins undergo post-translational modification with three cleavage events removing the signal peptide and excising an amino acid sequence designated p27. This generates two peptides, termed F1 and F2, which bind covalently and subsequently trimerise to generate the 847A or 847B antigen.

847A covalently bound peptides have a theoretical mass of 57,868.9 – 65,325.6 Da, while the trimerised form has a theoretical molecular mass of 173,606.7 – 195,976.8 Da. 847B covalently bound peptides have a theoretical mass of 59,089.1 – 65,545.8 Da, while the trimerised form has a theoretical mass of 174,267.3 – 196,637.4 Da. The biological function of 847A and 847B recombinant antigens is to elicit neutralising antibodies against RSV.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The active substances are manufactured in Wyeth BioPharma, Andover MA, USA. Appropriate GMP authorisation is in place. GMP authorisation is also available for sites responsible for testing and storage.

The 847A and 847B manuacturing processes are highly similar with some specified differences. The 847A and 847B AS manufacturing process follows a standard method for recombinant protein

production. The recombinant protein is produced in CHO cells and involves several bioprocessing steps and purification steps. The manufacturing process is sufficiently well described with process parameters provided and in-process controls in place.

A single 847A or 847B AS batch is manufactured from individual production fed-batch bioreactors to produce commercial scale material. The upstream bioprocessing steps include the thawing of a WCB following multiple step expansion and harvest. In-process tests for control (IPT-C) is defined as an in-process test with associated acceptance criteria. Adequate IPT-C have been established for the upstream and the downstream processes.

The downstream purification process comprises of seven steps with ultrafiltration/diafiltration (UF/DF) steps, chromatography steps, a viral retaining filtration (VRF) step, a formulation and filtration step. The antigen is dispensed in specified storage containers for storage.

Cleaning validation data were requested for the resins and have been provided. Process parameters have been registered in the dossier.

The reprocessing procedures registered for 847A and 847B are identical between both. Reprocessing procedures have been registered for two steps of the process. Criteria for a reprocessing event to occur are registered in the dossier.

Control of materials

A list of compendial and non-compendial raw materials, their compendial status and use within the manufacturing process has been provided for 847A and 847B antigens. Specifications have been registered for non-compendial raw materials and chromatography resins. The cell culture medium is chemically defined and protein free, containing no proteins or peptide components of animal, plant, or synthetic origin. The qualitative composition of the cell culture media used in the manufacture of 847A and 847B has been provided.

The development of the expression plasmids has been sufficiently well described, the construction process is in line with Ph. Eur. 0784 and plasmid maps have been included in the dossier.

The 847A expression plasmid produces a single copy of 847A transcript, however, during construction an identical, duplicate 847A sequence was incorporated into the expression plasmid that lacks the necessary upstream components to be expressed.

The 847B expression plasmid is a dual expression plasmid that contains two individual but identical 847B transgenes and both transgenes are expressed during production of the antigen.

No raw materials of animal origin were used in the development of the production cell lines.

Testing of the 847A and 847B MCB, WCB and end of production testing at the proposed limit of *in vitro* cell age (LIVCA EOPs) were carried out in line with ICH Q5A and Q5D. The information provided support that the genetic stability of the 847A and 847B cell substrates are maintained throughout the manufacturing process. Adventitious agent test results on the 847A and 847B MCB, WCB and LIVCA EOP were provided. Sufficient evidence that the methods used for screening cell banks for viral adventitious agents are suitably qualified for their intended purpose has been provided.

Control of critical steps and intermediates

Critical and non-critical process parameters associated with the manufacturing process of 847A and 847B antigens have been provided, and each parameter has been assigned a criticality status based on design of experiments' (DOE) analysis discussed in Module 3. In addition to process parameters, information is provided on in-process tests for control (IPT-C) that are carried out to ensure quality of the AS is maintained. Maximum cell age in the production bioreactor was identified as a critical

material attribute (CMA) that could impact quality of the AS and controls have been included for this CMA. The process parameters, IPT-Cs and CMA collectively provide control over the quality of the AS manufacturing process. In-process tests for monitoring (IPT-M) attributes have been included and several attributes are monitored regularly throughout the process. The dossier states that events where controls are outside of the specified ranges, an evaluation of the deviation is performed and any subsequent decision will be based on the outcome of an investigation.

A high-level overview of the test methods used for the in-process tests and validation of these methods has also been provided in the dossier. Compendial methods used include Mycoplasma testing (Ph. Eur. 2.6.7), bioburden testing (Ph. Eur. 2.6.12) and endotoxin testing (Ph. Eur. 2.6.14).

Hold times have been registered for each step.

Process validation and/or evaluation

A standard approach to process validation has been taken (three commercial-scale batches for 847A and four commercial-scale batches 847B) following pre-approved protocols. The site of commercial manufacture for both 847A and 847B is Pfizer (formerly Wyeth BioPharma), Andover, Massachusetts, USA. All manufacturing steps registered in Module 3 for 847A and 847B have been validated.

For the upstream process in both 847A and 847B, process validation results were provided. Results met their validation acceptance criteria, which included PPs, CPPs and IPT-Cs registered in Module 3.

For downstream processes in both 847A and 847B, process validation results have been provided. All results for 847A and 847B met their validation acceptance criteria, and the validation acceptance criteria included PP ranges, CPP ranges and IPT-Cs that have been registered in Module 3.

Impurity clearance

The impurities identified during process validation, and their associated acceptance criteria for AS, are identical between 847A and 847B AS. The process and product related impurities have been discussed. These impurities were determined by risk assessment performed based on an *in-silico* evaluation, product dosing regimen and established risk factors. Acceptance criteria for validation of clearance are acceptable considering that a low dose final product is administered to the patient. HC DNA acceptance criteria aligns with the WHO recommendation of 10 ng/dose. Actual HC DNA data obtained is significantly below this. The process is suitable for clearance of identified impurities.

Hold times

Hold times were validated in small scale studies. Within the validation data provided for hold times, changes in quality attributes have been observed over the hold time tested at the harvest hold step, pre-final filter hold step and pre-freeze hold step. A retrospective analysis of GMP batches was performed to support the proposed hold times of the pre-final filter hold step and the pre-freeze hold step.

Shipping validation

The same shipping validation study was supplied to support shipping of both 847A and 847B.

Resin and filter lifetime studies

The number of cycles for each resin has been included in the dossier. 847A and 847B were used interchangeably to determine the total number of cycles for each resin. Therefore, the Process Validation provided supports both 847A and 847B processes. The data provided to support the proposed resin lifetimes are considered acceptable. The resin lifetime studies are ongoing according to the registered protocol. Membrane performance and lifetimes are also defined in the dossier.

Reprocessing

The reprocessing validation provided is common to both 847A and 847B. Data provided in the dossier demonstrated no significant change in quality between pre- and post-reprocessing at small scale. No commercial scale reprocessing has been performed thus far. Testing will be carried out when a reprocessing event occurs. The predefined acceptance criteria for validation of commercial scale reprocessing have been registered in the dossier and are considered acceptable.

Quality Attributes

Critical quality attributes (CQAs) of the 847A AS and 847B AS were determined based on the quality target product profile of the FP and the quality attribute's potential to impact safety or efficacy of the FP. Clarity, colouration, pH, protein concentration, identity, bioburden, endotoxin, relative prefusion content, impurity content, purity and CHO host cell proteins (HCP) are included in the specifications. The rationale for assigning criticality to the attributes is provided in the dossier and is acceptable. The applicant states that CHO DNA was not listed as a CQA as it is effectively cleared during purification. It was considered acceptable to exclude routine HC DNA testing based on the clearance data provided.

Process Characterisation Studies

The approach adopted by the applicant uses 'cause and effect matrices' (C&E) to determine if the unit operation requires further investigation. If it is determined that further investigation is required, small scale studies are used to determine whether the process parameters within a unit operation are critical or non-critical. Criticality was determined by studying statistically significant changes to relevant AS quality attributes caused by altering process parameters across a range. A statistically significant change in one quality attribute determined that parameter to be a critical process parameter which will be controlled within the proven acceptable range (PAR). Unit operations that do not need further investigation based on C&E are listed as non-CPP and are assigned normal operating ranges (NOR) based on what the applicant terms 'relevant process history' (RPH), manufacturing experience and subject matter expert judgement.

The approach to determine CPPs was common to 847A and 847B. Process parameter ranges of the thaw, seed expansion, and harvest steps were assigned NORs using a Prior Knowledge approach. Given that the active substance is not produced until the production bioreactor stage, it is considered acceptable to base the ranges on process knowledge. An initial C&E risk assessment and One-factor-at-a-time (OFAT) experiments were used to identify the process parameters for further study and ten process parameters were identified. The ten process parameters were then studied in a DOE. Only a high-level summary of the DOE is provided. The experimental results of DOE were not provided, such as prediction profiles, contour plots etc. or the statistical approach to determine significance. However, since a conservative approach was used, further details of the DOE are not requested. The characterisation studies and identified CPPs/non-CPPs associated with the upstream process are acceptable.

The strategy used to assign CPPs for downstream unit operations for 847A and 847B was the same as the upstream strategy described previously, with the same AS quality attributes used for testing. The C&E identified at least one process parameter requiring investigation in each step of the downstream processing, and those parameters were investigated with small-scale studies. Again, process parameters that had no impact on AS quality over the ranges tested were assigned as non-CPPs and parameters that caused a statistically significant impact on the quality of the AS were classed as CPPs. Small-scale studies found a statistically significant impact on certain parameters; however, justification was provided to list these parameters as non-CPP as while their impact was statistically significant, the magnitude of the effect was deemed to be small.

Hold times are defined. The process characterisation studies for the downstream process are extensive. Overall, the approach and CPPs assigned are acceptable based on the information provided.

Control Strategy

The Control strategy is identical for 847A and 847B. The applicant has provided a comprehensive overview of the control strategy associated with 847A DS and 847B DS. The control strategy is in line with an enhanced approach to manufacturing process development as outlined in ICH Q11. The control strategy has been divided into eight elements (listed above in the report) that will adequately control the process performance attributes and ensure that the 847A DS and 847B DS consistently meets the critical quality attributes. The list of DS attributes, the control implemented for each, the control element and supporting data has been provided in the dossier in tabulated form. Overall, the proposed control strategy is acceptable to ensure the quality of 847A DS and 847B DS.

Manufacturing process development

Development history of 847A and 847B is provided with clear chronological description that describes the significant changes that occurred over three process changes. The development history also lists the intended use for each manufactured batch.

The development history has provided information on the changes made between each process. Comparative tables and summaries of these changes have been provided. The changes were introduced to both 847A and 847B processes, therefore both processes remained largely aligned throughout development.

Comparability

The batches of 847A and 847B used in clinical development are clearly listed in the dossier. Two comparability studies have been provided for each 847A and 847B DS development history, one comparing Process 1 to Process 2 and the second comparing Process 2 to Process 3. The comparability studies include comparison of release specification and heightened characterisation studies (primary structure, disulfide bond, molecular mass, secondary structure and tertiary structure).

Following a request for appropriate comparability criteria, the applicant adopted an approach of using Process 3, i.e. the post-change batches, to generate appropriate comparability criteria and demonstrated that the Process 2 batches met the comparability acceptance criteria. Comparability has been demonstrated between Process 2 and Process 3.

Extended characterisation used the reference material, from Process 2 and Process 3 from each of 847A and 847B to demonstrate comparability. This is considered acceptable for extended characterisation. Overall, results of the extended characterisation comparability study support that the quality of 847A and 847B manufactured with Process 2 and Process 3 is comparable.

In-Process extractables and leachables

A risk assessment was performed, addressing relevant factors, and each contact material was assigned a relative risk factor (RRF). Appropriate justifications were provided for identified materials that were subsequently omitted from the extractables testing. The remaining parts that received a higher risk score were assessed for extractables. No part tested above the analytical evaluation threshold (AET) and as a result, the risk as regards extractables can be considered as negligible.

Risk Assessment of Process Reagent Impurities

The applicant has identified three process reagent impurities. Upon request, the dossier has been updated to include the maximum allowable levels of two of those impurities. Furthermore, the maximum concentration of one of these impurities has been registered in the dossier. Taken together,

the residual amounts of the three process reagents are adequately controlled. The maximum levels of each process related impurity are the same across the 847A and 847B manufacturing process, therefore, it is agreed that 847A does represent a worst case scenario for the calculation of impurity levels.

A risk assessment has been carried out to evaluate whether any impurity exceeds the safety concern threshold based on worst-case scenario AS production, a 1000-fold safety factor, a 70 kg person for calculation and an assumption of no process-related clearance of the impurity. As the indication is for pregnant females or elderly individuals, a 70 kg assumption could be too high. However, as the safety clearance threshold is exceeded for all potential impurities, in addition to an assumption of no clearance of impurities during downstream processing, this is not further pursued.

Characterisation

847A and 847B can exist in two conformations, prefusion and post-fusion conformations. Vaccination has the highest efficacy when targeted against the prefusion conformation and this AS is intended to generate neutralising antibodies specifically against the prefusion conformation. The characterisation carried out of the AS includes evaluation of the primary structure, post-translational modifications, N-linked oligosaccharides, molecular mass, higher order structure, size variants and prefusion F content. Characterisation for both 847A and 847B was carried out with either the reference material or the parent batch from which the reference material was derived. The characterisation strategy is identical for both active substances and the studies are adequate to characterise 847A and 847B. Initially, data on only a single batch were provided for each of 847A and 847B. Data from additional batches (10 batches of 847A and 11 batches of 847B) have been provided upon request to support characterisation. The batches presented in Module 3 (847A and 847B) can be considered representative of AS manufactured using the commercial process.

A photostability study was carried out in line with ICH Q1B, indicating that 847A and 847B are photolabile.

A similar impurity profile is observed for both 847A and 847B. The impurities identified include process related impurities, product related impurities and contaminants, including HCP, HC DNA, bioburden and endotoxin. Overall, the impurities have been adequately discussed and the purification process shows consistent and effective removal of the identified impurities. The specified impurities were present in material used in clinical trials.

2.4.2.3. Specification

The proposed specifications for 847A AS and 847B AS include appropriate specifications for identity, potency, purity, physicochemical attributes (clarity; colouration; pH) and microbiological properties (bioburden and endotoxin).

Adequate justification was provided for the specification acceptance criteria for each quality attribute listed in the specifications. The proposed AS specifications have been determined from several production batches of 847A and several batches of 847B using statistical analysis of release data, stability data, product knowledge, development studies and compendial requirements.

Analytical procedures

The analytical methods have been sufficiently well described and appropriately validated in accordance with ICH Q2(R1). The analytical procedures used in the control of 847A and 847B are standard procedures for recombinant proteins. Appearance (clarity, colouration), pH, bioburden and endotoxin

are compendial methods used and are described in Ph. Eur. 2.2.2, Ph. Eur. 2.2.3, Ph. Eur. 2.6.12 and Ph. Eur. 2.6.14 respectively.

The remaining tests (protein concentration, identity, potency, impurity content, purity and CHO HCP testing) are non-compendial and common between 847A and 847B AS. A high-level overview of non-compendial methods has been provided but the level of detail is sufficient.

Batch analysis

To date, several batches of 847A AS have been manufactured during development as reported in Module 3, however in this section, data is only provided on fewer batches (including the three process validation batches). For 847B, it has been reported in Module 3 that several batches of 847B have been manufactured to date, however in this section, data has only been provided for fewer batches (including four process validation batches). Of these batches presented, several 847A AS batches have been manufactured at commercial scale and several 847B AS batches have been manufactured at commercial scale. The MAH has provided justification for the exclusion of additional batches as they were either non-GMP batches or were batches produced to evaluate process changes or gain process understanding.

All batches, across the three processes, met the pre-defined acceptance criteria in place at the time of testing. There were no trends observed. Overall, the results for purity, impurities and potency are consistent throughout development and the information provided is acceptable.

Reference standards

All reference materials used to date have been registered in the dossier. Throughout 847A development, there have been four clinical reference materials (CRM), a primary reference material (PRM) and a working reference material (WRM). For 847B, there have been three CRMs, one PRM and one WRM.

Extended characterisation has been performed on the 847A CRM, 20J156M003 (DT4295) and the 847B CRM 20J157M003-FP8067-847B, with data provided. Parent batches used in the generation of the 847A and 847B PRM and WRM were also included in the extended characterisation and comparability studies.

The MAH has confirmed that if a new PRM is required, it will be introduced by variation to the MAA.

Container closure

The proposed container closure for 847A and 847B AS is an ethylene vinyl acetate (EVA) container with a nominal volume of 8.3 L. The choice of material is suitably justified and is supported by pharmacopoeial compliance of materials and stability data. Specifications and extractables/leachables studies are addressed. It has been stated that the product contact layer, ethylene vinyl acetate monomaterial (EVAM), properties have been tested and are in compliance with Ph. Eur. 3.1.7.

2.4.2.4. Stability

The stability programme is designed to follow ICH guidelines for stability of active substance (ICH Guideline Q1A: Stability Testing of New Drug Substances and Products; ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products). The stability indicating properties identified in Module 3 have been defined and are included in the stability testing panel.

Primary stability studies are ongoing with active substance manufactured using the commercial process. These studies include at least three commercial-scale process validation batches of both 847A

and 847B AS. Any confirmed out-of-specification result, or significant negative trend in the ongoing studies, should be reported to the Rapporteur and EMA.

The 847A AS shelf life is supported by real time stability data up to 24 months and up to 9 months when stored at -40°C ± 10°C and stored in commercially registered containers. The 847B AS shelf life is supported with real time stability data up to 24 months, and up to 6 months when stored at -40°C ± 10°C in commercially registered containers.

Accelerated studies at 5°C ± 3°C are completed for 847A and 847B with 6 months of data.

Stressed studies at 25°C ± 2°C/60 ± 5% are available. Thermal cycling studies have been provided to support that temporary excursions from the proposed storage conditions do not have an impact upon quality attributes. A photostability study in line with ICH Q1B (option 2) demonstrated that the product is photolabile.

The provided stability data are considered sufficient to support the claimed shelf life for both 847A and 847B AS.

2.4.3. Finished medicinal product

2.4.3.1. Lyophilised powder

2.4.3.1.1. Description of the product and pharmaceutical development

Description of the product

The finished product (FP) is a sterile lyophilised powder for injection that consists of equal amounts of two stabilised active substance antigens, 847A and 847B. The lyophilised finished product is presented in a 2 mL clear glass vial sealed with a stopper and an aluminium overseal with flip-off plastic cap.

The finished product presentation has a target strength of 120 µg/vial; it is designed to deliver a 60 µg dose of each prefusion protein, equivalent to 120 µg dose of total protein in a 0.5 mL injection. There is no manufacturing overage.

The finished product contains no preservatives and is single use. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except for Tris hydrochloride which is controlled to an in-house specification. There are no novel excipients used in the finished product formulation. After reconstitution, the finished product contains trometamol, trometamol hydrochloride, sucrose, mannitol, polysorbate 80, sodium chloride, hydrochloric acid (for pH adjustment) and water for injections.

Pharmaceutical development

The applicant has based their formulation development on a Quality Target Product Profile (QTPP). The formulation development for the AS and FP is well described. Early studies suggested that a liquid FP formulation would not provide sufficient stability at 2-8°C, the typical storage temperature for a vaccine; therefore, a lyophilised dosage form was the focus for FP development. The rationale and studies employed to determine the use and concentration of the buffers and stabilises are clearly presented.

The manufacturing process development history, from formulation development through clinical development and onto commercial development has been presented. There have been three distinct FP processes through development. Comparability has been demonstrated.

Process development and characterisation studies have been presented for each unit operation of the finished product manufacturing process. Risk assessment was used to identify process parameters that required evaluation and the experimental plan, parameters and QAs evaluated are clearly outlined.

The process characterisation studies are considered to address the relevant process parameters and include a comprehensive description of the development of the lyophilisation cycle which included thermal analysis of the finished product formulation, lab and pilot scale to commercial scale lyophilisation cycle development, lyophilisation process robustness and lyophiliser load uniformity for the commercial scale freeze dryers.

The container closure development is adequately described (see container closure section).

The choice of the container closure is justified in Module 3, considering the physical/chemical properties of the product, extractable and leachable studies, microbiological attributes and stability data.

2.4.3.1.2. Manufacture of the product and process controls

Manufacture

Manufacture and batch release are conducted by Pfizer Manufacturing Belgium N.V. (Pfizer Puurs). Batch release is also conducted by Pfizer Ireland Pharmaceuticals (Pfizer Grange Castle). Appropriate GMP authorisations are provided for all sites involved in the manufacture of the finished product.

The target finished product batch size is defined. The manufacturing process of finished product (FP) includes active substance thawing, buffer and bulk finished product formulation, sterile filtration, aseptic filling, lyophilisation, capping and inspection. The bulk finished product can be stored or transferred directly to the filling line. At the filling line, the bulk finished product is filtered and aseptically filled into vials. Each filled vial is partially stoppered prior to lyophilisation. Upon completion of the lyophilisation cycle, the vials are fully stoppered and then capped and stored at 2-8°C before inspection. The description of the manufacturing process is clear and detailed. Relevant process parameters and in process tests (IPTs) are detailed with set points or ranges.

Reprocessing is proposed if the bioburden reducing filter fails to meet the post-use integrity test criteria, or in the event of a technical issue that compromises the integrity of the system. It is proposed that the bulk finished product may be reprocessed once into a holding vessel using a new and identical 0.2 µm bioburden reducing filter. This is accepted.

Process controls

The process controls include a combination of critical material attributes (CMA), critical process parameters (CPP), non-critical process parameters (non-CPP), and in-process tests for control (IPT-C) and monitoring (IPT-M). The proposed ranges and acceptance criteria are supported by pharmaceutical development and validation data and are acceptable. The applicant clarified that in the event that results are outside of the acceptable ranges process parameters or in process tests, the quality procedures at the manufacturing site do not differentiate between deviations to CPPs, non-CPPs, IPT-Ms or IPT-Cs in their investigation approach. Proposed hold times are supported by media fill and in-process hold time validation.

Process validation

Process validation studies included validation of the manufacturing process, hold times, the aseptic filling process, filter validation, reprocessing validation, capping validation and shipping validation.

Three consecutive successful process validation lots met the pre-determined protocol acceptance criteria for the study demonstrating that the finished product manufacturing process, executed within established operating parameters, consistently produces finished product that meets its pre-determined quality attributes. The lots were manufactured at the intended commercial scale. All the registered process parameters and IPCs listed in Module 3 were appropriately validated in these campaigns. Where process parameter ranges have been set, they have been challenged in the process validation studies. Maximum hold times were also validated.

Post manufacture of the finished product process validation lots, a confirmatory validation study was performed to support post-validation changes.

The aseptic process was validated by representative media fills.

Shipping was validated. The simulated study represents the worst case scenario for actual shipping conditions.

A concurrent validation approach for reprocessing is proposed in cases where the bioburden reduction filter fails to meet the post-use integrity test, or if a technical issue occurs that compromises the integrity of the system. A validation protocol was provided. This is accepted.

2.4.3.1.3. Product specification

Specifications

The specification of the finished product includes tests for appearance (before reconstitution), residual moisture, reconstitution time, clarity, and colouration (after reconstitution), visible and subvisible particles, pH, osmolality, protein concentration, 847A and 847B content, uniformity of dosage units polysorbate 80 (PS80) concentration, identity, relative prefusion content (potency), product-related impurities, endotoxins, sterility and container closure integrity.

Testing for FP is in compliance with the relevant requirements of ICH Q6B and Ph. Eur. Monographs for Products of Recombinant DNA Technology (0784), Vaccines for Human Use (0153) and Parenteral Preparations (0520).

The tests performed for stability assessment are indicated. The same acceptance criteria are applied to tests performed on release and stability. The approach to stability testing is mainly acceptable as those tests not performed are not stability indicating.

Finished Product Specification

The applicant was requested to review the acceptance criteria for several parameters The acceptance criteria for the specifications have now been appropriately justified.

A nitrosamine risk assessment has been conducted and is provided in Module 3. No risk for nitrosamine formation was identified. A satisfactory summary of the risk assessment for elemental impurities in accordance with ICH Q3D was provided.

Analytical procedures

Residual moisture, appearance after reconstitution, pH and osmolality, uniformity of dosage units and endotoxins are tested according to Ph. Eur. methods. In house methods are detailed.

Sufficient information is provided on compendial and non-compendial methods. In house methods include detail on procedural steps, sample and reference standard preparation, replicates, system

suitability, acceptance criteria and calculations as relevant. All methods have been appropriately validated in accordance with ICH Q2(R1).

Batch analysis

Batch analysis data has been provided for several "parent batches" of finished product including three process validation lots. The batches were either batches intended for clinical use but not used, stability batches, process validation batches or confirmatory batches. The batch data were all within the proposed specifications and show that the manufacturing process can produce a finished product of consistent quality.

Reference materials

Throughout development, there have been several reference standards; clinical reference materials (CRM), a primary reference material (PRM) and a working reference material (WRM). The approach to establishing FP RMs is similar to the approach adopted for AS RMs.

Multiple issues related to qualification, consistency across the different lots, and stability of the CRM used for release testing of clinical and PPQ lots were identified. These issues potentially impacted the comparability assessment for RSVpreF FP manufactured during the different development stages. This was raised as a Major Objection (MO). From the information provided in the response it could be concluded that CRMs were suitable for their intended use and enable consistent attribute determination over time and across lots. Data was also provided to demonstrate that primary reference standard has been appropriately bridged to the clinical reference standard. The MO was resolved.

Appropriate bridging data was provided for the initial clinical reference standards. Bridging data was also provided between the clinical reference standard and primary reference standard.

Container closure

The primary container closure system clear and colourless Type I borosilicate glass or, alternatively, aluminosilicate glass vials, with a 2 ml fill volume and a 13 mm crown diameter. Vials are stoppered with synthetic chlorobutyl rubber stoppers and sealed with an aluminium vial seal with polypropylene flip of caps. Compliance with Ph. Eur. 3.2.1, for vials, and Ph. Eur. 3.2.9, for stoppers, is declared. The name and address of manufacturers, dimensions, representatively schematic drawings and quality control tests are provided for the vials, stoppers and seals.

Sterilisation and depyrogenation of the vials by dry heat and steam sterilisation of stoppers, is detailed in Module 3.

2.4.3.1.4. Stability of the product

A finished product shelf-life of 24 months when stored at the recommended temperature of 2-8°C is proposed.

Stability has been studied under long-term conditions (5 ± 3°C), accelerated conditions of (30 ± 2°C/65 ± 5% relative humidity (RH)), as well as thermal stress, thermal cycling and photostability conditions. Stability studies have been carried out in accordance with current ICH guidelines for stability of finished product. The containers used in the stability studies are the same as those proposed for routine storage, and both the proposed borosilicate and aluminosilicate glass vials have been used in the stability studies.

Results from stability studies on finished product stored at the long-term condition of 5 ± 3°C are presented for several primary lots and several supportive lots. This includes three process validation lots. All data remained within the proposed commercial stability acceptance criteria and there have

been no significant changes in terms of quality for the finished product. Results from stability studies on finished product stored at the accelerated condition of 30 ± 2°C/ 65 ± 5% RH are presented for several primary lots; and at 25 ± 2°C/60 ± 5% RH for several primary and supportive lots. Currently there is up to 6 months of data available for primary and supportive stability lots. Slight increase in product-related impurities was observed on some lots. Residual moisture is also observed to increase slightly. All results generated to date remained within the proposed commercial stability acceptance criteria and there have been no significant changes in terms of quality for the finished product.

Results from stability studies on finished product stored at the thermal stress condition of 40 ± 2°C/75 ± 5% RH are presented for several primary lots and several supportive lots. 1 month data is available for all lots. Increases in moisture, protein concentration and changes in product-related impurities were seen in some of the lots, but all results remained well within the proposed commercial stability acceptance criteria and no significant changes were observed.

The accelerated studies up to 30 ± 2°C/ 65 ± 5% RH showed stability up to 6 months. The thermal stressed studies investigated excursions above the recommended storage condition up to 40 ± 2°C/75 ± 5% RH and demonstrated stability up to 1 month.

However, although accelerated and thermal stressed stability studies demonstrate stability at excursions beyond 2-8°C, the product information states and therefore permits only the following:

The unopened vial is stable for 5 days when stored at temperatures from 8°C to 30°C. At the end of this period Abrysvo should be used or discarded. This information is used to guide healthcare professionals in case of temporary temperature excursions only.

Data from thermal cycling studies where the finished product is stored at 30 ± 2°C/65 ± 5% RH for two months followed by long-term storage at 5 ± 3°C (Thermal Cycling 2), with 12 months of data currently available, supports the time out of refrigeration during the manufacturing, assembly, labelling, packaging and shipping of the product.

The in-use period in the Product information, after reconstitution, 4 hours at 15°C to 30°C, is supported by pharmaceutical development data. Photostability studies demonstrate the finished product is not photolabile.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The results of the stability studies support the finished product shelf-life claim of 24 months when stored at the recommended temperature of 2-8°C.

2.4.3.2. Solvent - Water for Injection

2.4.3.2.1. Description of the product and pharmaceutical development

The water for injection solvent complies with Ph.Eur. and is presented in a pre-filled syringe. The target fill volume includes an overfill which ensures a nominal injection volume of 0.5 ml. The solvent is filled into a type I borosilicate glass syringe with Luer lock adapter, plunger and tip cap with cap cover. The elastomeric tip cap that is the product contact surface meets the requirements of USP <381> and Ph. Eur. 3.2.9 and is not manufactured from natural rubber latex. The closure for the syringes is a plunger stopper composed of chlorobutyl rubber that is not made with natural rubber latex. The final assembled vaccine consists of a finished product vial, a sterile water diluent syringe,

and a vial adapter in a secondary packaged kit. In addition, a needle can be included in the packaging. See container closure section.

CE certificates are provided for the co-packaged vial adaptor and needle. The applicant provided evidence of compliance of the PFS with the relevant GSPRs.

Pharmaceutical development

The selection of sterile water as a solvent for the finished product is supported by clinical development. The sterile water solvent was selected based on safety and immunogenicity data from both phase 1/2 and phase 2 studies and was the sole solvent utilised in the phase 3 clinical study. The studies conducted by the applicant support the fill weight target and fill weight check acceptance criteria and demonstrate the required volume of injection (≥0.5 ml) could be delivered even at worst case conditions.

The process control strategy includes the relevant controls on filling, filtration, and sterilisation parameters. The parameter choices are either justified by, development work, process validation or reference conditions of the Ph. Eur. with respect to terminal sterilisation parameters. The finished product specification release and stability acceptance criteria are based on compendial requirements for sterile water.

2.4.3.2.2. Manufacture of the product and process controls

Pfizer Manufacturing Belgium NV (Pfizer Puurs) performs manufacture, testing, primary packaging, secondary Packaging, QA rlease of the diluent. Appropriate GMP authorisation is in place. The batch size range has been defined.

The manufacturing process consists of the filtration of water for injection (WFI) and WFI bulk is then filled into syringes, the plunger is added to the syringe and the syringe is terminally sterilised by steam sterilisation in an autoclave according to a cycle conforming to Ph. Eur. 5.1.1 conditions. Detail of the inspection, vaccine kit assembly at both proposed secondary packaging sites and shipping to distribution centres are also described.

Details of the control of the process via critical and non-critical parameters, IPT-C and IPT-M tests are also provided. Parameter ranges have been demonstrated to be acceptable through process development and/or process validation. In process tests are carried out The bioburden tests have been suitably verified. The ambient bioburden control limit prior to sterilisation (≤100 CFU/100 mL) is in line with the EMA Guideline on sterilisation of the medicinal product for processes applying a Ph. Eur. 5.1.1 steam sterilisation reference cycle.

The manufacturing process and controls are adequately described. Manufacturing process validation has been successfully conducted on three consecutive lots. A summary is provided of the validation of the terminal sterilisation process. The steam sterilisation cycle uses Ph. Eur. 5.1.1 reference cycle i.e. a sterilisation time of ≥15 mins at a sterilisation temperature of ≥121°C is specified in Module 3. As per the EMA Guideline on sterilisation of the medicinal product for sterilisation using a reference condition of the Ph. Eur. 5.1.1 (≥121°C, ≥15 min in all units) validation data for the sterilisation cycle is not required to be submitted in the quality dossier. None the less, a validation summary is presented. Process hold times have been validated based on the shortest hold times per process step of each of the three validation batches. Labelling, packaging and shipping have been suitably qualified.

2.4.3.2.3. Product specification

The solvent specification includes tests for appearance, subvisible particles, conductivity, total organic carbon, oxidisable substance, residue on evaporation, extractable volume, endotoxin, sterility and container closure integrity.

The same acceptance criteria are applied to both release and stability.

The proposed specification is in line with Ph. Eur. (0169: Sterilised Water for Injections) version 11.1.

Analytical methods

Reference is made to compendial monographs in lieu of a description for the relevant analytical procedures.

It is stated that compendial procedures were verified or validated for use in accordance with the applicable pharmacopoeias, unless otherwise justified.

Batch analysis

Batch analysis is presented for several batches of the sterile water solvent, including the three process validation lots manufactured in the commercial scale range. All batches met the acceptance criteria at the time of release, although the non-process validation lots were only tested for certain attributes.

The specification is considered justified as it is aligned with Ph. Eur. (0169: Sterilised Water for Injections) monograph.

Reference materials

There is no reference material required for sterile water diluent.

Container closure

Compliance with Ph. Eur. 3.2.1, for syringe barrels, and Ph. Eur. 3.2.9, for the product contact tip cap elastomer and plunger stoppers, is declared.

The syringes and plunger stoppers are received at the finished product manufacturing site ready-to-use, washed, siliconised, and sterilised. Compliance with ISO 11135-1, CPMP/QWP/159/01 and ISO 10993-7 is declared. Compliance with ISO 11137-2 is declared.

The name and address of manufacture and sterilisation sites, dimensions, representatively schematic drawings, and quality control tests are provided for the syringes and plunger stoppers.

The choice of the container closure is justified in Module 3, considering the physical/chemical properties of the product, extractable and leachable studies, microbiological attributes and stability data.

2.4.3.2.4. Stability of the product

The proposed shelf life is 36 months when stored at 2 - 32°C based on extrapolation of the available data in line with ICH Q1E.

The stability programme is line with ICH Q1A (R2): Stability Testing of New Active substances and Products.

Stability studies have been conducted at long term (5 ± 3°C and 25 ± 2°C/60 ± 5% RH or 30 ± 2°C/65 ± 5% RH), accelerated 40 ± 2°C/75 ± 5% RH), thermal stress (50 ± 2°C), thermal cycling conditions and photostability.

Several sterile water solvent lots are included in the primary stability studies, The accelerated studies are complete for all primary stability lots with 6 months data available. Thermal stress studies are also complete with 2 weeks data available from 4 clinical lots. Photostability has been completed on one clinical lot. Thermal cycling studies are ongoing.

Analytical procedures utilised in the stability studies are in line with those described in Module 3. All parameters met the proposed commercial stability specification where there have been no significant changes observed in any parameter. The data presented supports the proposed shelf life at the intended storage conditions. The extrapolation of the data to the proposed shelf life is considered reasonable considering the available long term and accelerated data.

2.4.3.3. Adventitious agents

The applicant has identified materials of animal origin used during the manufacture of 847A and 847B that includes filters, flasks, tubing and flexible containers. The applicant states that the materials manufactured with components derived from animal origin meet the requirements of EMA/410/01 and this is acceptable.

Testing has been performed to demonstrate that 847A and 847B unprocessed bulk are free from adventitious agents. MCB, WCB and LIVCA testing for adventitious agents has been provided in Module 3 and all cell line material tested negative for adventitious agents. Testing of unprocessed bulk for mycoplasma, bioburden and viral agents has been provided for batches of 847A and 847B.Unprocessed bulk for 847A and 847B showed absence of mycoplasma, bioburden and viral agents.

Viral clearance of the purification process was also evaluated. The rationale for the choice of viruses used in the evaluation has been provided and is acceptable. Viral clearance validation reports have been provided that demonstrate no toxicity or interference and that they are suitably qualified for their intended purpose.

Overall, the results of the viral clearance studies demonstrated the manufacturing process has sufficient capacity to remove viruses.

Retrovirus-like particles (RVLP) were quantified Based on the viral clearance studies, the retrovirus safety margins are acceptable for both 847A and 847B.

2.4.3.4. GMO

Not applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Module 3 of the Abrysvo dossier is of good quality. The 847A and 847B active substance manufacturing processes are standard production of recombinant proteins in CHO cells. Details of developmental genetics, the generation of cell banks, characterisation control strategy, commercial scale process validation, specifications, analytical methods, container closure and shelf-life are provided, and information is described in adequate detail. Overall, the quality of the 847A and 847B active substances is considered acceptable.

For the finished product (FP), the description of the product, pharmaceutical development, manufacturing process controls, control of the product, container closure and stability information are clearly described in adequate detail for both the lyophilised finished product and sterile water solvent.

An MO was raised on the FP reference standard. Multiple issues related to qualification, consistency across the different lots, and stability of the CRM used for release testing of clinical and PPQ lots were identified. These issues potentially impacted the comparability assessment for RSVpreF FP manufactured during the different development stages. From the information provided in the response it could be concluded that both CRMs were suitable for their intended use and enable consistent attribute determination over time and across lots. Data was also provided to demonstrate that the primary reference standard has been appropriately bridged to the clinical reference standard. The MO was resolved.

An MO was also raised on the new active substance claim since differences in the basis structural element of Abrysvo and Arexvy (already licensed on the EU market) were identified but had not been justified as being substantial.

Subsequently, further information was provided. As the RSV, subgroup B, stabilised prefusion F protein (847B) active substance is derived from a different RSV strain than is present in Arexvy, it can be considered as a new active substance in line with EMA/CHMP/CMDh/CAT/BWP/828612/2022.

For the 847A active substance, the applicant highlighted amino acid differences that represent substantial modification to the basic structural element, contributing to improved thermal/chemical stability and higher neutralising antibody responses. This justification is considered sufficient to accept that 847A is a new active substance.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Pharmacology

The two major glycoproteins on the surface of the RSV virion are the attachment glycoprotein (G) and the fusion glycoprotein (F). RSV F is a primary target for vaccine-induced protection as it is required for fusion and entry of RSV into host cells. The trimeric RSV fusion (F) glycoprotein is a primary target of neutralizing antibodies elicited by RSV infection and is the basis for the engineered antigens in Pfizer's RSV vaccine candidate. RSV F is a molecular device that fuses the viral and host cell membranes during cell entry. It exists in two key, antigenically distinct forms - prefusion and postfusion.

F has long been a key antigen for RSV vaccine development. Prefusion F is the primary form recognised by neutralizing antibodies in human serum (VR-VTR-10879).

Many prefusion-specific monoclonal antibodies (mAbs) target an antigenic site (site Ø) located at the apex of the globular domain of prefusion F. This epitope is disrupted during the rearrangement from prefusion to postfusion. Unlike postfusion F, prefusion F is the active form of the protein and is capable

of mediating membrane fusion during cell entry. Therefore, prefusion F is the primary target of neutralizing antibodies that block RSV infection.

Pharmacology studies performed demonstrated that prefusion F elicits higher titre neutralizing antibodies than postfusion F in experimental animals.

Structure-guided protein engineering was used to design stabilised prefusion F constructs, (VR-VTR-10914). Each soluble F construct is comprised of an RSV F ectodomain that was engineered through the addition several internal mutations, to "lock" the protein into its prefusion conformation. Each ectodomain contained a C-terminal T4 bacteriophage fibritin foldon trimerisation domain. Structural analysis, in silico protein design, and high throughput mutagenesis were used to generate novel F constructs.

These constructs were tested *in vitro* for stability in the prefusion conformation under stress conditions, using reactivity with prefusion specific mAbs as the primary assay for prefusion conformation. Using in silico antigen design, constructs incorporated combinations of targeted protein engineering chemistries, including 1) engineered disulfide bond mutations, 2) cavity-filling mutations, and 3) electrostatic mutations. Disulfides were introduced to immobilise more flexible regions of prefusion F by tethering them to more rigid regions and prevent re-arrangement to the postfusion form.

Combinations of these chemistries were examined in nearly 400 F protein constructs to identify the most stable prefusion F for preclinical immunogenicity testing. A selection of the most stable constructs identified through *in vitro* testing was evaluated for the ability to elicit RSV neutralizing antibodies in animal immunisation studies.

This combination of *in vitro* conformational stability testing and animal immunogenicity testing was the basis for selecting the lead prefusion F vaccine antigen, 847. To make the stabilised prefusion F vaccine antigens for Pfizer's RSVpreF investigational vaccine, the 847 stabilizing mutations, which were identified on the background of A2 (a standard laboratory RSV strain), were introduced into the background F sequences of two contemporary wild type RSV strains, Ontario for subgroup A (847A) and Buenos Aires for subgroup B (847B).

The rationale for the bivalent vaccine is sound. Historically, RSV A was thought to cause most RSV disease. However, more extensive epidemiology studies have shown that either RSV A or RSV B subgroups can dominate in a season and can also be evenly distributed across seasons. Both are associated with severe disease and can co-circulate.

Following the *in vitro* screening of F constructs for prefusion stability resulted in selection of 11 top candidates for *in vivo* immunogenicity evaluation. These top candidates were advanced into dose ranging immunogenicity studies in mice. From these studies, three of the most immunogenic candidates were selected for further preclinical immunogenicity evaluation in cotton rats.

The stabilizing mutations of the most immunogenic of the selected constructs were introduced to F backgrounds from recently circulating RSV strains to generate the investigational vaccine antigens, 847A and 847B. Preparations of 847A were confirmed to contain prefusion F by X-ray crystallography and electron cryomicroscopy with image reconstruction, (VR-VTR-10880).

In vivo assessments of the RSV investigational vaccine

Mice

Several of the most stable novel prefusion F constructs were more immunogenic in mice compared to a wild-type postfusion F antigen, (VR-VTR-10385). Three prefusion F constructs, 847, 852, and 851, were consistently more immunogenic than DS-Cav1 as assessed by RSV 50% and 90% neutralizing

titres. The 847, 852 and 851 vaccine candidates were prioritised for further preclinical immunogenicity testing in cotton rats.

Cotton Rats

Immunisation of cotton rats (VR-VTR-10386) showed a clear dose-dependent neutralizing antibody response to the novel prefusion constructs and identified the top vaccine candidate, construct 847, which elicited higher overall responses than DS-Cav1, 851, and 852, both with and without aluminium phosphate.

A second study in cotton rats (VR-VTR-10387) evaluated the immunogenicity of a dose range of monovalent 847A strain (Ontario), monovalent B strain (Buenos Aires) and a bivalent 847A + 847B combination in cotton rats to determine if there is an added benefit to a bivalent formulation. Improved neutralizing antibody responses across RSV A and B viruses with a bivalent formulation (847A + 847B) was observed, compared to a monovalent 847A vaccine candidate.

In both these rat studies palivizumab was used as a control, to serve as a potential threshold of protection. Palivizumab was dosed in rats at 15 mg/kg. A dose of 10 mg/kg has been demonstrated in the literature (Johnson, 1997) to confer near complete protection in the lungs of cotton rats. Protection in cotton rats corresponded to a serum antibody trough concentration at the time of challenge of ~ 30 - 40 µg/ml. In the pharmacology studies, a 15 mg/kg palivizumab dose was used as a more conservative dose to ensure maintenance at or above protective levels.

Rhesus Macaques

A study in rhesus macaques (VR-VTR-10388) evaluated the immunogenicity of a stabilised prefusion F protein candidate with and without aluminium hydroxide [$Al(OH)_3$] as compared to the same dose levels of a postfusion F protein.

Again, in this monkey study palivizumab was used as a control, to serve as a potential threshold of protection. The chosen 15 mg/kg palivizumab dose in monkeys, was not justified. It is not known if the desired serum concentration of ~ 30 - 40 µg/mL was achieved with the 15 mg/kg palivizumab in these animals. However, animals who were dosed with 60 µg of prefusion 847 elicited a similar 50% neutralising antibody titre to animals that received palivizumab.

It was noted that all non-clinical PD studies – except the study in Rhesus Macaques (VR-VTR-10388), have been conducted in female animals. For the provided proof-of-concept (immunogenicity) studies, this is agreed. Potential gender differences with respect to induced immune responses, vaccine efficacy, etc. should be investigated in the human target population. The applicant was asked to explain why this immunogenicity study was performed in male monkeys. The reason for this was based on animal availability, and the approach generally taken in the CRO where the study was performed is to conduct immunogenicity studies in male animals.

The neutralising activity of the RSV prefusion F vaccine was investigated using RSV laboratory and clinical strains (VR-VTR-10391). Immune sera from cotton rats (VTR-10938 /CR 2017-14) and rhesus macaques (Rh 2017-04) that received two doses of bivalent RSVpreF were further tested for their ability to neutralise recently circulating RSV A and RSV B clinical isolates.

In this study the serum from adjuvanted vaccine treated rats and monkeys, and serum from non-adjuvanted vaccinated rats was used to demonstrate efficacy against circulating RSV strains. Serum from the adjuvant vaccine treated animals was better at neutralising RSV strains than non-adjuvanted.

Efficacy studies

Two studies evaluating the vaccine antigens in various formulations were performed to assess safety, efficacy, immunogenicity, and risk for enhanced respiratory pathology in cotton rats. Cotton rats are 100-fold more susceptible to RSV than mice and have been used for several decades for RSV vaccine efficacy and disease enhancement evaluation (Prince et al, 1999; Prince et al, 1978).

In the first study (Evaluation of Safety, Efficacy and Immunogenicity of Candidate Vaccines in the RSV Cotton Rat Model, Study Number: VR-VTR-10390 / XV-154, (PRL-RSV-2016-06)), cotton rats were vaccinated IM at Days 0 and 28 with bivalent 847 (25 µg 847A + 25 µg 847B) with or without $Al(OH)_3$, with the original FI-RSV Lot 100, or with PBS control. During the course of this animal study, three cotton rats, 109330 (group 8), 109317 (group 6) and 109300 (group 5) had medical incidents. The cotton rats found dead were considered unrelated to the administration of the RSV vaccines. All three animals showed no signs of injury, were well groomed, well-nourished and showed no signs of dehydration. Neither did the cotton rats have a history of malocclusion or showed signs of it when found dead. A full necropsy was performed and macroscopy did not show anything obvious. The applicant was asked to explain what the animal pathologist ultimately determined to be the cause of death. The applicant provided a table with observations described by the assigned CRO on the three animal deaths that occurred. The cause of death was not determined in the pathological evaluation, as stated in the observations provided by the in-life test facility. However, it was confirmed that no animal administered the RSVpreF vaccine candidate was affected by the incidents.

A second study (VR-VTR-10938) was performed where cotton rats were vaccinated IM with 847A and 847B alone (30 µg each; 60 µg total protein) either with $Al(OH)_3$ (0.2 mg per dose) or with CpG 24555/$Al(OH)_3$ (0.1 mg/0.15 mg per dose).

Efficacy studies in cotton rats demonstrated that the bivalent RSV 847 prefusion F vaccine candidate (RSVpreF) prevents RSV infection in cotton rats, does not induce enhanced respiratory pathology, and elicits potent RSV neutralizing antibodies, particularly when adsorbed to $Al(OH)_3$. The studies measured alveolitis, but unfortunately did not measure markers of a Th2 response which is also associated with ERD. However, this product is indicated for adults and not intended at this point for RSV-naïve subjects or infant immunisation. Therefore, in line with EMA/CHMP/257022/2017 and WHO 2020, a preliminary assessment of the risk that vaccine-associated enhanced RSV disease could occur is not required.

These studies both demonstrated that the bivalent vaccine prevents RSV infection in cotton rats (as detected by viral shedding), does not induce enhanced respiratory pathology, and elicits potent RSV neutralising antibodies. The second study, VR-VTR-10938, was conducted later when the planned study design for the first-in-human study (C3671001) was being established. The dose in the second study included a dose level representative of the lowest planned clinical dose of 60 µg (30 µg of each drug substance).

No secondary pharmacology, safety pharmacology or pharmacodynamic drug interaction studies were performed. This is acceptable as these studies are generally not considered necessary to support the development and licensure of vaccines for infectious diseases (WHO, 2005; WHO, 2014).

The recombinant, bivalent, stabilised prefusion RSV F subunit vaccine candidate (RSVpreF) contains two F antigens, 847A from RSV subgroup A and 847B from subgroup B, present in equal amounts in a lyophilised dosage form for reconstitution. Based on clinical safety and immunogenicity data, the final formulation selected for pivotal efficacy studies was RSVpreF 120 µg without $Al(OH)_3$, although complete protection in the upper airways of the Cotton Rat studies required inclusion of $Al(OH)_3$ or CpG 24555/$Al(OH)_3$ with the bivalent 847 prefusion F vaccine candidate.

In this sense, it is not clear whether the RSVpreF materials used in the non-clinical PD studies are sufficiently representative of the material used in the clinic and commercially. The applicant was asked

to draw a plausible conclusion on the representativeness of the RSVpreF material used in the non-clinical pharmacodynamic studies for the clinic. In response the applicant provided an adequate overview of the tested RSVpreF material used in the non-clinical PD studies, the corresponding DP and DS batch numbers, and the production methods/processes submitted originally in Module 3 of the MAA dossier. Equally, a plausible conclusion on the representativeness of the RSVpreF material (used in the non-clinical pharmacodynamic studies) for the clinical use was subsequently submitted.

2.5.2. Pharmacokinetics

No dedicated pharmacokinetics or ADME studies for RSVpreF have been performed. This is acceptable as such studies are not considered necessary for vaccine products (WHO, 2005; WHO, 2014).

2.5.3. Toxicology

RSVpreF were tested in a repeat-dose toxicity study in rats and in a combined fertility and pre- and postnatal developmental toxicity study in pregnant and lactating rabbits. In both studies, the vaccine formulations, with or without $Al(OH)_3$, were administered IM (120 µg each of 847A and 847B, total of 240 µg antigens) at 2x the selected clinical dose (total of 120 µg antigens).

Repeat-dose administrations of RSVpreF (1 dose every 3 or 2 weeks) for a total of 3 doses to Wistar Han rats were tolerated without evidence of systemic toxicity and produced a functional antibody response and anticipated local inflammatory reaction. Non-adverse immune responses and/or inflammatory reactions were evident at the injection sites and draining lymph nodes, and clinical pathology changes, when present, were consistent with immune stimulation or inflammation at the injection sites. These findings were interpreted to be non-adverse because of limited severity, lack of systemic findings, and absence of clinical signs. RSVpreF-related changes in neutrophils, acute phase proteins, and albumin: globulin ratio as well as microscopic findings at the injection site and in the draining lymph nodes were consistent with those seen with administration of vaccines. All findings were typical of those observed with administration of other vaccines, including aluminium-containing vaccines.

The applicant states that the Wistar Han rat was used as it is an immunologically relevant species as it develops a neutralizing antibody response to RSV antigens. However, females in Group 3 administered RSVpreF without $Al(OH)_3$ did not exhibit a functional antibody response to either RSV A or RSV B. Geometric mean titres identical to control groups, and below the LOD. Group 4 females responded to RSVpreF + $Al(OH)_3$, demonstrating the capability to induce an immune response in female HW rats. Group 3 females did not respond to RSVpreF, either A or B component. The applicant was asked to explain the lack of a response in this group. In response the applicant provided procedural details from the study that demonstrate that control solution could not have been inadvertently administered to this group of female animals. In addition, Group 3 males clearly showed an immune response, excluding the possibility of being dosed with a control formulation, as these two groups were sequentially dosed. No deviations of dosing errors were noted. The lack of immune response to RSVpreF in female rats appears to be a true species-specific effect.

The RSV B neutralisation assay is considered qualified for use in the detection of antibodies present in serum. Both assays were evaluated for performance parameters including assay precision, intermediate precision, and dilutional linearity using serum samples sourced from humans and various animal species, including the Wistar Han rat. The lack of response in female rats has been sufficiently explained. These assays were used to measure antibodies in Study AB22373 in which robust RSV B antibody responses were measured in female rabbits and were successfully used for early phase clinical testing as well.

In a fertility, reproductive, and developmental study in NZW rabbits, following administration of RSVpreF with or without $Al(OH)_3$ twice premating and twice during gestation (for a total of 4 doses), there were no indications of maternal systemic toxicity or effects on mating performance or fertility in female rabbits or on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. Rabbits administered RSVpreF (both with and without $Al(OH)_3$) elicited an immune response to RSV A and RSV B, and these responses were detectable in fetuses and kits from the caesarean and littering groups, respectively. At gestation day 29, fetuses had comparable RSV A and B titres in Group 3 (clinical formulation without $Al(OH)_3$). At PND 35, kit titres for RSV A and RSV B were approximately 5 times lower than the maternal titres.

Based on the nonclinical toxicity studies, findings related to IM administration of RSVpreF with or without Al(OH)3 were limited to nonadverse microscopic findings at the injection sites (chronic active inflammation) and the draining lymph nodes (increased cellularity of the germinal centres and accumulation of macrophages). Inflammatory changes at the injection site and increased germinal centre cellularity of the draining lymph node were consistent with findings typically observed with the IM administration of vaccines (especially aluminium-containing vaccines) and demonstrated evidence of reversibility.

Although it was consistently demonstrated in the nonclinical studies that immune responses were higher in animals administered RSVpreF with $Al(OH)_3$ compared with animals administered RSVpreF without $Al(OH)_3$, the final formulation without $Al(OH)_3$ was selected based on the safety and immunogenicity data from 2 Phase 1/2 studies (C3671001 and C3671002) and the efficacy evaluation in the human challenge study (WI257521). In studies C3671001 and C3671002, $Al(OH)_3$ or $CpG/Al(OH)_3$ did not notably enhance the immune response to RSVpreF. Therefore, based on clinical safety and immunogenicity data, the final formulation selected for pivotal efficacy studies was RSVpreF 120 µg without Al(OH)3.

In general, the toxicology studies are in line with the WHO Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines (2020), supporting the dose level, dosing schedule and route of administration of RSVpreF to humans.

2.5.4. Ecotoxicity/environmental risk assessment

The absence of ERA studies for vaccines are justified according to the Guideline (EMEA/CHMP/SWP/4447/00), which states,

> *"In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment. The same applies to vaccines and herbal medicinal products."*

This product is both a vaccine and a protein.

The statement provided by the applicant that due to the nature of its constituents an ERA is not required for this vaccine can be accepted, the statement has been signed and dated by the expert preparing it, and the CV of the expert is provided.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, RSVpreF is not expected to pose a risk to the environment.

2.5.5. Discussion on non-clinical aspects

Pharmacology

Pharmacology studies performed demonstrated that prefusion F elicits higher titre neutralizing antibodies than postfusion F in experimental animals. The immunogenicity of the chosen antigens of RSVpreF, 847A and 847B, was evaluated and demonstrated in mice, cotton rats, Wistar Han rats, NZW rabbits, and nonhuman primates.

The *in vivo* data demonstrate, in RSV-naïve experimental animals, that immunisation with stabilised prefusion F elicits much higher neutralizing titres than immunisation with postfusion F. In the cotton rat model, immunisation with RSVpreF protects cotton rats from RSV shedding and does not enhance respiratory pathology upon infectious RSV challenge.

The immunogenicity of the prefusion F constructs was assessed in mice, cotton rats and monkeys. In cotton rats and monkeys used palivizumab as a control, to serve as a potential threshold of protection.

All non-clinical PD studies – except the study in Rhesus Macaques (VR-VTR-10388), have been conducted in female animals. For the provided proof-of-concept (immunogenicity) studies, this is agreed. Potential gender differences with respect to induced immune responses, vaccine efficacy, etc. have been investigated in the human target population (study C3671001, C3671002). Immunogenicity studies were performed only in male animals as this is the approach used in the chosen CRO.

The neutralising activity of the RSV prefusion F vaccine was investigated using RSV laboratory and clinical strains.

Demonstration of preclinical efficacy and absence of vaccine-enhanced pathology was assessed in a cotton rat RSV challenge model. Various doses were used in these studies and the dose in the second study included a dose level representative of the lowest planned clinical dose of 60 µg (30 µg of each drug substance).

During the course of this animal study (Evaluation of Safety, Efficacy and Immunogenicity of Candidate Vaccines in the RSV Cotton Rat Model, Study Number: VR-VTR-10390 / XV-154, (PRL-RSV-2016-06)), three cotton rats, 109330 (group 8), 109317 (group 6) and 109300 (group 5) had medical incidents. The cotton rats found dead were considered unrelated to the administration of the RSV vaccines. All three animals showed no signs of injury, were well groomed, well-nourished and showed no signs of dehydration. Neither did the cotton rats have a history of malocclusion or showed signs of it when found dead. A full necropsy was performed and macroscopy did not show anything obvious. The cause of death was not determined in the pathological evaluation, however, it was confirmed that no animal administered the RSVpreF vaccine candidate was affected by the incidents.

The recombinant, bivalent, stabilised prefusion RSV F subunit vaccine candidate (RSVpreF) contains two F antigens, 847A from RSV subgroup A and 847B from subgroup B, present in equal amounts in a lyophilised dosage form for reconstitution. Based on clinical safety and immunogenicity data, the final formulation selected for pivotal efficacy studies was RSVpreF 120 µg without Al(OH)3, although complete protection in the upper airways of the Cotton Rat studies required inclusion of Al(OH)3 or CpG 24555/Al(OH)3 with the bivalent 847 prefusion F vaccine candidate.

In this sense, it is not clear whether the RSVpreF materials used in the non-clinical PD studies are sufficiently representative of the material used in the clinic and commercially. The applicant provided an adequate overview of the tested RSVpreF material used in the non-clinical PD studies, the corresponding DP and DS batch numbers, and the production methods/processes submitted originally in Module 3 of the MAA dossier. Equally, a plausible conclusion on the representativeness of the

RSVpreF material (used in the non-clinical pharmacodynamic studies) for the clinical use was subsequently submitted.

Adsorption of the 847A and 847B antigens to $Al(OH)_3$ alone further enhances neutralizing antibody titres. However, based on clinical safety and immunogenicity data, the final clinical formulation selected for pivotal efficacy studies was RSVpreF 120 µg without $Al(OH)_3$.

No secondary pharmacology, safety pharmacology or pharmacodynamic drug interaction studies were performed. This is acceptable as these studies are generally not considered necessary to support the development and licensure of vaccines for infectious diseases (WHO, 2005; WHO, 2014).

Pharmacokinetics

Pharmacokinetic studies have not been conducted with RSVpreF. Such studies are not considered necessary for vaccine products (WHO, 2005; WHO, 2014).

Toxicology

The nonclinical safety of RSVpreF was evaluated in a GLP-compliant repeat-dose toxicity study in rats, and in a combined fertility and pre- and postnatal development study in pregnant and lactating rabbits. While the commercial formulation will be RSVpreF without any adjuvants and is supported by nonclinical data of RSVpreF alone, evaluations of the vaccine with $Al(OH)_3$ were also performed in the same studies.

Repeat-dose administrations of RSVpreF for a total of 3 doses to Wistar Han rats were tolerated without evidence of systemic toxicity and produced a functional antibody response and anticipated local inflammatory reaction. RSVpreF-related changes in neutrophils, acute phase proteins, and albumin: globulin ratio as well as microscopic findings at the injection site and in the draining lymph nodes were consistent with those seen with administration of vaccines. However it was noted that female rats administered RSVpreF without $Al(OH)_3$ did not exhibit a functional antibody response to either RSV A or RSV B. Geometric mean titres identical to control groups, and below the LOD. Female rats responded to RSVpreF + $Al(OH)_3$, demonstrating the capability to induce an immune response in female HW rats. The applicant explained that the lack of a response in this group was a species-specific response as robust RSV antibody responses were measured in female rabbits and humans.

The RSV neutralisation assay is considered qualified for use in the detection of antibodies present in serum These assays were used to measure antibodies in Study AB22373 in which robust RSV B antibody responses were measured in female rabbits and were successfully used for early phase clinical testing as well.

In a fertility, reproductive, and developmental study in NZW rabbits, following administration of RSVpreF with or without $Al(OH)_3$ twice premating and twice during gestation, there were no indications of maternal systemic toxicity or effects on mating performance or fertility in female rabbits or on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. Rabbits administered RSVpreF (both with and without $Al(OH)_3$) elicited an immune response to RSV A and RSV B, and these responses were detectable in fetuses and kits from the caesarean and littering groups, respectively. At gestation day 29, fetuses had comparable RSV A and B titres in Group 3 (clinical formulation without $Al(OH)_3$). At PND 35, kit titres for RSV A and RSV B were approximately 5 times lower than the maternal titres.

ERA

The applicant has provided a statement that due to the nature of its constituents an ERA is not required for this vaccine and this can be accepted. The statement has been signed and dated by the expert preparing it, and the CV of the expert is provided.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, RSVpreF is not expected to pose a risk to the environment.

2.5.6. Conclusion on the non-clinical aspects

The pharmacology and toxicology studies performed are in line with the WHO Guidelines (2005, 2014 and 2020), supporting the dose, dosing schedule and route of administration of RSVpreF to humans. The absence of pharmacokinetic studies is acceptable to the CHMP. The applicant has provided acceptable responses to the concerns raised by the Committee; therefore, the non-clinical package can now be considered acceptable in support of the MAA.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Phase 1 and 2 studies of safety and immunogenicity, including co-administration

C3671001	A Phase 1/2, placebo-controlled, randomised, observer-blind, dose-finding, first-in-human study to describe the safety, tolerability, and immunogenicity of RSVpreF vaccine in healthy adults (US Study)	Healthy male and female participants 18-85 years of age
C3671002	A Phase 1/2, placebo-controlled, randomised, observer-blind, dose finding, first-in-human study to describe the safety, tolerability, and immunogenicity of an adjuvanted (CpG) RSVpreF vaccine in healthy older adults (Australian study)	Healthy male and female subjects 65-85 years of age
C3671004	A Phase 2b, placebo-controlled, randomised, observer-blind study to evaluate the safety, tolerability, and immunogenicity of RSVpreF vaccine when administered concomitantly with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy non-pregnant women 18 through 49 years of age (US Study)	Healthy non-pregnant female participants 18-49 years of age

Phase 2 and 3 studies that included an evaluation of efficacy

Study / Status	Description / Location	Study Population	RSVpreF Dose / Treatment Groups / Number of Vaccinated Participants	Primary and Secondary Objectives
C3671013 Ongoing	A Phase 3 study to evaluate the efficacy, immunogenicity, and safety of respiratory syncytial virus (RSV) prefusion F subunit vaccine in adults (Global Study: US, Canada, Finland, Japan, The Netherlands, South Africa, Argentina)	Healthy male and female participants ≥ 60 years of age	Placebo (N=17,136) RSVpreF 120 µg (N=17,148)	**PRIMARY** **Efficacy and Safety** • To demonstrate the efficacy of RSVpreF in preventing LRTI-RSV in the first RSV season following vaccination. • To describe the safety profile of RSVpreF as measured by the percentage of participants reporting local reactions, systemic events, AEs, and SAEs. **SECONDARY** **Efficacy and Immunogenicity** • To demonstrate the efficacy of RSVpreF in preventing sLRTI-RSV in the first RSV season following vaccination. • To describe the efficacy of RSVpreF in preventing LRTI-RSV across 2 RSV seasons following vaccination. • To describe the efficacy of RSVpreF in preventing LRTI-RSV in the second RSV season. • To describe the efficacy of RSVpreF in preventing ARI-RSV at each RSV season and across 2 RSV seasons following vaccination. • To describe the efficacy of RSVpreF in preventing sLRTI-RSV across 2 RSV seasons following vaccination. • To describe the efficacy of RSVpreF in preventing sLRTI-RSV in the second RSV season. • To describe the immune responses induced by RSVpreF following vaccination.
WI257521 Completed	A Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, immunogenicity and efficacy of a respiratory syncytial virus vaccine (RSVpreF) in a virus challenge model in healthy adults (UK study)	Healthy male and/or female participants 18-50 years of age	Placebo (N=35) RSVpreF 120 µg (N=35) Note: Challenge virus received by 31 participants in each group	**PRIMARY** **Efficacy** • To evaluate the effect of RSVpreF, in reducing the incidence or severity of infection or disease due to RSV-A Memphis 37b when compared to placebo **SECONDARY** **Efficacy and Safety** • To further evaluate the effect of RSVpreF, in reducing the incidence of infection or disease due to RSV-A Memphis 37b, compared to placebo. • To further evaluate the effect of RSVpreF, in reducing infection due to RSV-A Memphis 37b compared to placebo • To further evaluate the effect of RSVpreF, in reducing symptomatic infection due to RSV-A Memphis 37b, compared to placebo • To evaluate the effect of RSVpreF, in reducing the incidence of RSV-A Memphis 37b infection compared to placebo

Study / Status	Description / Location	Study Population	RSVpreF Dose / Treatment Groups / Number of Vaccinated Participants	Primary and Secondary Objectives
C3671003 Completed	A Phase 2b, randomized, placebo-controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of a respiratory syncytial virus (RSV) vaccine in pregnant women 18 through 49 years of age and their infants (Global Study: US, Argentina, Chile, South Africa)	Healthy pregnant women 18 through 49 years of age, between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination	Placebo (N=117) RSVpreF 120 µg (N=115) RSVpreF 120 µg + $Al(OH)_3$ (N=117) RSVpreF 240 µg (N=116) RSVpreF 240 µg + $Al(OH)_3$ (N=114)	**PRIMARY** **Safety (Maternal participants)** • To describe the safety and tolerability of an RSV vaccine **Safety (Infant participants)** • To assess the safety of maternal immunization in infants born to women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy **SECONDARY** **Immunogenicity (Maternal participants)** • To describe the immune responses elicited by an RSV vaccine **Immunogenicity (Infant participants)** • To describe RSV antibody levels in infants born to women ≥18 through ≤49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy

Study / Status	Description / Location	Study Population	RSVpreF Dose / Treatment Groups / Number of Vaccinated Participants	Primary and Secondary Objectives
C3671008 Ongoing	A Phase 3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of a respiratory syncytial virus (RSV) prefusion F subunit vaccine in infants born to women vaccinated during pregnancy (Global Study: Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, and the US.	Healthy pregnant women ≤49 years of age, between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination	Placebo (N= 3675)[a] RSVpreF 120 µg (N= 3682)[a]	**PRIMARY** **Efficacy and Safety (Infant participants)** • To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV • To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV • To describe the safety of RSVpreF **Safety (Maternal participants)** • To describe the safety and tolerability of RSVpreF **SECONDARY** **Efficacy and Safety (Infant participants)** • To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV • To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI • To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV

Other studies

C3671014 was a lot-to-lot consistency study in healthy adults. This study is completed and the CSR was included in Module 5.

C3671006 is an influenza vaccine co-administration study in adults 65+ years. The topline data, including the primary immunogenicity endpoints, and the CSR were submitted during the procedure.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Not applicable

2.6.2.2. Pharmacodynamics

Not applicable

2.6.3. Discussion on clinical pharmacology

Not applicable

2.6.4. Conclusions on clinical pharmacology

Not applicable

2.6.5. Clinical efficacy

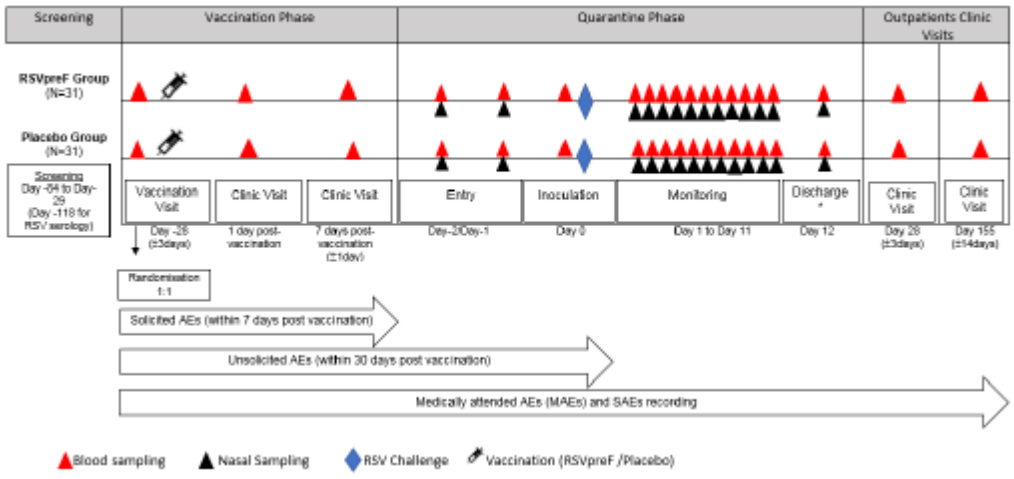
2.6.5.1. Dose response studies and main clinical studies

Dose-response studies and main clinical studies

WI257521 – Human challenge study in healthy adults 18-50 years

This was a randomised, double-blind and placebo-controlled study to evaluate the efficacy of RSVpreF (120 µg) in a virus challenge model in healthy male and female subjects aged 18-50 years.

Figure 1: **Study Schematic: On-study Participant Progression**



The primary objective was to evaluate the effect of RSVpreF in reducing the incidence or the severity of infection or disease due to RSV-A Memphis 37b compared to placebo in ~72 healthy male and female subjects aged 18-50 years. Vaccine was administered on Day -28 (±3 days) and challenge was on Day 0 using RSV-A Memphis 37b 4.5 $\log_{10}$ PFU administered intranasally (2 x 250 µL per nostril).

The primary analysis was conducted in the ITT-Challenge (ITTc) Analysis Set, which included all randomised, vaccinated and challenged subjects. The primary endpoint was qRT-PCR-confirmed symptomatic RSV infection (Variant 1), defined as:

- qRT-PCR-confirmed RSV infection based on two detectable (≥LLOD) qRT-PCR measurements (on 2 or more consecutive days), starting two days post-viral challenge (Day +2) up to discharge from quarantine AND
- Either one or more positive clinical symptoms of any grade from two different categories in the symptom scoring system or one Grade 2 symptom from any category.

VE was derived from the Relative Risk (RR), where VE = 1-RR and RR is the ratio of the proportion of participants infected in the vaccine arm to the proportion of participants infected in the placebo arm. The 95% confidence interval was derived using the Farrington-Manning method. As an exploratory proof of concept study, no adjustment for Type I error was planned in regard to the primary endpoint family. Up to 72 participants were to be enrolled with 62 participants challenged with virus.

There were 70 subjects randomised and 62 were challenged (ITTc set). The age range was 19-50 years with mean in the range 24-27 years. The majority was male (71%) and White (overall 93%).

qRT-PCR-confirmed symptomatic RSV infection (Variant 1, Day 2 to Day 12)
Based on this definition (see above), 2 (6.5%) subjects were classed as infected in the RSVpreF group vs. 15 (48.4%) in the placebo group. VE was computed as 86.7%, with a lower bound of the 95% CI >50%. The median time to onset was 2.8 days for placebo and 4.8 days for RSVpreF.

qRT-PCR-confirmed symptomatic RSV infection (Variant 2, Day 2 to Day 12)
Participants had to have 2 positive quantifiable (≥LLOQ) qRT-PCR results within 4 consecutive time points AND either have one or more symptoms of any grade from 2 different categories (URT, LRT, Systemic) OR have one symptom of grade 2 or higher within the time period. Based on this definition there were no cases in the RSVpreF group but the rate was 13/31 (41.9%) in the placebo group and VE was computed as 100.0% with a lower bound of the 95% CI >70%.

qRT-PCR-confirmed symptomatic RSV infection (Variant 3, Day 2 to Day 12)
Participants had to have 2 positive quantifiable (≥LLOQ) qRT-PCR results at any time point AND have one or more symptoms of grade 1 or higher within the time period. Based on this definition, there were no cases in the RSVpreF group, but the rate was 18/31 (58.1%) in the placebo group and VE was computed as 100.0% with a lower bound of the 95% CI >80%.

qRT-PCR-confirmed symptomatic RSV infection (Variant 4, Day 2 to Day 12)
Participants had to have 2 positive (detected) qRT-PCR results within 4 consecutive time points AND have a TSS ≥ 2 within the time period. Based on this definition, the case rates were 2/31 (6.5%) in the RSVpreF group vs. 17/31 (54.8%) in the placebo group and VE was computed as 88.2% with a lower bound of the 95% CI near to 60%.

qRT-PCR-confirmed symptomatic RSV infection (Variant 5, Day 2 to Day 12)
Participants had to have 2 quantifiable positive (≥LLOQ) qRT-PCR results AND either have one or more symptoms of any grade from 2 different categories (URT, LRT, Systemic) OR have one symptom of grade 2 or higher within the time period. Based on this definition, there were no cases in the RSVpreF group vs. 13/31 (41.9%) in the placebo group and VE was computed as 100% with a lower bound of the 95% CI >70%. The median time to onset in the placebo group was 3.3 days.

The viral load AUC was significantly lower with RSVpreF and the peak viral load was markedly lower with a mean difference vs. placebo of -3.3245 $\log_{10}$ copies/mL. In the subgroup with laboratory-confirmed infection, the mean difference was -2.6270 $\log_{10}$ copies/mL. The median duration of viral detection was 18.0 hours for RSVpreF and 131.6 hours for placebo in the ITTc population.

For the sum of the TSS, geometric means were 2.1 for the RSVpreF group vs. 10.8 for the placebo group (median 0.0 vs. 16.0). The geometric mean ratio was 0.26.

Pre-vaccination NA_{50} titres were comparable in the two groups. At Day 12 post-challenge, the GMT ~doubled in the placebo group. At Days 28 and 155, the titres were still much higher in the RSVpreF group vs. the placebo group. At 7 days after vaccination, there was a marked increase in the CD4+ T-cell response in RSVpreF group, indicating a TH1 response. In the placebo group, an increase in both RSV F-specific and M-specific CD4+ T-cell response (TH1) was observed for day 10 after challenge vs. pre-challenge but no such increase in CD4+ T-cell responses was noted in the RSVpreF group. RSV F-

and M-specific CD8+ T-cell responses were not detected in the RSVpreF or placebo participants at any time points evaluated.

C3671013 - Efficacy in older adults

This was a Phase 3 randomised and double-blind, placebo-controlled vaccine efficacy study in generally healthy subjects aged from 60 years. There were 240 sites in 7 countries (Argentina, Canada, US, Finland, Netherlands, S. Africa and Japan). The study was initiated August 2021 and the CSR dated 22 September 2022 reflects data up to 8 July 2022 for cases and 14 July 2022 for some other endpoints.

Methods

There was stratification of eligible subjects at randomisation by age group: 60-69 years (aim at least 6,000), 70-79 years (aim at least 6,000) and 80+ years (aim at least 800). Approximately 10% were to have stable chronic cardiopulmonary conditions. Subjects with unstable illnesses and immunosuppressed persons were excluded.

Subjects were randomised 1:1 to vaccine or placebo, given IM into the deltoid. The vaccine contained 120 µg of the RSV prefusion F antigen (60 µg of each of A and B). Placebo contained the excipients.

The primary efficacy objective, estimand and endpoint, and the most important secondary efficacy endpoint (severe RSV LRTI; sLRTI), are shown in the table below.

Table 1: The primary efficacy objectives, estimands and endpoints

Objectives	Endpoints	Estimands
Primary Efficacy:	**Primary Efficacy:**	**Primary Efficacy:**
To demonstrate the efficacy of RSVpreF in preventing LRTI-RSV in the first RSV season following vaccination.	LRTI-RSV cases.	In participants in compliance with the key protocol criteria (evaluable efficacy population): 1. VE, defined as the relative risk reduction of first-episode LRTI-RSV cases with ≥2 LRTI signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination). 2. VE, defined as the relative risk reduction of first-episode LRTI-RSV cases with ≥3 LRTI signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season

Key Secondary Efficacy:	**Key Secondary Efficacy:**	**Key Secondary Efficacy:**
To demonstrate the efficacy of RSVpreF in preventing sLRTI-RSV in the first RSV season following vaccination.	sLRTI-RSV cases.	In participants in compliance with the key protocol criteria (evaluable efficacy population): VE, defined as the relative risk reduction of first-episode sLRTI-RSV cases in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination).

Other secondary endpoints included efficacy for LRTI-RSV across two seasons and only in the second season, and efficacy for any acute respiratory illness (ARI) confirmed to be due to RSV.

Starting on Day 15 (Day 1 = day of vaccination), there was active surveillance for acute respiratory illness (ARI) symptoms and subjects used e-diaries or equivalent technology. Subjects completed a questionnaire if they developed symptoms of an ARI during the RSV season and were to collect mid-turbinate nasal swabs on days 2-3 of symptom(s) for RT-PCR testing. The table below shows the endpoint assessments and definitions.

Table 2: Endpoint Assessment and Definitions

Study Endpoints/Assessments	Study Definitions
ARI	An illness involving 1 or more of the following 7 respiratory illness symptoms, lasting more than 1 day: • New or increased sore throat • New or increased cough • New or increased nasal congestion • New or increased nasal discharge • New or increased wheezing • New or increased sputum production • New or increased shortness of breath
RSV-positive test	RSV RT-PCR–positive test result by Pfizer central laboratory **OR** RSV-positive test result by certified laboratory with NAAT for RSV, if RSV RT-PCR test result by Pfizer central laboratory is not available.
ARI-RSV	ARI-RSV will be defined as an ARI with RT-PCR–confirmed RSV infection within 7 days of ARI symptom onset.
LRTI	LRTI will be defined as an ARI with ≥2 or ≥3 of the following LRTI signs/symptoms during the illness • New or increased cough • New or increased wheezing • New or increased sputum production • New or increased shortness of breath • Tachypnea (≥25 breaths/min or ≥15% increase from resting baseline)
LRTI-RSV with at least 2 symptoms	LRTI-RSV with at least 2 symptoms will be defined as an ARI with ≥2 of the 5 LRTI signs/symptoms lasting more than 1 day during the same illness, **plus** RT-PCR–confirmed RSV infection within 7 days of ARI symptom onset.
LRTI-RSV with at least 3 symptoms	LRTI-RSV with at least 3 symptoms will be defined as an ARI with ≥3 of the 5 LRTI signs/symptoms lasting more than 1 day during the same illness, **plus** RT-PCR–confirmed RSV infection within 7 days of ARI symptom onset.
sLRTI-RSV	LRTI-RSV criteria plus at least 1 of the following: • Hospitalization due to LRTI-RSV • New/increased oxygen supplementation • New/increased mechanical ventilation, including CPAP

This was case-driven study. With a 5% type I error (2-sided) for LRTI-RSV cases, to have minimum 90% power to demonstrate that the lower bound of the 2-sided 95% CI for RSVpreF VE is >20%, 59 LRTI-RSV cases were required in the evaluable efficacy population, assuming that the true vaccine efficacy is 70% for LRTI-RSV as defined above. With a conservative assumption of an attack rate of 0.35% for LRTI-RSV, allowing for up to 10% non-evaluable, approximately 30,000 subjects were required to accrue 59 cases. If case accrual was lower than expected, the study permitted enrolment of subjects in the Southern Hemisphere (SH) or additional subjects in the NH in the following year, with maximum enrolment up to 45,000.

The evaluable efficacy population was the primary population for efficacy analyses (see table below for definition). The analyses were repeated on the mITT efficacy population.

Table 3: Defined analysis set & description

Defined Analysis Set	Description
mITT efficacy population	All participants who were randomized and received study intervention.
Evaluable efficacy population	All study participants who meet the following criteria: 1. Are eligible for the study. 2. Received study intervention to which they were randomized (RSVpreF or placebo). 3. A minimum follow-up through Day 15 after vaccination (Day 1 is the day of vaccination). 4. Had no major protocol violations before the symptom onset date of the confirmed ARI or LRTI case.

VE was defined as VE = 100 × (1 - risk ratio). Risk ratio was the case count of first-episode confirmed cases in the RSVpreF group vs. the corresponding case count in the placebo group. The CI of the VE used the conditional exact test based on the binomial distribution of the number of cases in the RSVpreF group, given the total number of cases in both groups. Two methods were used for sensitivity analysis of VE: one method adjusted the follow-up time (1-IR ratio) and the other method used the time to the first episode of case onset (1-HR). For the primary endpoint, analyses were performed for RSV A+ and RSV B+, separately.

For the primary efficacy objective and key secondary objective, RSVpreF was to be compared to placebo, with sequential testing of the following 3 hypotheses, where H_0 and H_a represent the null and alternative hypotheses, respectively:

1. H_0: VE ≤20% vs H_a: VE >20% against first episode of LRTI-RSV with ≥2 symptoms (as defined by ≥2 of the 5 LRTI signs/symptoms in the first RSV season)
2. H_0: VE ≤20% vs H_a: VE >20% against first episode of LRTI-RSV with ≥3 symptoms (as defined by ≥3 of the 5 LRTI signs/symptoms in the first RSV season)
3. H_0: VE ≤20% vs H_a: VE >20% against first episode of sLRTI-RSV in the first RSV season

The 3 hypothesis tests were to be tested sequentially as ordered, with an overall type I error of 5% (2-sided) or a 1-sided alpha of 2.5%. No additional endpoints were included in the confirmatory testing strategy for this study.

An interim analysis was planned when at least 29 evaluable first-episode LRTI-RSV cases with ≥2 symptoms were accrued and it was actually conducted when 44 first-episode LRTI-RSV cases with ≥2 symptoms had accrued in the first RSV season.

All study participants remained in blinded follow-up after the interim analysis. After the DMC declared success of first-episode LRTI-RSV cases with ≥2 symptoms, there were 16 first-episode LRTI-RSV cases with ≥3 symptoms accrued so the interim analysis of that endpoint was also conducted. However, <12 cases of first-episode sLRTI-RSV had accrued as of the cut-off date so no interim analysis of this endpoint was conducted.

Results

As of the data cut-off date (14 July 2022), 34,284 subjects had been randomised and received study intervention. There was a low rate of withdrawals in either group (5.3%) after vaccination and the most common reasons were withdrawal by the subject (2.6%) and lost to follow-up (1.9%). Demographic and baseline characteristics were balanced between the RSVpreF and placebo groups.

Table 4: Demographic and baseline characteristics were balanced between the RSVpreF and placebo groups

	Vaccine Group (as Administered)		
	RSVpreF 120 µg (N[a]=17215) n[b] (%)	Placebo (N[a]=17069) n[b] (%)	Total (N[a]=34284) n[b] (%)
60-69 Years	10756 (62.5)	10680 (62.6)	21436 (62.5)
70-79 Years	5488 (31.9)	5431 (31.8)	10919 (31.8)
≥80 Years	970 (5.6)	958 (5.6)	1928 (5.6)
Mean (SD)	68.3 (6.14)	68.3 (6.18)	68.3 (6.16)
Median	67.0	67.0	67.0
(Min, max)	(59, 95)	(60, 97)	(59, 97)
Country			
USA	10319 (59.9)	10182 (59.7)	20501 (59.8)
Argentina	3660 (21.3)	3657 (21.4)	7317 (21.3)
Japan	1159 (6.7)	1156 (6.8)	2315 (6.8)
The Netherlands	687 (4.0)	681 (4.0)	1368 (4.0)
Canada	509 (3.0)	506 (3.0)	1015 (3.0)
South Africa	495 (2.9)	497 (2.9)	992 (2.9)
Finland	386 (2.2)	390 (2.3)	776 (2.3)
Prespecified significant conditions[d]			
With ≥1 prespecified significant condition	8867 (51.5)	8831 (51.7)	17698 (51.6)
Current tobacco use	2642 (15.3)	2571 (15.1)	5213 (15.2)
Diabetes	3224 (18.7)	3284 (19.2)	6508 (19.0)
Lung disease[e]	1956 (11.4)	2040 (12.0)	3996 (11.7)
Heart disease[f]	2221 (12.9)	2233 (13.1)	4454 (13.0)
Liver disease	335 (1.9)	329 (1.9)	664 (1.9)
Renal disease	502 (2.9)	459 (2.7)	961 (2.8)
With ≥1 chronic cardiopulmonary condition	2595 (15.1)	2640 (15.5)	5235 (15.3)
Asthma	1541 (9.0)	1508 (8.8)	3049 (8.9)
Chronic obstructive pulmonary disease (COPD)	1012 (5.9)	1080 (6.3)	2092 (6.1)
Congestive heart failure (CHF)	293 (1.7)	307 (1.8)	600 (1.8)
With no prespecified significant conditions	8348 (48.5)	8238 (48.3)	16586 (48.4)
Respiratory rate at baseline (breaths/min)[c]			
n	17188	17050	34238
Mean (SD)	15.7 (2.14)	15.7 (2.24)	15.7 (2.19)
Median	16.0	16.0	16.0
(Min, max[g])	(8, 29)	(6, 92)	(6, 92)

For the primary analysis, the lower bound of the confidence interval was >20%. This was also the case for the other calculations of VE based on the IR ratio and the HR.

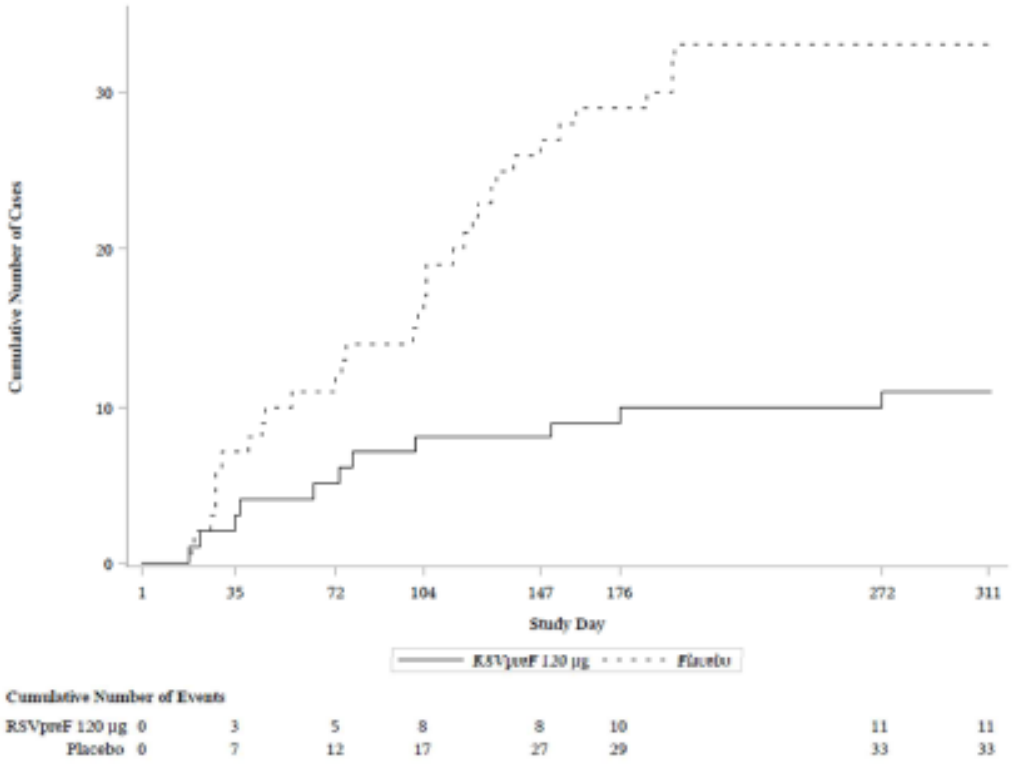
Based on 11 cases, the lower bounds of the CIs for VE efficacy against RSV A were >0.

Based on 33 cases, the lower bounds of the CIs for VE against RSV B were just under 0 or just over 0 depending on method of calculation.

Table 5: Vaccine Efficacy of RSVpreF Against First Episode of LRTI-RSV With ≥2 Symptoms – Evaluable Efficacy Population

	Vaccine Group (as Randomized)											
	RSVpreF 120 µg (N[a] = 16306) (PYO[b] = 9226)			Placebo (N[a] = 16308) (PYO[b] = 9211)			VE = 1 - Risk Ratio		VE = 1 - IR Ratio		VE = 1 - Hazard Ratio	
Efficacy Endpoint	n[c]	%	IR[d] (per 1000 PYO)	n[c]	%	IR[d] (per 1000 PYO)	VE[e] (%)	(96.66% CI)[e]	VE[f] (%)	(96.66% CI)[f]	VE[g] (%)	(96.66% CI)[g]
First episode of LRTI-RSV with ≥2 symptoms	11	0.07	1.19	33	0.20	3.58	66.7	(28.8, 85.8)	66.7	(28.9, 85.8)	66.7	(32.8, 85.0)
Subgroup A[h]	1	0.01	0.11	9	0.06	0.98	88.9	(10.6, 99.8)	88.9	(10.7, 99.8)	88.9	(33.6, 99.6)
Subgroup B[h]	10	0.06	1.08	23	0.14	2.50	56.5	(-0.7, 82.8)	56.6	(-0.5, 82.9)	56.5	(5.8, 81.6)

Figure 2: Cumulative Case Accrual Curve From Day of Vaccination, First Episode of LRTI-RSV With ≥2 Symptoms – Evaluable Efficacy Population



For LRTI-RSV cases with ≥2 symptoms with onset from Day 15, the median duration per episode was 12.0 days in the RSVpreF group and 11.5 days in the placebo group. Similar results applied to the mITT population, with only one additional first-episode LRTI-RSV case with ≥2 symptoms reported before Day 15 (from Day 1 [vaccination date]) in the placebo group.

In the evaluable efficacy population there were 17 subjects with 17 episodes of LRTI-RSV with ≥3 symptoms reported after vaccination, of which one was reported before Day 15 so that 16 episodes were included in the VE analysis as shown below. Results were consistent across methods of calculating VE with lower bounds of 96.66% CIs >30%.

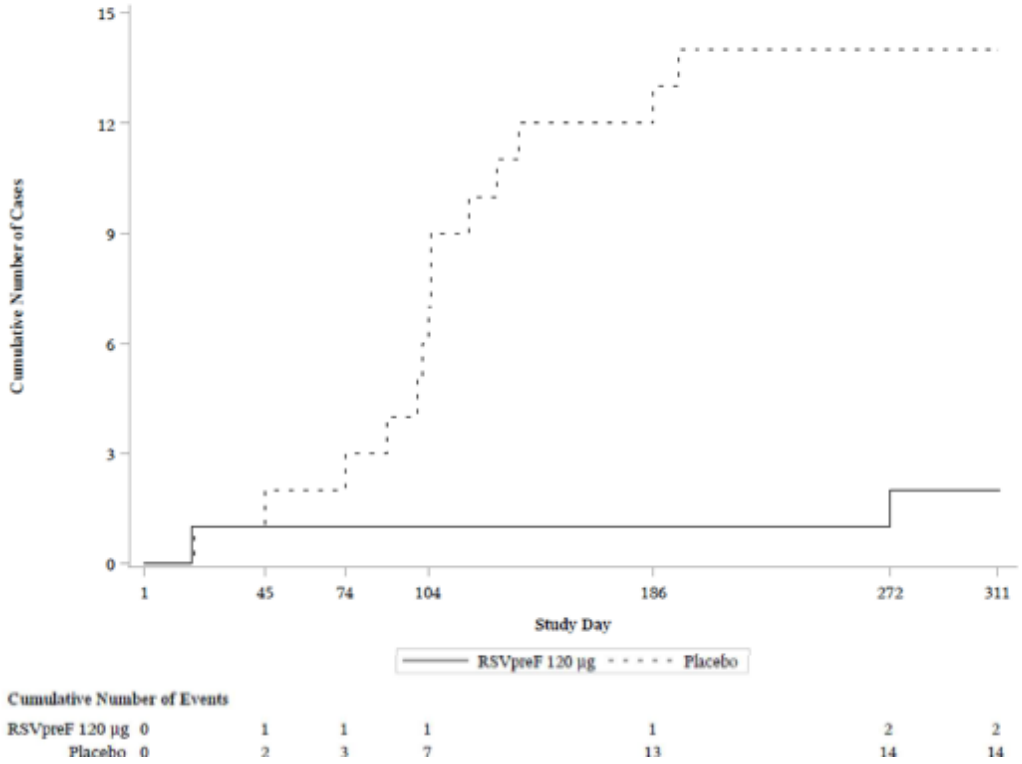
With only 4 cases due to RSV A, it can only be pointed out that there was one case in the vaccine group and 3 in the placebo group.

For RSV B, with 1 and 10 cases in respective groups, the lower bounds of the 96.66% Cis were >20% regardless of method of calculation.

Table 6: Vaccine Efficacy of RSVpreF Against First Episode of LRTI-RSV With ≥3 Symptoms – Evaluable Efficacy Population

	Vaccine Group (as Randomized)											
	RSVpreF 120 µg (N[a] = 16306) (PYO[b] = 9226)			Placebo (N[a] = 16308) (PYO[b] = 9211)			VE = 1 - Risk Ratio		VE = 1 - IR Ratio		VE = 1 - Hazard Ratio	
Efficacy Endpoint	n[c]	%	IR[d] (per 1000 PYO)	n[c]	%	IR[d] (per 1000 PYO)	VE[e] (%)	(96.66% CI)[e]	VE[f] (%)	(96.66% CI)[f]	VE[g] (%)	(96.66% CI)[g]
First episode of LRTI-RSV with ≥3 symptoms	2	0.01	0.22	14	0.09	1.52	85.7	(32.0, 98.7)	85.7	(32.1, 98.7)	85.7	(43.9, 98.2)
Subgroup A[h]	1	0.01	0.11	3	0.02	0.33	66.7	(-393.7, 99.6)	66.7	(-392.9, 99.6)	66.9	(-208.2, 98.9)
Subgroup B[h]	1	0.01	0.11	10	0.06	1.09	90.0	(21.8, 99.8)	90.0	(21.9, 99.8)	90.0	(41.3, 99.6)

Figure 3: Cumulative Case Accrual Curve From Day of Vaccination, First Episode of LRTI-RSV With ≥3 Symptoms – Evaluable Efficacy Population



The median duration per episode was 10.5 days in the RSVpreF group and 15.5 days in the placebo group. In the mITT population there was one additional first-episode LRTI-RSV case with ≥3 symptoms reported before Day 15 in the placebo group.

- **Ancillary analyses**

In the evaluable efficacy population there were 82 subjects with 83 episodes of ARI-RSV reported after vaccination, of which 2 were reported before Day 15 so 80 were included in the VE analysis with results as shown below. The median duration per episode was 8.5 days in the RSVpreF group and 11.0 days in the placebo group. Efficacy against ARI-RSV was demonstrated, with lower bounds of the 95% CI above 35% regardless of method of calculation. Similar results applied to the mITT population.

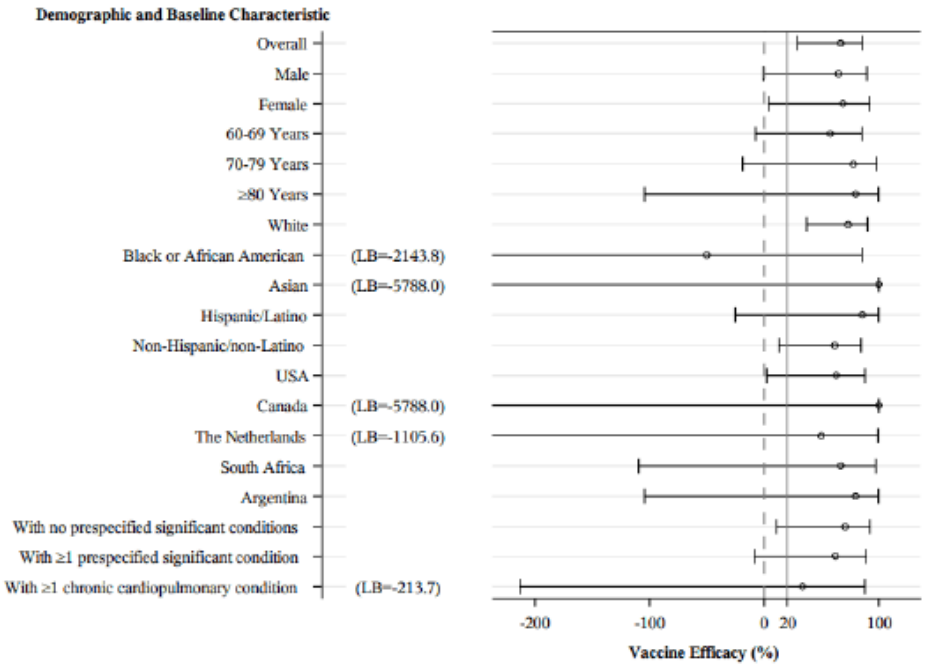
Table 7: **Vaccine Efficacy of RSVpreF Agains First Episode of ARI-RSV – Evaluable Efficacy Population**

	Vaccine Group (as Randomized)											
	RSVpreF 120 µg (N[a] = 16306) (PYO[b] = 9226)			Placebo (N[a] = 16308) (PYO[b] = 9211)			VE = 1 - Risk Ratio		VE = 1 - IR Ratio		VE = 1 - Hazard Ratio	
Efficacy Endpoint	n[c]	%	IR[d] (per 1000 PYO)	n[c]	%	IR[d] (per 1000 PYO)	VE[e] (%)	(95% CI)[e]	VE[f] (%)	(95% CI)[f]	VE[g] (%)	(95% CI)[g]
First episode of ARI-RSV	22	0.13	2.38	58	0.36	6.30	62.1	(37.1, 77.9)	62.1	(37.2, 77.9)	62.1	(39.1, 77.3)
Subgroup A[h]	4	0.02	0.43	12	0.07	1.30	66.7	(-10.0, 92.2)	66.7	(-9.8, 92.2)	66.8	(4.6, 90.7)
Subgroup B[h]	18	0.11	1.95	45	0.28	4.89	60.0	(29.5, 78.2)	60.1	(29.6, 78.2)	60.0	(32.2, 77.4)

Across the larger subgroups, VE point estimates for first-episode LRTI-RSV with ≥2 symptoms were generally similar to those observed in the main analysis. The lower bound of the 96.66% CI was >zero for female subjects, white subjects, non-Hispanic/Latino subjects, USA subjects and for those with no pre-specified significant conditions.

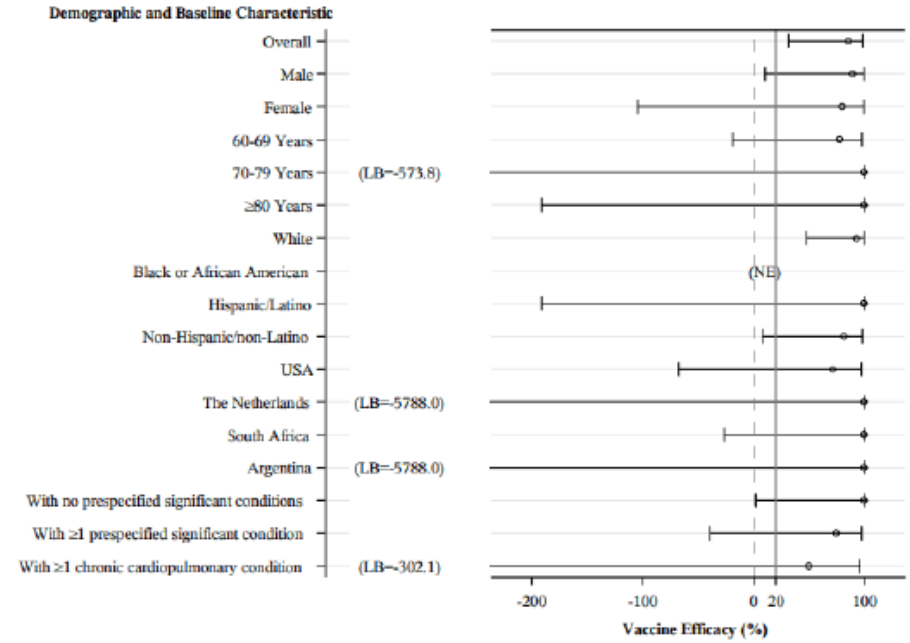
In this regard, it should be noted that the majority of subjects was enrolled in the US (~21,200), followed by Argentina (~8,100) and Japan (~2300). Just over 1,000 was enrolled in each of S. Africa and Canada, with ~1500 in Netherlands and ~800 in Finland. The only subgroup for which the point estimate of efficacy was not in favour of RSVpreF was the Black and African American population, comprising ~4400 subjects. However, the point estimate was favourable for RSVpreF in S. Africa.

Table 8: Forest Plot of Vaccine Efficacy of RSVpreF Against First Episode of LRTI-RSV With ≥2 Symptoms by Demographic and Baseline Characteristic Subgroups– Evaluable Efficacy Population



For first-episode LRTI-RSV with ≥3 symptoms, the lower bounds of the 96.66% CI were >zero for males, white and non-Hispanic/Latino subjects and those without pre-specified significant conditions.

Table 9: Forest Plot of Vaccine Efficacy of RSVpreF Against First Episode of LRTI-RSV With ≥2 Symptoms by Demographic and Baseline Characteristic Subgroups– Evaluable Efficacy Population



The table below describes the case duration.

Table 10: *RSV Cases Duration – Evaluable Efficacy Population*

	Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] = 16306) (PYO[b] = 9226)	Placebo (N[a] = 16308) (PYO[b] = 9211)	Total (N[a] = 32614) (PYO[b] = 18437)
LRTI-RSV with ≥2 symptoms cases having symptom onset from Day 15 throughout the surveillance period			
Total duration (days)[c]	250	507	757
Duration per episode (days)			
n	11	34	45
Mean (SD)	22.7 (27.99)	14.9 (11.18)	16.8 (16.83)
Median	12.0	11.5	12.0
Q1-Q3	7-32	9-17	8-17
(Min, max)	(5, 99)	(3, 62)	(3, 99)
Duration per participant (days)			
n	11	33	44
Mean (SD)	22.7 (27.99)	15.4 (11.26)	17.2 (16.94)
Median	12.0	12.0	12.0
Q1-Q3	7-32	10-18	8-18
(Min, max)	(5, 99)	(3, 62)	(3, 99)
LRTI-RSV with ≥3 symptoms cases having symptom onset from Day 15 throughout the surveillance period			
Total duration (days)[c]	21	270	291
Duration per episode (days)			
n	2	14	16
Mean (SD)	10.5 (7.78)	19.3 (14.39)	18.2 (13.87)
Median	10.5	15.5	15.5
Q1-Q3	5-16	10-24	10-21
(Min, max)	(5, 16)	(5, 62)	(5, 62)
Duration per participant (days)			
n	2	14	16
Mean (SD)	10.5 (7.78)	19.3 (14.39)	18.2 (13.87)
Median	10.5	15.5	15.5
Q1-Q3	5-16	10-24	10-21
(Min, max)	(5, 16)	(5, 62)	(5, 62)
ARI-RSV cases having symptom onset from Day 15 throughout the surveillance period			
Total duration (days)[c]	332	882	1214
Duration per episode (days)			
n	22	59	81
Mean (SD)	15.1 (20.90)	14.9 (10.66)	15.0 (14.04)
Median	8.5	11.0	10.0
Q1-Q3	7-12	8-18	8-16
(Min, max)	(3, 99)	(3, 62)	(3, 99)
Duration per participant (days)			
n	22	58	80
Mean (SD)	15.1 (20.90)	15.2 (10.70)	15.2 (14.10)
Median	8.5	12.0	11.0
Q1-Q3	7-12	8-18	8-17
(Min, max)	(3, 99)	(3, 62)	(3, 99)

Abbreviation(s): ARI-RSV = acute respiratory illness associated with RSV; LRTI-RSV = lower respiratory tract illness associated with RSV; PYO = person-years observation; RSV = respiratory syncytial virus.
Note: All ARI-RSV or LRTI episodes with symptom onset date through surveillance cutoff date (08Jul2022) were included. Because not all nasal swabs collected from ARI visits were tested for RSV positivity, the actual case count for ARI-RSV may be higher than the number reported in this table.
Note: One participant could report multiple episodes of RSV cases during the surveillance period. A new case episode is defined for each separate unplanned illness visit, with a new symptom onset date that is later than the symptom resolution date from the previous unplanned illness visit.
a. N = number of participants (at risk) in the specified vaccine group, or the total sample. These values are the denominators for the percentage calculations.
b. PYO is defined as the total ARI surveillance duration days across all participants at risk within each vaccine group or total, then divided by 365.25. ARI surveillance duration is from vaccination date through death/discontinuation/surveillance cutoff date/major protocol deviation, whichever is earlier. Minimum required surveillance duration is 15 days (14 days after vaccination) to accrue primary endpoint cases for evaluable efficacy population.
c. For each participant, the total duration was calculated as the specified RSV case last symptom resolution date – first symptom onset date + 1.
If a symptom was ongoing at cutoff, the surveillance cutoff date was used for the calculation. For partial symptom onset dates, the first day of the month (when day was unknown) or year (when both month and day were unknown), or vaccination date, whichever was later, was used to impute; for partial symptom resolution dates, the last day of the month (when day was unknown) or year (when both month and day were unknown) or surveillance cutoff date, whichever was earlier, was used to impute. Total duration is the sum of all RSV cases duration across all participants within the specified group (or total).
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (14:52) Source Data: adeff Table Generation: 22AUG2022 (22:28)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_Primary/adeff_dur_eval

Efficacy in infants born to vaccinated pregnant women

The two studies described in this section are as follows:

C3671003: A Phase 2b, randomised, placebo-controlled, observer-blinded trial to evaluate the safety and immunogenicity of RSVpreF vaccine in pregnant women 18 through 49 years of age and their infants. The supplementary CSR for C3671003 provides additional the results for exploratory efficacy endpoints in infants born to vaccinated and unvaccinated mothers. Although efficacy was exploratory, the study is included here since it directly preceded the Phase 3 efficacy study.

C3671008: A Phase 3, randomised, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of RSVpreF vaccine in infants born to women vaccinated during pregnancy. Some, but not all, aspects of methodology were the same as in the Phase 2b study.

C3671003

Eligible healthy women were aged 18 to 49 years and were between 24 0/7 and 36 0/7 weeks of gestation (determined from ultrasound results obtained at ≥18 weeks) on the day of planned vaccination. They were to have an uncomplicated singleton pregnancy achieved without assisted reproduction, with no known increased risk for complications and no significant fetal abnormalities on ultrasound. They were receiving prenatal standard of care with a negative urinalysis for protein and glucose at the screening visit (Visit 0) except that trace proteinuria was acceptable if the blood pressure was normal. The BMI was to be <40 kg/m2 at the screening visit.

Subjects were randomised in equal numbers into five groups to receive RSVpreF 120 µg (60 µg A and 60 µg B) or 240 µg (120 µg A and 120 µg B), each with or without aluminium hydroxide, or placebo (saline). All injections were into the deltoid.

The primary and secondary objectives concerned safety and immunogenicity.

Table 11: Objectives, Endpoints, and Estimands – Maternal Participants

Type	Objective	Endpoints	Estimands
Primary Safety Section 5.3	To describe the safety and tolerability of an RSV vaccine	• Prespecified local reactions within 7 days after vaccination • Prespecified systemic events within 7 days after vaccination • AEs from the time of vaccination through 1 month after vaccination • Obstetric complications, MAEs, and SAEs throughout the study	In maternal participants receiving 1 dose of IP: • The percentage of maternal participants reporting local reactions • The percentage of maternal participants reporting systemic events • The percentage of maternal participants reporting AEs • The percentage of maternal participants reporting obstetric complications, MAEs, and SAEs

Secondary Immunogenicity Section 5.1.1	To describe the immune responses elicited by an RSV vaccine	• RSV A– and RSV B–neutralizing antibody titers measured:
		  • before vaccination
		  • 2 weeks after vaccination
		  • 1 month after vaccination
		  • at delivery[a]
			In maternal participants receiving 1 dose of IP and in compliance with the key protocol criteria (evaluable participants):
			• The immune response, estimated by the GMT for RSV A– and RSV B–neutralizing antibody titers.
			• The immune response, estimated by the GMFR from baseline in RSV A– and RSV B–neutralizing antibody titers.
			• GMR, estimated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers of the RSV vaccine group and the placebo group.

Table 12: Objectives, Endpoints, and Estimands, - Infant Participants

Type	Objective	Endpoints	Estimands
Primary Safety Section 5.3	To assess the safety of maternal immunization in infants born to women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy	• Specific birth outcomes • AEs from birth to 1 month of age • SAEs, AEs of special interest (congenital anomalies, developmental delay), and MAEs through 12 months of age • Congenital anomalies (defined as structural or functional anomalies [eg, metabolic disorders] that occur during intrauterine life and can be identified prenatally, at birth or later in life[16])	In infant participants born to the maternal participants receiving 1 dose of IP: • The percentage of infant participants with specific birth outcomes • The percentage of infant participants having AEs • The percentage of infant participants having SAEs, AEs of special interest (congenital anomalies, developmental delay), and MAEs
Secondary Immunogenicity Section 5.1.1.3	To describe RSV antibody levels in infants born to women ≥18 through ≤49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy	RSV A– and RSV B–neutralizing antibody titers measured at: • birth[a] • 1 month • 2 months • 4 months • 6 months Note: Infant participants were randomly assigned to 1 of 2 blood sampling schedules.	In infant participants born to maternal participants receiving 1 dose of IP and in compliance with the key protocol criteria (evaluable participants): • Functional antibody levels estimated by the GMT for RSV A– and RSV B–neutralizing antibody titers • GMR, estimated by the ratio of the GMTs for RSV A– and RSV–B neutralizing antibody titers of the RSV vaccine group and the placebo group

Table 13: Efficacy in infants was exploratory.

Type	Objective	Endpoints
Exploratory Efficacy Section 5.2	To describe rates of RSV-positive LRTI in the study population To describe respiratory tract illness in the study population To describe the distribution of other pathogens causing acute respiratory tract illness in the study population[b]	• All LRTI caused by RSV determined by RT-PCR • All acute respiratory tract illnesses caused by RSV determined by RT-PCR • All acute LRTIs • All acute URTIs • All acute respiratory tract illnesses • PCR-based assay positivity for non-RSV respiratory pathogens in midturbinate swabs obtained at unplanned acute respiratory tract illness visits[b]

Case ascertainment involved contact of the infant's parent/legal guardian(s) every 7 to 10 days after delivery until the 6-month follow-up visit. The criteria to prompt an acute illness visit required 1 or more of the following signs or symptoms:

- Difficulty breathing, laboured breathing or rapid breathing for any duration;
- Inability to feed for any duration due to respiratory tract illness;
- Thick discharge from the nose for 48 hours or more;
- Any other respiratory symptom of concern.

If the infant could not attend the visit because of hospitalisation or treatment at another medical facility, the data were to be recorded in the CRF based on any available medical records.

Medically significant RSV-associated LRTI was defined based on meeting the following criteria to be considered an "RSV LRTI case" for analysis and reporting purposes:
One or more of the following signs of LRTI:

- Nasal flaring,
- Lower chest wall indrawing or subcostal retractions,
- Rhonchi,
- Grunting,
- Wheezing,
- Crackles/rales/crepitations

Plus one of the following signs/symptoms of medically significant respiratory disease:

- Increased respiratory rate,
- ≥60 breaths/min (<2 months of age [<60 days of age])
- ≥45 breaths/min (2 to 6 months of age [60 days to 180 days of age])
- Use of mechanical ventilation (intubation or non-invasive positive pressure ventilation),
- Difficulty feeding,
- Signs of dehydration: sunken fontanelle, dry/sticky mucous membranes, skin tenting

AND

- Proven RSV by positive RT-PCR.

Before unblinding the data, additional definitions of LRTI (medically attended LRTI and medically attended severe LRTI) were established and applied to the analysis of LRTIs.

The sample size for the study was not driven by any specific hypothesis testing. The plan was to enrol up to 650 pregnant women with randomisation into one of five groups as above. There was no stratification applied at randomisation.

Unblinded site personnel prepared and administered the vaccine and placebo for injection since the appearance of vaccine and placebo was not identical. The study subjects, investigators, study co-ordinators and all other study site staff were blinded to treatment assignment.

Subjects (total 579; 114-117 per group) were enrolled in Argentina, Chile, South Africa and the US. Most randomised subjects completed vaccination and completed delivery of their infants in the study. Women who delivered within 1 month of vaccination were not eligible to complete the 1 month after vaccination visit. The most frequent reason for withdrawal during the study was lost to follow-up. Most infants completed the 1 month and 6 month visit and the most frequent reason for withdrawal during the study was lost to follow-up.

Demographic characteristics of women were similar across vaccine groups with a median age at vaccination of ~27 years and median gestational age at vaccination of ~30 weeks. One fifth or less were enrolled at 24 to <27 weeks of gestation. With only one country in the N. hemisphere, it appears that the vast majority of pregnant women were enrolled in the USA.

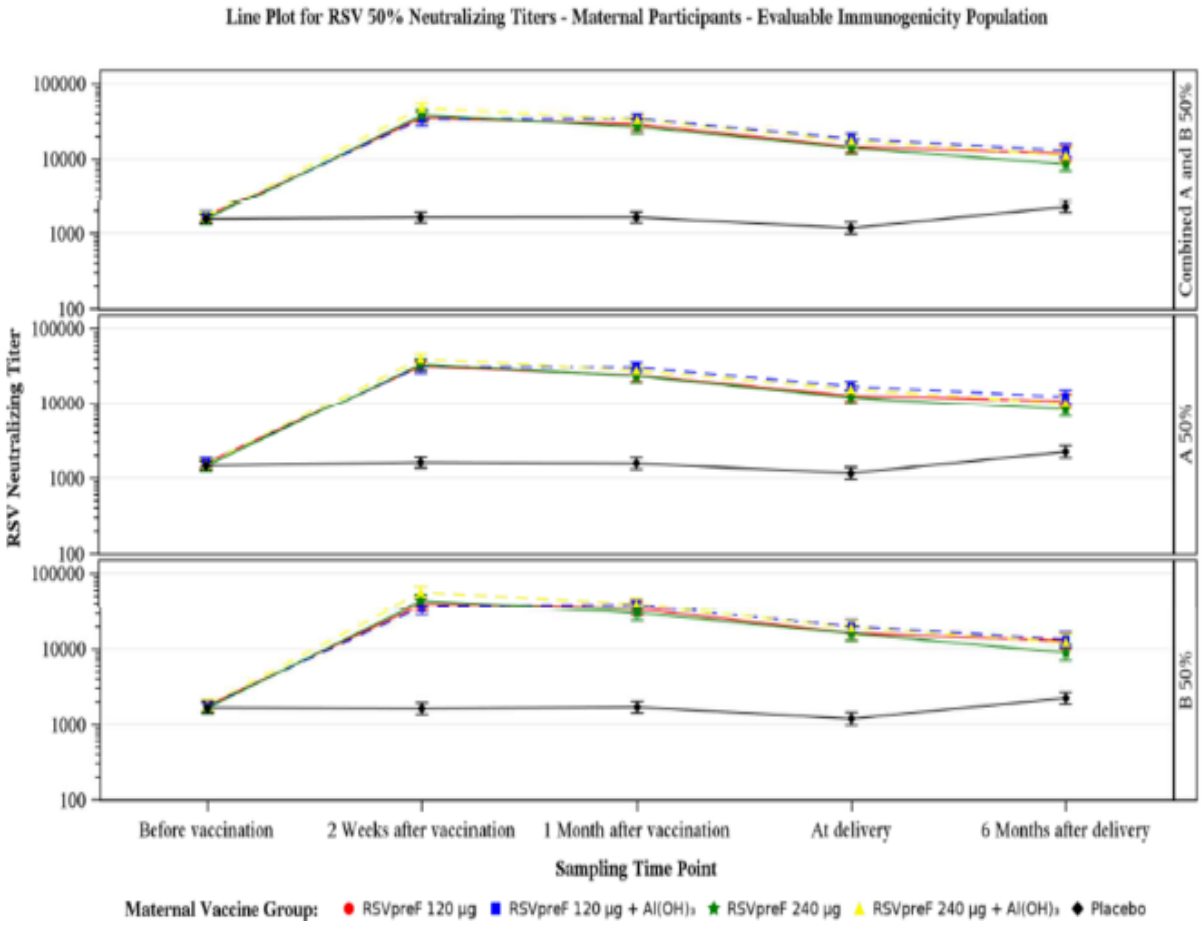
Table 14: *Demographic Characteristics – Maternal Participants – Safety Population*

	Vaccine Group (as Administered)					
	RSVpreF 120 µg (N[a]=115) n[b] (%)	RSVpreF 120 µg + Al(OH)$_3$ (N[a]=117) n[b] (%)	RSVpreF 240 µg (N[a]=116) n[b] (%)	RSVpreF 240 µg + Al(OH)$_3$ (N[a]=114) n[b] (%)	Placebo (N[a]=117) n[b] (%)	Total (N[a]=579) n[b] (%)
Median	28.0	27.0	28.0	27.0	26.0	27.0
Min, max	(18, 36)	(18, 39)	(19, 41)	(18, 42)	(18, 40)	(18, 42)
Gestational age at vaccination (weeks)						
N	115	117	116	114	117	579
Mean (SD)	30.1 (3.6)	30.0 (3.3)	30.2 (3.4)	30.7 (3.4)	30.4 (3.5)	30.3 (3.4)
Median	30.0	29.7	30.2	31.1	30.7	30.4
Min, max	(24.0, 36.1)	(24.0, 36.0)	(24.0, 35.9)	(24.0, 36.0)	(24.0, 36.0)	(24.0, 36.1)
Gestational age at vaccination						
24 to <27 Weeks	25 (21.7)	21 (17.9)	27 (23.3)	19 (16.7)	22 (18.8)	114 (19.7)
27 to <30 Weeks	31 (27.0)	41 (35.0)	29 (25.0)	22 (19.3)	29 (24.8)	152 (26.3)
30 to <33 Weeks	29 (25.2)	29 (24.8)	26 (22.4)	39 (34.2)	33 (28.2)	156 (26.9)
≥33 Weeks	30 (26.1)	26 (22.2)	34 (29.3)	34 (29.8)	33 (28.2)	157 (27.1)
Cohort						
Northern hemisphere	102 (88.7)	104 (88.9)	103 (88.8)	101 (88.6)	104 (88.9)	514 (88.8)
Southern hemisphere	13 (11.3)	13 (11.1)	13 (11.2)	13 (11.4)	13 (11.1)	65 (11.2)

Half of the infants born to randomised women were female and the majority was born at term with a median gestational age of 39 weeks and range from ~31-42 weeks.

In pregnant women, all doses and formulations of RSVpreF induced NA_{50} increments from baseline to RSV A and RSV B and the GMTs were higher than in those who received placebo from 2 weeks post-dose until 6 months after delivery. The figure shows the combined (i.e. RSV A and B) NA_{50} titres as an example.

Figure 4: Line Plot for RSV 50% Neutralizing Titers – Maternal Participants – Evaluable Immunogenicity Population



In general, the combined RSV A and RSV B NA_{50} GMTs at one month after vaccination with RSVpreF formulated with $Al(OH)_3$ were higher compared to RSVpreF alone but GMTs were similar in those who received 120 µg or 240 µg of RSVpreF.

Titres peaked at 2 weeks post-dose, at which time the higher antigen dose appeared to elicit higher GMTs vs. the lower antigen dose and there did seem to be some benefit for adding $Al(OH)_3$ to the higher dose. At delivery and at 6 months post-delivery, the GMTs were still higher than at pre-vaccination.

With the minority enrolled in the S. hemisphere, the GMTs did not show any major differences vs. those enrolled in the N. hemisphere at 2 weeks post-dose but trended higher at one month. There was no consistent trend in terms of peak GMTs according to gestational age at time of maternal vaccination.

Table 15: RSV 50% Neutralizing Titer GMTs and GMRs – Maternal Participants – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)								
		RSVpreF 120 µg		RSVpreF 120 µg + Al(OH)3		RSVpreF 240 µg		RSVpreF 240 µg + Al(OH)3		Placebo
RSV Subgroup	Time Point	GMT[b] (n[c]) (95% CI)[b]	GMR[d] (95% CI)[d]	GMT[b] (n[c]) (95% CI)[b]	GMR[d] (95% CI)[d]	GMT[b] (n[c]) (95% CI)[b]	GMR[d] (95% CI)[d]	GMT[b] (n[c]) (95% CI)[b]	GMR[d] (95% CI)[d]	GMT[b] (n[c]) (95% CI)[b]
Combined A and B 50%	Before vaccination	1662 (111) (1457.0, 1896.8)	1.1 (0.9,1.3)	1664 (112) (1420.8, 1949.0)	1.1 (0.9,1.3)	1536 (112) (1314.4, 1794.3)	1.0 (0.8,1.2)	1651 (110) (1424.7, 1913.0)	1.1 (0.9,1.3)	1541 (114) (1352.1, 1756.6)
	2 Weeks after vaccination	35324 (102) (30291.6, 41193.4)	22.0 (17.7,27.4)	33930 (100) (27651.6, 41635.1)	21.1 (16.3,27.3)	37985 (99) (31879.5, 45260.3)	23.6 (18.7,29.9)	47240 (101) (40532.1, 55058.6)	29.4 (23.6,36.6)	1606 (104) (1370.6, 1882.3)
	1 Month after vaccination[a]	28821 (102) (23777.6, 34934.8)	17.8 (13.9,23.0)	34295 (98) (29708.4, 39589.5)	21.2 (17.1,26.4)	26811 (97) (21660.0, 33185.8)	16.6 (12.7,21.7)	33131 (96) (28710.6, 38232.8)	20.5 (16.5,25.5)	1616 (97) (1369.7, 1906.6)
	At delivery	14445 (107) (12190.4, 17116.3)	12.4 (9.7,15.8)	18557 (109) (15825.1, 21759.7)	15.9 (12.5,20.2)	13994 (103) (11561.6, 16938.1)	12.0 (9.2,15.6)	17393 (103) (14524.3, 20828.4)	14.9 (11.6,19.2)	1167 (111) (975.4, 1395.9)
	6 Months after delivery	11851 (99) (9579.1, 14661.3)	5.4 (4.1,7.0)	12881 (95) (10490.4, 15815.8)	5.8 (4.5,7.6)	8522 (98) (6885.5, 10546.4)	3.9 (2.9,5.0)	11144 (91) (8837.6, 14052.1)	5.0 (3.8,6.7)	2212 (98) (1870.2, 2615.4)
A 50%	Before vaccination	1574 (111) (1369.2, 1808.7)	1.1 (0.9,1.3)	1577 (112) (1343.2, 1850.9)	1.1 (0.9,1.3)	1432 (112) (1221.3, 1678.2)	1.0 (0.8,1.2)	1521 (110) (1318.6, 1754.4)	1.0 (0.9,1.3)	1450 (114) (1263.5, 1663.3)
	2 Weeks after vaccination	31871 (102) (27687.5, 36685.8)	20.0 (16.1,24.7)	31644 (100) (25759.8, 38873.3)	19.8 (15.3,25.7)	33532 (99) (28298.3, 39733.8)	21.0 (16.6,26.5)	39874 (101) (33992.0, 46773.6)	25.0 (19.9,31.3)	1597 (104) (1357.6, 1879.4)
	1 Month after vaccination[a]	24149 (102) (19744.0, 29537.1)	15.6 (11.9,20.4)	31007 (98) (26875.8, 35773.7)	20.0 (15.9,25.1)	23692 (97) (19234.9, 29182.2)	15.3 (11.6,20.1)	28106 (96) (24409.9, 32362.2)	18.1 (14.5,22.8)	1549 (97) (1294.9, 1853.7)
	At delivery	12914 (107) (10781.2, 15469.2)	11.2 (8.7,14.5)	17259 (109) (14982.9, 19881.3)	15.0 (11.9,18.9)	12231 (103) (9925.5, 15071.8)	10.6 (8.1,14.0)	15814 (103) (13512.2, 18507.5)	13.8 (10.8,17.5)	1150 (111) (957.4, 1380.3)
	6 Months after delivery	10986 (99) (8864.6, 13615.0)	5.0 (3.8,6.6)	12456 (95) (10115.4, 15337.4)	5.7 (4.3,7.5)	8132 (98) (6654.6, 9937.2)	3.7 (2.8,4.8)	10146 (91) (8115.0, 12685.9)	4.6 (3.5,6.1)	2204 (98) (1831.9, 2652.3)
B 50%	Before vaccination	1756 (111) (1513.0, 2038.3)	1.1 (0.9,1.3)	1756 (112) (1475.2, 2090.8)	1.1 (0.8,1.3)	1647 (112) (1387.5, 1955.6)	1.0 (0.8,1.3)	1792 (110) (1510.8, 2125.2)	1.1 (0.9,1.4)	1652 (115) (1419.8, 1923.2)
	2 Weeks after vaccination	39152 (102) (31938.0, 47996.6)	24.2 (18.5,31.7)	36382 (100) (28841.0, 45893.9)	22.5 (16.9,30.1)	43030 (99) (35419.6, 52275.2)	26.6 (20.5,34.6)	55967 (101) (46848.7, 66861.1)	34.7 (27.0,44.4)	1615 (104) (1354.4, 1926.1)
	1 Month after vaccination[a]	34397 (102) (28139.5, 42046.9)	20.4 (15.7,26.6)	37931 (98) (31958.7, 45019.8)	22.5 (17.6,28.7)	30339 (97) (23978.7, 38387.3)	18.0 (13.5,24.1)	39055 (96) (32898.8, 46363.2)	23.2 (18.2,29.6)	1686 (97) (1415.4, 2007.3)
	At delivery	16157 (107) (12864.8, 20291.4)	13.6 (10.1,18.4)	19952 (109) (16221.3, 24540.1)	16.8 (12.7,22.3)	16011 (103) (12916.4, 19847.7)	13.5 (10.1,18.0)	19130 (103) (15276.7, 23955.2)	16.2 (12.0,21.7)	1184 (111) (977.1, 1435.7)
	6 Months after delivery	12784 (99) (10205.6, 16013.3)	5.8 (4.3,7.7)	13320 (95) (10614.5, 16715.8)	6.0 (4.5,8.0)	8930 (98) (6967.1, 11445.8)	4.0 (3.0,5.5)	12240 (91) (9416.3, 15909.6)	5.5 (4.0,7.6)	2219 (98) (1852.2, 2658.3)

Maternal-to-infant placental transfer ratios of NA_{50} titres (according to the statistical analysis plan these are ratios for maternal vs. infant titres at time of birth; see footnote c regarding calculation) for of RSV A, RSV B and combined were >1 for all vaccine groups.

There was no consistent pattern for maternal to infant placental transfer ratios when presented according to hemisphere and gestational age at time of maternal immunisation.

The figure below also shows the GMTs in mothers and infants.

Table 16: Maternal-to-Infant Placental Transfer Ratio of RSV 50% Neutralizing Titers – Evaluable Immunogenicity Population

	Maternal Vaccine Group (as Randomized)				
RSV Subgroup	RSVpreF 120 µg GM[a] (n[b]) (95% CI)[c]	RSVpreF 120 µg + Al(OH)$_3$ GM[a] (n[b]) (95% CI)[c]	RSVpreF 240 µg GM[a] (n[b]) (95% CI)[c]	RSVpreF 240 µg + Al(OH)$_3$ GM[a] (n[b]) (95% CI)[c]	Placebo GM[a] (n[b]) (95% CI)[c]
Combined A and B 50%	1.83 (99) (1.44, 2.31)	1.39 (108) (1.15, 1.68)	1.64 (102) (1.37, 1.96)	1.65 (102) (1.43, 1.91)	1.78 (106) (1.46, 2.17)
A 50%	1.77 (99) (1.40, 2.23)	1.35 (108) (1.14, 1.61)	1.69 (102) (1.38, 2.07)	1.55 (102) (1.30, 1.84)	1.85 (106) (1.50, 2.29)
B 50%	1.89 (99) (1.42, 2.51)	1.43 (109) (1.13, 1.79)	1.59 (102) (1.32, 1.92)	1.75 (103) (1.48, 2.08)	1.71 (106) (1.41, 2.07)

Abbreviation: RSV = respiratory syncytial virus.
Note: The lower limit of quantitation (LLOQ) values for neutralization titer were A 50% = 50; B 50% = 70. Assay results below the LLOQ were set to 0.5 * LLOQ.
a. Geometric means (GMs) were calculated using all participants with available data for both maternal and infant.
b. n = Number of participants with valid and determinate assay results for both maternal and infant.
c. For each mother-infant dyad, the transfer ratio was calculated as the ratio of the infant's RSV-neutralizing titer to the mother's. Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the ratios.

Figure 5: Maternal-to-Infant Placental Transfer Ratio of RSV 50% Neutralizing Titer – Evaluable Immunogenicity Population

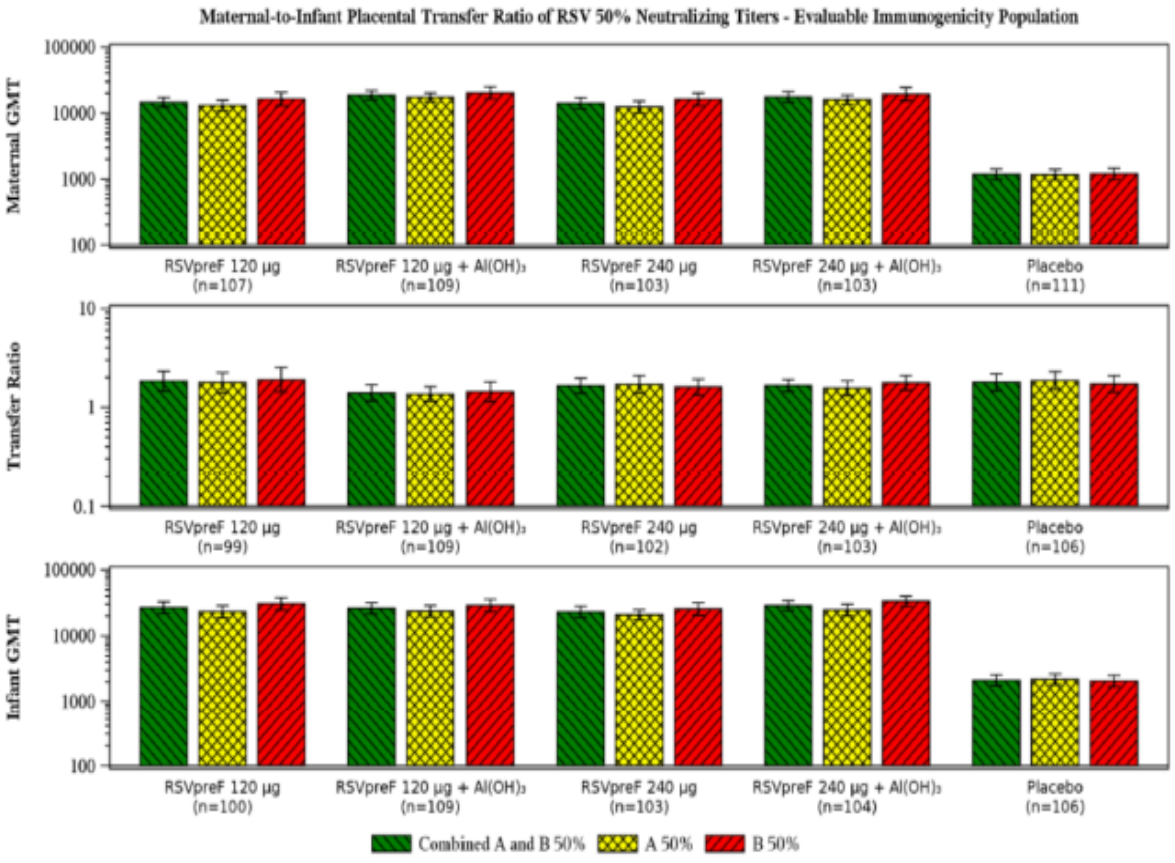


Figure 6: Maternal-to-Infant Placental Transfer Ratio of RSV 50% Neutralizing Titers – by Subgroup – Evaluable Immunogenicity Population

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg	RSVpreF 120 µg + Al(OH)3	RSVpreF 240 µg	RSVpreF 240 µg + Al(OH)3	Placebo
Subgroup Variable	Subgroup	RSV Subgroup	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]
Cohort	Northern Hemisphere	Combined A and B 50%	1.91 (88) (1.66, 2.20)	1.45 (96) (1.30, 1.63)	1.67 (92) (1.45, 1.92)	1.63 (91) (1.44, 1.86)	1.70 (95) (1.45, 2.00)
		A 50%	1.91 (88) (1.66, 2.20)	1.44 (96) (1.29, 1.61)	1.65 (92) (1.43, 1.90)	1.63 (91) (1.44, 1.86)	1.78 (95) (1.50, 2.10)
		B 50%	1.91 (88) (1.63, 2.23)	1.47 (96) (1.28, 1.68)	1.69 (92) (1.44, 1.97)	1.64 (91) (1.42, 1.89)	1.63 (95) (1.40, 1.92)
	Southern Hemisphere	Combined A and B 50%	1.29 (11) (0.16, 10.33)	0.95 (12) (0.18, 4.92)	1.44 (10) (0.31, 6.57)	1.81 (11) (0.68, 4.79)	2.58 (11) (0.56, 11.89)
		A 50%	0.95 (11) (0.13, 7.13)	0.81 (12) (0.20, 3.31)	2.15 (10) (0.31, 14.88)	1.01 (11) (0.26, 4.02)	2.69 (11) (0.53, 13.67)
		B 50%	1.74 (11) (0.13, 23.74)	1.15 (13) (0.17, 7.51)	0.96 (10) (0.23, 3.98)	2.95 (12) (1.02, 8.57)	2.48 (11) (0.58, 10.50)

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg	RSVpreF 120 µg + Al(OH)3	RSVpreF 240 µg	RSVpreF 240 µg + Al(OH)3	Placebo
Subgroup Variable	Subgroup	RSV Subgroup	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]
Maternal GA at Vaccination	24 to <27 Weeks	Combined A and B 50%	1.18 (21) (0.64, 2.19)	1.35 (21) (1.04, 1.74)	1.79 (24) (1.42, 2.26)	1.73 (16) (1.30, 2.31)	1.64 (21) (0.88, 3.04)
		A 50%	1.18 (21) (0.65, 2.16)	1.32 (21) (1.03, 1.69)	1.69 (24) (1.30, 2.18)	1.86 (16) (1.36, 2.55)	1.67 (21) (0.90, 3.10)
		B 50%	1.18 (21) (0.63, 2.24)	1.37 (21) (1.02, 1.85)	1.90 (24) (1.50, 2.40)	1.61 (16) (1.19, 2.17)	1.60 (21) (0.85, 3.01)
	27 to <30 Weeks	Combined A and B 50%	2.21 (26) (1.58, 3.07)	1.58 (38) (1.31, 1.91)	1.79 (26) (1.24, 2.57)	1.79 (19) (1.06, 3.05)	1.52 (26) (0.96, 2.43)
		A 50%	2.54 (26) (1.61, 4.00)	1.58 (38) (1.32, 1.90)	2.09 (26) (1.18, 3.71)	1.28 (19) (0.60, 2.75)	1.55 (26) (0.92, 2.61)
		B 50%	1.92 (26) (1.41, 2.62)	1.58 (38) (1.26, 1.98)	1.52 (26) (1.12, 2.08)	2.42 (20) (1.30, 4.49)	1.50 (26) (0.98, 2.28)
	30 to <33 Weeks	Combined A and B 50%	1.46 (26) (0.81, 2.63)	1.45 (25) (0.93, 2.26)	1.71 (19) (1.17, 2.50)	1.50 (36) (1.18, 1.90)	1.86 (30) (1.37, 2.51)
		A 50%	1.44 (26) (0.81, 2.54)	1.32 (25) (0.99, 1.77)	1.62 (19) (1.16, 2.27)	1.47 (36) (1.17, 1.86)	2.04 (30) (1.47, 2.81)
		B 50%	1.49 (26) (0.81, 2.74)	1.60 (26) (0.83, 3.10)	1.79 (19) (1.13, 2.86)	1.52 (36) (1.17, 1.98)	1.69 (30) (1.26, 2.28)
	≥33 Weeks	Combined A and B 50%	2.69 (26) (1.86, 3.89)	1.10 (24) (0.56, 2.16)	1.41 (33) (0.93, 2.14)	1.72 (31) (1.38, 2.14)	2.08 (29) (1.51, 2.86)
		A 50%	2.10 (26) (1.65, 2.66)	1.09 (24) (0.56, 2.12)	1.47 (33) (0.99, 2.17)	1.68 (31) (1.36, 2.08)	2.13 (29) (1.52, 2.99)
		B 50%	3.46 (26) (1.74, 6.85)	1.10 (24) (0.55, 2.23)	1.36 (33) (0.87, 2.13)	1.75 (31) (1.36, 2.26)	2.02 (29) (1.47, 2.78)

Abbreviations: GA = gestational age; RSV = respiratory syncytial virus.
Note: The lower limit of quantitation (LLOQ) values for neutralization titer were A 50% = 50; B 50% = 70. Assay results below the LLOQ were set to 0.5 * LLOQ.
a. Geometric means (GMs) were calculated using all participants with available data for both maternal and infant.
b. n = Number of participants with valid and determinate assay results for both maternal and infant.
c. For each mother-infant dyad, the transfer ratio was calculated as the ratio of the infant's RSV-neutralizing titer to the mother's. Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the ratios.

Very few infants were delivered within 2 weeks of maternal vaccination. However, for these few data, transfer ratios calculated for subgroups defined by maternal immunisation within or more than 14 days before delivery suggested that early delivery was associated with low transfer. This is in keeping with peak maternal immune responses at about 2 weeks post-dose.

When the calculation was repeated with a 30-day window cut-off, delivery within 30 days gave lower transfer ratios.

Figure 7: Maternal-to-Infant Placental Transfer Ratio of RSV 50% Neutralizing Titers – 30 Day Maternal Vaccination-to-Delivery Window – Evaluable Immunogenicity Population

		Maternal Vaccine Group (as Randomized)				
		RSVpreF 120 µg	RSVpreF 120 µg + Al(OH)$_3$	RSVpreF 240 µg	RSVpreF 240 µg + Al(OH)$_3$	Placebo
RSV Subgroup	Timing of Maternal Vaccination Prior to Delivery	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]
Combined A and B 50%	≤30 Days	2.31 (8) (1.52, 3.51)	0.79 (12) (0.19, 3.23)	1.41 (10) (0.52, 3.84)	1.37 (9) (0.95, 1.99)	2.35 (11) (1.24, 4.48)
	>30 Days	1.79 (91) (1.39, 2.31)	1.49 (96) (1.29, 1.72)	1.67 (92) (1.40, 1.99)	1.68 (93) (1.44, 1.96)	1.72 (95) (1.40, 2.13)
A 50%	≤30 Days	2.41 (8) (1.58, 3.69)	0.81 (12) (0.20, 3.22)	2.22 (10) (0.45, 11.03)	1.48 (9) (0.98, 2.24)	2.33 (11) (1.16, 4.67)
	>30 Days	1.72 (91) (1.34, 2.21)	1.44 (96) (1.28, 1.62)	1.64 (92) (1.38, 1.95)	1.56 (93) (1.29, 1.88)	1.81 (95) (1.44, 2.26)
B 50%	≤30 Days	2.22 (8) (1.30, 3.78)	0.77 (12) (0.18, 3.31)	0.90 (10) (0.44, 1.85)	1.28 (9) (0.88, 1.86)	2.38 (11) (1.27, 4.45)
	>30 Days	1.86 (91) (1.37, 2.53)	1.54 (97) (1.26, 1.88)	1.70 (92) (1.40, 2.06)	1.81 (94) (1.51, 2.17)	1.64 (95) (1.34, 2.02)

Note: The groups for this table(< 30 days and >30 days) were determined by comparing delivery (date - vaccination date + 1) to 30.
a. Geometric means (GMs) were calculated using all participants with available data for both maternal and infant.
b. n = Number of participants with valid and determinate assay results for both maternal and infant.
c. For each mother-infant dyad, the transfer ratio was calculated as the ratio of the infant's RSV-neutralizing titer to the mother's. Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the ratios.

Following birth, infant NA_{50} titres declined slowly over 6 months. At month 6 the titres in infants born to vaccinated mothers remained higher than those born to mothers assigned to placebo.

Figure 8: Line Plot for RSV 50% Neutralizing Titers – Infant Participants – Evaluable Immunogenicity Population

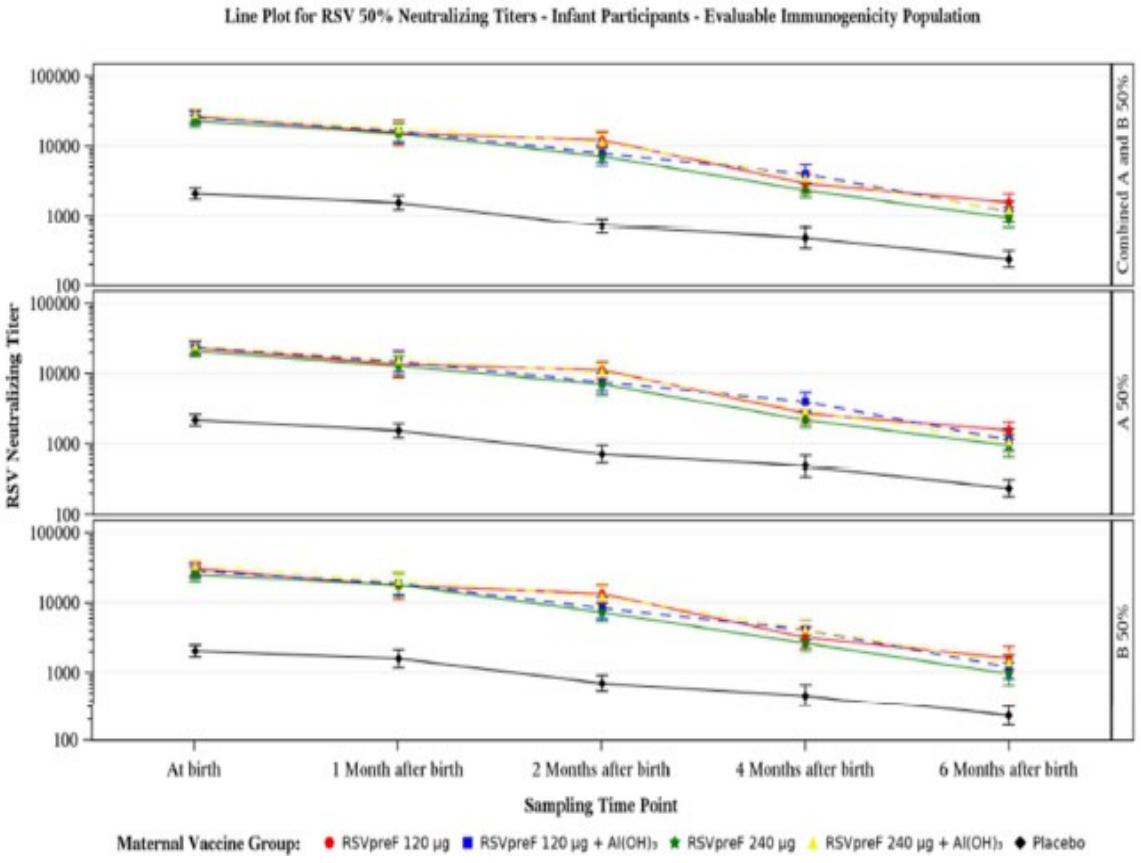


Table 17: RSV 50% Neutralizing Titer GMTs and GMRs – Infant Participants – Evaluable Immunogenicity Population

		Maternal Vaccine Group (as Randomized)								
		RSVpreF 120 µg		RSVpreF 120 µg + Al(OH)3		RSVpreF 240 µg		RSVpreF 240 µg + Al(OH)3		Placebo
RSV Subgroup	Timepoint	GMT[a] (n[b]) (95% CI)[a]	GMR[c] (95% CI)[c]	GMT[a] (n[b]) (95% CI)[a]	GMR[c] (95% CI)[c]	GMT[a] (n[b]) (95% CI)[a]	GMR[c] (95% CI)[c]	GMT[a] (n[b]) (95% CI)[a]	GMR[c] (95% CI)[c]	GMT[a] (n[b]) (95% CI)[a]
Combined A and B 50%	At birth	26298 (100) (21457.5, 32230.1)	12.6 (9.6,16.5)	25654 (108) (21050.5, 31264.7)	12.3 (9.4,16.1)	22706 (103) (18796.3, 27428.7)	10.9 (8.4,14.1)	28368 (103) (24009.7, 33517.1)	13.6 (10.6,17.4)	2089 (106) (1736.3, 2513.0)
	1 Month after birth	15352 (37) (10075.0, 23394.3)	9.9 (6.2,16.0)	16189 (37) (11506.9, 22776.5)	10.4 (6.9,15.7)	15073 (33) (10821.5, 20995.5)	9.7 (6.5,14.5)	17694 (41) (14065.1, 22259.3)	11.4 (8.3,15.8)	1549 (30) (1223.4, 1961.9)
	2 Months after birth	12215 (27) (9383.8, 15901.5)	17.4 (12.3,24.8)	7886 (35) (5857.7, 10616.2)	11.2 (7.7,16.4)	7095 (37) (5198.1, 9685.2)	10.1 (6.9,14.9)	11420 (35) (8658.8, 15060.8)	16.3 (11.3,23.4)	701 (40) (549.8, 893.8)
	4 Months after birth	2910 (35) (2135.8, 3965.1)	6.2 (3.9,9.8)	3996 (30) (2960.9, 5393.6)	8.5 (5.4,13.4)	2339 (34) (1849.3, 2957.4)	5.0 (3.3,7.6)	3484 (31) (2701.4, 4493.7)	7.4 (4.9,11.4)	468 (36) (330.0, 663.6)
	6 Months after birth	1569 (35) (1181.4, 2082.5)	6.8 (4.6,9.9)	1159 (39) (822.1, 1634.4)	5.0 (3.2,7.7)	943 (40) (658.2, 1350.8)	4.1 (2.6,6.3)	1203 (29) (862.7, 1676.7)	5.2 (3.4,7.9)	232 (39) (177.1, 304.9)
A 50%	At birth	22904 (100) (18636.8, 28147.5)	10.7 (8.1,14.1)	23281 (108) (19155.8, 28294.3)	10.8 (8.3,14.2)	20530 (103) (17271.7, 24403.0)	9.5 (7.4,12.3)	24290 (103) (19858.5, 29710.2)	11.3 (8.6,14.9)	2150 (106) (1776.7, 2602.6)
	1 Month after birth	13532 (37) (8775.4, 20865.4)	8.9 (5.5,14.5)	14667 (37) (10428.4, 20627.6)	9.7 (6.5,14.5)	12685 (33) (9161.6, 17563.9)	8.4 (5.7,12.4)	15383 (41) (12253.4, 19311.4)	10.2 (7.4,14.0)	1514 (30) (1200.9, 1908.0)
	2 Months after birth	11127 (27) (8424.3, 14695.8)	15.8 (10.7,23.4)	7455 (35) (5517.1, 10073.8)	10.6 (7.1,15.9)	6943 (37) (4890.5, 9858.0)	9.9 (6.4,15.4)	10552 (35) (8019.3, 13884.7)	15.0 (10.2,22.1)	702 (40) (529.5, 930.8)
	4 Months after birth	2673 (35) (1904.5, 3753.0)	5.6 (3.5,9.0)	3919 (30) (2905.9, 5285.8)	8.2 (5.2,12.9)	2148 (34) (1681.5, 2743.3)	4.5 (2.9,6.8)	2936 (31) (2217.6, 3887.3)	6.1 (3.9,9.6)	478 (36) (336.3, 680.2)
	6 Months after birth	1529 (35) (1164.8, 2008.3)	6.6 (4.5,9.6)	1124 (39) (790.0, 1600.4)	4.8 (3.1,7.5)	930 (40) (643.0, 1344.2)	4.0 (2.5,6.3)	1048 (29) (747.6, 1468.5)	4.5 (2.9,6.9)	233 (39) (176.2, 307.0)
B 50%	At birth	30195 (100) (24308.9, 37506.3)	14.9 (11.1,19.9)	28437 (109) (22968.2, 35207.9)	14.0 (10.5,18.7)	25112 (103) (20172.4, 31262.1)	12.4 (9.2,16.6)	32967 (104) (27494.5, 39529.5)	16.2 (12.5,21.2)	2029 (106) (1669.5, 2466.2)
	1 Month after birth	17418 (37) (11133.3, 27251.5)	11.0 (6.5,18.6)	18708 (38) (12994.4, 26934.9)	11.8 (7.4,18.7)	17911 (33) (12397.2, 25876.7)	11.3 (7.1,17.9)	20353 (41) (15477.7, 26762.8)	12.8 (8.6,19.1)	1586 (30) (1181.0, 2129.1)
	2 Months after birth	13411 (27) (10016.5, 17955.2)	19.2 (13.1,28.0)	8341 (35) (5847.7, 11898.6)	11.9 (7.7,18.3)	7251 (37) (5387.9, 9757.8)	10.4 (7.0,15.2)	12359 (35) (9060.4, 16857.4)	17.7 (11.9,26.2)	700 (40) (542.3, 903.6)
	4 Months after birth	3168 (35) (2261.8, 4436.5)	6.9 (4.2,11.4)	4075 (30) (2952.0, 5624.6)	8.9 (5.5,14.5)	2621 (35) (2029.1, 3385.5)	5.7 (3.7,9.0)	4135 (31) (3093.4, 5526.2)	9.0 (5.7,14.4)	458 (36) (313.6, 668.3)
	6 Months after birth	1609 (35) (1094.5, 2364.3)	7.3 (4.5,11.8)	1195 (39) (805.8, 1772.0)	5.4 (3.3,8.8)	956 (40) (656.8, 1392.7)	4.3 (2.7,7.0)	1381 (29) (966.6, 1972.0)	6.2 (3.9,9.9)	221 (40) (162.9, 300.9)

In pregnant women who received any candidate vaccine formulation the prefusion F binding IgG GMCs were comparable regardless of Al[OH]$_3$ or antigen dose. Maternal vaccination with the RSVpreF vaccine at all doses and formulations yielded high serum IgG concentrations in infants to both RSV A and RSV B that were also higher than those in the infants born to mothers given placebo. RSV A and RSV B prefusion F binding IgG GMCs were similar in infants regardless of the RSVpreF formulation (with or without Al[OH]3) or dose level received by their mothers.

RSV-associated LRTI in infants ranged from 0 to 2 infants in the RSVpreF groups and 3 infants in the placebo group. RSV-associated (RSV A or RSV B) acute respiratory tract illnesses in infants ranged from 2 to 8 infants across RSVpreF groups and 13 infants in the placebo group. LRTI in infants ranged from 3 to 7 infants in the RSVpreF groups and 6 infants in the placebo group.

When all vaccine groups were combined and compared to placebo, the point estimates for VE (pooled across RSVpreF formulations) against RSV-associated medically significant infant LRTI, medically attended LRTI and medically attended severe LRTI were 75%, 75% and 83%, respectively (see

footnotes for additional information on LRTI definitions). In this Phase 2 study, with few cases, the 95% confidence intervals for the estimates of vaccine efficacy all include zero. The results for the N. hemisphere infants alone were similar with respective point estimates for VE of 75%, 85% and 92%.

Table 18: Efficacy of Maternal Vaccination Against RSV-Associated Lower Respiratory Tract Illness in Infants – Infant Participants – Safety Population

	Maternal Vaccine Group (as Administered)		
	RSVpreF (N=456)	Placebo (N=116)	
Endpoint Description	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (95% CI)[b]
Medically significant LRTI[a]	3(0.7)	3(2.6)	75% (-90%, 97%)
Medically attended LRTI[d]	5(1.1)	5(4.3)	75% (-11%, 94%)
Medically attended Severe LRTI[e]	2(0.4)	3(2.6)	83% (-48%, 99%)

Abbreviation: LRTI = lower respiratory tract illness.
Medically attended visit = infant participant has been taken to or seen by a healthcare provider (eg, outpatient or inpatient visit, emergency room, urgent care, or home visit).
a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations.
b. Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group.
c. Defined as presence of one or more of the following physical examination signs: nasal flaring, lower chest wall indrawing or subcostal retractions, rhonchi, grunting, wheezing, crackles/rales/crepitations; plus 1 of the following: tachypnea (respiratory rate ≥60 breaths per minute (<2 months [<60 days] of age) or ≥45 breaths per minute (2 to 6 months [≥60 days to ≤180 days] of age)), use of mechanical ventilation (intubation or noninvasive positive pressure ventilation), difficulty feeding, signs of dehydration: sunken fontanelle, dry/sticky mucous membranes, tenting of skin.
d. Defined as a medically attended visit and presence of 1 of the following signs of lower respiratory tract illness: tachypnea (respiratory rate ≥60 breaths per minute [<2 months [60 days] of age) or ≥50 breaths per minute (≥2 to 12 months of age)); peripheral capillary oxygen saturation (SpO2) measured in room air <95%; chest wall indrawing.
e. Defined as a medically attended visit and presence of 1 of the following signs of severe lower respiratory tract illness: tachypnea (respiratory rate ≥70 breaths per minute (<2 months [60 days] of age) or ≥60 breaths per minute (≥2 to 12 months of age)); SpO2 measured in room air <93%; high-flow nasal cannula or mechanical ventilation (invasive or noninvasive); ICU admission for >4 hours; unresponsive/unconscious.

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Methods

Pregnant women were eligible as follows:

1. Estimated at 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination based on LMP and the earliest US performed in the first or second trimester
2. Uncomplicated, singleton pregnancy with no known increased risk for complications
3. Receiving prenatal standard of care based on country requirements.
4. No significant abnormalities on fetal anomaly ultrasound examination at ≥18 weeks
5. Negative HIV antibody test, syphilis test and HbsAg
6. Planned delivery at a study participating hospital or birthing facility

Exclusions included the following:

1. Pre-pregnancy BMI >40 kg/m^2
2. Bleeding diathesis or condition associated with prolonged bleeding
3. History of severe adverse reaction associated with a vaccine and/or IMP component
4. Current pregnancy resulting from in-vitro fertilisation
5. Prior preterm delivery at ≤34 weeks of gestation, prior stillbirth, prior neonatal death or infant with a known genetic disorder or significant congenital anomaly
6. Major illness and/or immunodeficiency or rheumatologic disorder requiring chronic treatment with immunosuppression within the year prior to study
7. Receipt of monoclonal antibodies within one year prior or systemic corticosteroids for >14 days within 28 days
8. Receipt of blood or plasma products or immunoglobulin within 60 days or expectation of receipt except for Rho(D) immune globulin

Vaccination was delayed in case of i) a febrile illness (body temperature ≥38°C); ii) other acute illness within 48 hours; iii) malaria within the last 7 days; or iv) receipt of inactivated vaccine within 14 days or live vaccine within 28 days. Immunosuppressive therapy was prohibited during the course of the

study. Non-study vaccines were not given concomitantly with study assignment or within 7 days and there was a 14-day window applied to pertussis-containing vaccines such as Tdap.

- **Treatments**

Pregnant women were randomised to receive RSVpreF containing 120 µg (60 µg of each of RSV A and B preF) or a matching placebo consisting of vaccine excipients.

- **Objectives**

The primary objective in pregnant women was safety. The primary efficacy and safety objectives in infants are shown below.

Study Objectives – Infant Participants

Primary Efficacy Objectives – Infant Participants	Estimands	Primary Efficacy Endpoints – Infant Participants
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	RSV-positive MA-LRTI as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants).	Severe MA-LRTIs due to RSV as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

Primary Safety Objective – Infant Participants	Estimand	Primary Safety Endpoints – Infant Participants
To describe the safety of RSVpreF.	• In infant participants born to maternal participants receiving 1 dose of investigational product, the percentage of participants with each safety endpoint in each vaccine group.	• Specific birth outcomes. • AEs from birth to 1 month of age. • SAEs and NDCMCs: o from birth through 6 months of age *(first RSV season for all infant participants).* o from birth through 12 months of age *(for all infant participants).* o from birth through 24 months of age *(for infant participants born to maternal participants enrolled during the first year of the study).*

- **Outcomes/endpoints**

The definitions applied to infant efficacy endpoints are shown in the table.

Table 19: Primary and Secondary Endpoint Events and Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
Medically attended visit	Infant participant has been taken to or seen by a healthcare provider (eg, outpatient or inpatient visit, emergency room, urgent care, or home visit)
MA-RTI visit for infant participant	A medically attended visit AND 1 or more of the following RTI signs and symptoms: • Nasal discharge for 24 hours or more • Difficulty breathing, labored breathing, or rapid breathing for any duration • Cough • Inability to feed for any duration because of respiratory symptoms • Apnea • Any other respiratory symptom of concern
RSV-positive test[a]	• RSV RT-PCR–positive test result by Pfizer central laboratory **OR** • RSV-positive test result by certified laboratory with NAAT for RSV
MA-RTI due to RSV[b]	• An MA-RTI visit **AND** • RSV-positive test result as described in Section 8.1.1.1
MA-LRTI due to any cause	• Infant with an MA-RTI visit **AND** • Fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age], ≥50 bpm for ≥2 months to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <95% **OR** • Chest wall indrawing
MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age] or ≥50 bpm for ≥2 to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <95% **OR** • Chest wall indrawing AND • RSV-positive test result as described in Section 8.1.1.1
Hospitalized RTI due to RSV[b]	An RTI due to RSV that results in hospitalization

Study Endpoints/Assessments	Study Definitions
Severe MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for ≥2 months to <12 months of age, or ≥50 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <93% **OR** • High-flow nasal cannula or mechanical ventilation (ie, invasive or noninvasive) **OR** • ICU admission for >4 hours **OR** • Failure to respond/unconscious AND • RSV-positive test result as described in Section 8.1.1.1
Protocol-defined primary endpoint	• Any MA-LRTI or severe MA-LRTI due to RSV as determined by an EAC

Abbreviations: bpm = breaths per minute; EAC = endpoint adjudication committee; ICU = intensive care unit; MA-LRTI = medically attended lower respiratory tract illness; MA-RTI = medically attended respiratory tract illness; NAAT = nucleic acid amplification technology; RR = respiratory rate; RSV = respiratory syncytial virus; RTI = respiratory tract illness; SpO_2 = oxygen saturation.

a. RSV-positive testing is defined as a positive RSV test (see Section 8.1.1.1) conducted on a sample obtained during the medically attended visit or within 10 days (where Day 1 is the day of the MA-RTI visit) as detailed in Section 8.11.7.

b. The EAC will determine if the endpoint criteria have been met upon review of the site source documentation from the MA-RTI visit and RTI study visits, including all available RSV test results.

There was an active surveillance period in infants from 72 h after birth through 6 months after delivery (Visit 3). Respiratory distress events within 72 hours of birth were not captured as MA-RTI events but as AEs/SAEs (if applicable). Study staff were to contact the infant's parent(s)/legal guardian(s) approximately every week electronically, by phone call or face-to-face. If the infant had an event requiring a healthcare visit, the site staff were to determine if MA-RTI criteria were met:

- Nasal discharge for 24 hours or more
- Difficulty breathing, laboured breathing, or rapid breathing for any duration
- Cough
- Inability to feed for any duration due to respiratory symptoms
- Apnoea
- Any other respiratory symptom of concern

If the criteria were met, the infant was to be seen optimally within 72 hours but within 10 days for an RTI study visit. Samples were analysed for RSV A, RSV B and other respiratory pathogens by PCR-based assays at Pfizer's central laboratory. Any RSV testing performed locally was considered valid if conducted in CLIA-certified central laboratories using a FDA-cleared nucleic acid amplification technology (NAAT)-based test for RSV.

The active surveillance period was followed by long-term surveillance for infants from 6 months after delivery (Visit 3; 180-210 days after birth) until the last study visit (maximum 24 months after birth). During this period, study staff contacted the parent(s)/legal guardian(s) approximately every month.

There was an EAC appointed to adjudicate all efficacy endpoints illness (MA-RTI, MA-LRTI or severe MA-LRTI). The EAC was blinded to vaccine assignment. All MA-RTI events were referred to the EAC for adjudication and the EAC's decision was regarded as the final confirmed endpoint classification of the event. The EAC adjudicated all RSV-positive MA-RTI cases through the active follow-up period up to 180 days after birth as well as all RSV-associated cases of hospitalisation and severe MA-LRTI. The Pfizer study team could also request that additional cases of interest be reported to the committee, including cases in which RSV testing was indeterminate or otherwise unclear.

Starting from time of vaccination (where Day 1 is the day of vaccination) until the end of the study, all women were monitored for MA-RTIs. Full details of the illness were to be recorded.

For purposes of analysis, the following populations were defined:

Population	Description
Enrolled	All maternal participants who sign the ICD.
Randomly assigned to investigational product	All maternal participants who are assigned a randomization number in the IRT system.
Evaluable efficacy – infant **(per-protocol)**	All infant participants who are eligible, are born to the maternal participants who received the investigational product to which they were randomized at least 14 days prior to delivery, did not receive palivizumab or another monoclonal antibody targeting RSV, have no major protocol violations, and did not have transfusions of more than 20 mL/kg of any blood products at <180 days.
Modified intent-to-treat (mITT) efficacy – infant	All infant participants who are born to vaccinated maternal participants.
Evaluable immunogenicity – infant	All infant participants who are eligible, are born to the maternal participants who received the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
Evaluable immunogenicity – maternal	All maternal participants who are eligible, receive the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
mITT immunogenicity – infant	All infant participants who are born to vaccinated maternal participants and have at least 1 valid and determinate assay result for the proposed analysis.
mITT immunogenicity – maternal	All randomized maternal participants who receive investigational product and have at least 1 valid and determinate assay result for the proposed analysis.
Safety – infant	All infant participants who are born to vaccinated maternal participants.
Safety – maternal	All randomized maternal participants who receive investigational product.

There were two primary efficacy endpoints (MA-LRTI and severe MA-LRTI) and the study could be declared a success based on one or both of these endpoints. The null hypothesis to be tested concerns VE for the primary endpoints. The RSV vaccine was compared to placebo testing the hypotheses H_0: VE ≤20% vs. H_a: VE >20%. For all secondary efficacy endpoints, the RSV vaccine was compared to placebo testing the hypotheses H_0: VE ≤0% vs H_a: VE >0%. Hypothesis testing of the secondary endpoints was conditional upon rejection of the null hypothesis for at least 1 of the primary endpoints.

In order for the study to have at least 90% power to reject the null hypothesis for MA-LRTI due to RSV when true VE is 60%, a total of 124 cases of MA-LRTI due to RSV within 90 days of birth were required in the evaluable population. This also accounted for potential use of an alpha of 1.25% 1-sided within the multiplicity adjustment.

There was no explicit case target for the endpoint of severe MA-LRTI due to RSV. Depending on the assumed true VE, power for that individual hypothesis may be lower, but the power for the primary endpoint family was to be at least 90%.

The incidence of the primary endpoints was expected to vary by region, with an assumed rate for MA-LRTI due to RSV through 90 days in low-incidence countries of ~1.75% and ~3.9% in other regions. With these assumptions, and also allowing for 60% VE and 10% of subjects being non-evaluable, it was planned to enrol ~6900 pregnant women.

The SAP (V 6.0) is dated 2 September 2022. It was developed and finalised before database lock for the first planned analysis. The table summarises the methods applied to the primary endpoints.

Table 20: Primary endpoints

Endpoint	Statistical Analysis Methods
Primary	• The analysis of efficacy will use a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups. The incidence of MA-LRTI due to RSV and severe MA-LRTI due to RSV in infant participants will be evaluated in both groups up to 90 days, 120 days, 150 days, and 180 days after birth. • The infant evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the infant mITT efficacy population. • The 2 primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV will be tested in parallel using a multiplicity adjustment procedure. Success of the trial requires rejection of the null hypothesis (ie, a CI lower bound >20%) for either one of the 2 primary endpoints. • The primary endpoint of severe MA-LRTI due to RSV may be demoted to a secondary endpoint if there are insufficient cases for an adequately powered analysis. During the trial, blinded accrual of cases will be monitored and prior to any unblinding, a decision rule for this change will be established based on the total number of cases of severe MA-LRTI due to RSV. • Testing of the 2 primary endpoints across the time intervals will follow a fixed sequence with a gatekeeping strategy. First, the hypothesis
	pertaining to the incidence of the 2 primary endpoints within 90 days after birth will be tested, at the full multiplicity-adjusted alpha level, using a multiplicity adjustment for the 2 endpoints. If that null hypothesis cannot be rejected, testing ends. Otherwise, testing proceeds to the incidence within 120 days after birth. Only primary endpoint(s) that are successful at all earlier time intervals will be considered at subsequent intervals. Testing will proceed to the endpoints evaluated at 150 days and 180 days, conditional on rejection of the null hypotheses for all earlier time intervals. Refer to the SAP for full details of the testing sequence and multiplicity correction strategy.

Endpoint	Statistical Analysis Methods
	• There may be up to 2 interim analyses of the MA-LRTI-due-to-RSV endpoint when there is an adequate number of cases (at least 43 cases within 90 days). Based on the fraction of cases included in an interim analysis, an alpha level will be derived based on a Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. For example, if there are 2 interim analyses at 43 cases and 62 cases, the appropriate 1-sided significance levels are 0.00014 at the first interim analysis, 0.0015 at the second interim analysis, and 0.0245 at the final analysis. Implementation of these 1-sided significance levels ensures the overall type 1 error for the primary endpoint will be no more than 0.025. See Section 9.5 for more details. • At the interim analyses there will also be an assessment for futility, based on conditional power for the MA-LRTI-due-to-RSV endpoint. If the probability of success at the end of the trial is low, given the interim analysis results and the initially assumed VE is applied to the remaining data, consideration will be given to stopping the study for futility. • CIs for VE will be calculated using the appropriate multiplicity-adjusted alpha level α. If the lower 100(1 - α)% confidence limit for VE exceeds 20%, the null hypothesis for that endpoint will be rejected. • At the end of the trial, the RSV vaccine may be deemed efficacious if there are 42 or fewer cases of MA-LRTI due to RSV in the RSV vaccine group out of the 124 total endpoint cases. This corresponds to an estimated VE = 49%, with a 97.6% CI = (21%, 68%). For severe MA-LRTI, assuming a total of 50 cases occur, the vaccine may be deemed efficacious if there are 13 or fewer cases in the RSV vaccine group. This corresponds to an estimated VE = 65%, with a 97.6% CI = (26%, 85%). For both of these examples, it is assumed a 1-sided alpha of 0.01225 applies to the endpoint in question.
	• Kaplan-Meier curves showing accrual of endpoint cases over 180 days will be presented. • There will be a sensitivity analysis of the primary endpoints to examine the impact of missing RSV swab results. Details are provided in the SAP.

The two primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV were tested in parallel using a Bonferroni multiplicity adjustment procedure, whereby alpha = 0.0125 (one-sided) is allocated to each endpoint.

The main analysis was also performed based on the mITT efficacy infant population. A supportive analysis of the primary endpoint was to be performed to address the potential intercurrent event of palivizumab administration via a composite estimand strategy in the mITT efficacy infant set. The endpoint was the occurrence of either MA-LRTI due to RSV (as defined for the main analysis) or receipt of palivizumab. VE was estimated in the same way as for the main analysis.

Where MA-LRTI and severe MA-LRTI visits had no accompanying valid central or local NAAT test results, positive or negative results were imputed. Based on a blinded review of swab results at the end of February 2022, approximately 22% of all swabs from MA-LRTI events with valid central lab results cases proved to be RSV-positive. Thus, a minority of the missing results were expected to be truly RSV-positive and imputation scenarios included:

- Missing swab results were assumed to be positive in the same proportion (by vaccine group) as the non-missing swab results in MA-LRTI events (missing-at-random assumption).
- For the vaccine group, missing swab results were assumed to be positive in higher proportions than the non-missing swab results in MA-LRTI events. In the placebo group missing swab results were assumed to be positive in the same proportion as the non-missing swab results in MA-LRTI events (missing-not-at-random assumption). A range of higher vaccine group positivity rates was assumed.

Multiple imputations were performed to randomly assign missing swab results. SAS PROC MI was used to generate 500 imputed data sets for each scenario. Mean and median VE across imputations, and the proportion of imputations with VE lower bound >20% were to be reported.

If any such events were adjudicated, only those that were confirmed by the EAC as MA-LRTI or severe MA-LRTI were to undergo imputation. The imputed RSV-positive cases will be added to the per-protocol cases and VE estimated in the same way as for the main analysis.

The study was planned such that interim analyses could be performed to assess efficacy and safety after at least 43 cases of MA-LRTI due to RSV within 90 days of birth had accrued. Only cases that had been fully adjudicated prior to taking a data snapshot were to be included in an interim analysis.

The analysis of efficacy was to use an O'Brien-Fleming alpha spending rule based on the fraction of cases of MA-LRTI due to RSV within 90 days available. The exact number of cases at each interim analysis was not fixed but no fewer than 43 cases were to be included in the first interim analysis and no fewer than 62 in the second interim analysis.

To control the overall type 1 error for the two primary endpoints at 2.5% 1-sided, a first interim analysis at 43 cases would use a 1-sided significance level of 0.014%. If a second interim analysis was performed at 62 cases, it would use a 1-sided significance level of 0.15%. The final analysis at the target number of cases would use a 1-sided significance level of 2.45%. In each case, this alpha would be split between the two endpoints using the Bonferroni correction.

Futility was to be assessed using conditional power. For example, if there were 62 cases available for the interim analysis, the table shows the case splits for which stopping the study was to be considered. The actual number of cases available could be slightly higher or lower than 62, and the decision rules amended accordingly.

Table 21: Example of Estimated Vaccine Efficacy and Confidence Intervals at an Interim Analysis

Total Cases	RSV Vaccine Group Cases	Placebo Group Cases	VE (CI)[a]	Notes
43 (First interim)	24	19	-26% (-145%, 34%)	Conditional power <20%,[b] possible futility declaration
43 (First interim)	6	37	84% (27%, 98%)	Maximum number of vaccine group cases permitted to declare VE >20%
62 (Second interim)	29	33	12% (-49%, 49%)	Conditional power <20%,[b] possible futility declaration
62 (Second interim)	14	48	71% (25%, 91%)	Maximum number of vaccine group cases permitted to declare VE >20%

Abbreviation: VE = vaccine efficacy.

a. Confidence level for efficacy declaration based on half the available alpha at each interim, assuming both MA-LRTI and severe MA-LRTI endpoints were inspected; 95% confidence level for futility.

b. Other conditional power levels may be considered as a trigger for a futility decision.

Results

Results are currently reported in a CSR of 6 December 2022. As of 2 September 2022, 7392 pregnant women had been randomised into the study, of which 3682 randomised to RSVpreF and 3675 randomised to placebo were included in the safety population. The safety population of infants comprised 3568 and 3558 born to mothers in respective randomised groups.

Table 22: Disposition of All Participants – Infant Participants

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg	Placebo	Total
	n[a] (%)	n[a] (%)	n[a] (%)
Enrolled[b]	3570	3558	7128
Planned 12 months follow-up	1599 (44.8)	1591 (44.7)	3190 (44.8)
Planned 24 months follow-up[c]	1971 (55.2)	1967 (55.3)	3938 (55.2)
Completed 1 month follow-up	3423 (95.9)	3400 (95.6)	6823 (95.7)
Withdrawn before 1 month after birth	52 (1.5)	60 (1.7)	112 (1.6)
Reason for withdrawal			
Death	2 (<0.1)	6 (0.2)	8 (0.1)
Lost to follow-up	22 (0.6)	26 (0.7)	48 (0.7)
Other	3 (<0.1)	6 (0.2)	9 (0.1)
Withdrawal by parent/guardian	25 (0.7)	22 (0.6)	47 (0.7)
Completed 6 months follow-up	2830 (79.3)	2824 (79.4)	5654 (79.3)
Withdrawn after 1 month but before 6 months after birth	92 (2.6)	83 (2.3)	175 (2.5)
Reason for withdrawal			
Death	3 (<0.1)	5 (0.1)	8 (0.1)
Lost to follow-up	54 (1.5)	36 (1.0)	90 (1.3)
Other	8 (0.2)	10 (0.3)	18 (0.3)
Withdrawal by parent/guardian	27 (0.8)	32 (0.9)	59 (0.8)
Completed 12 months follow-up	1631 (45.7)	1616 (45.4)	3247 (45.6)
Withdrawn after 6 months but before 12 months after birth	41 (1.1)	52 (1.5)	93 (1.3)
Reason for withdrawal			
Death	0	1 (<0.1)	1 (<0.1)
Lost to follow-up	31 (0.9)	35 (1.0)	66 (0.9)
Other	1 (<0.1)	7 (0.2)	8 (0.1)
Withdrawal by parent/guardian	9 (0.3)	9 (0.3)	18 (0.3)
Completed 24 months follow-up	3 (<0.1)	3 (<0.1)	6 (<0.1)
Withdrawn after 12 months but before 24 months after birth	36 (1.0)	34 (1.0)	70 (1.0)
Reason for withdrawal			
Lost to follow-up	30 (0.8)	25 (0.7)	55 (0.8)
Other	3 (<0.1)	3 (<0.1)	6 (<0.1)
Withdrawal by parent/guardian	3 (<0.1)	6 (0.2)	9 (0.1)
Completed the study as planned[d]	6 (0.2)	12 (0.3)	18 (0.3)
Ongoing[e]	3343 (93.6)	3317 (93.2)	6660 (93.4)

a. n = Number of participants in the specified category.
b. The values in this row are used as the denominators for the percentage calculations for vaccine groups for all rows except otherwise specified in footnote c.
c. The values in this row are used as the denominators for the percentage calculations for vaccine groups for rows related to 24 months completion/withdrawal.
d. Includes participants who completed the study as assigned to either 12 or 24 months after birth.
e. Ongoing refers to participants who were enrolled and have not yet completed or withdrawn.

The largest subgroup of pregnant women (44.7%) was in the gestational age range ≥32 weeks to ≤36 weeks at the time of vaccination. The median maternal age at the time of study vaccination was 29.0 years with a range from 14-47 years. Most had a history of 0 (33%) or 1 (~31%) prior pregnancies.

Table 23: Demographic Characteristics – Maternal Participants – Safety Population

	Vaccine Group (as Administered)		
	RSVpreF 120 µg (N[a]=3682) n[b] (%)	Placebo (N[a]=3675) n[b] (%)	Total (N[a]=7357) n[b] (%)
Gestational Age (GA) at vaccination (weeks)			
N	3682	3675	7357
Mean (SD)	30.83 (3.538)	30.82 (3.550)	30.83 (3.544)
Median (Range)	31.30 (24.0- 36.6)	31.30 (24.0- 36.9)	31.30 (24.0- 36.9)
Gestational Age (GA) at vaccination			
≥24 weeks to <28 weeks	941 (25.6)	909 (24.7)	1850 (25.1)
≥28 weeks to <32 weeks	1085 (29.5)	1128 (30.7)	2213 (30.1)
≥32 weeks to ≤36 weeks	1653 (44.9)	1632 (44.4)	3285 (44.7)
>36 weeks	3 (<0.1)	6 (0.2)	9 (0.1)

Half of the infants were female. Most infants were born at term (≥93.7% born at ≥37 weeks to <42 weeks). Birth outcomes for infants were similar for the RSVpreF and placebo groups. Most of the pre-term infants were near-term at birth (≥4.4% were ≥34 to <37 weeks GA).

Table 24: Analysis Populations – Infant Participants

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a]=3570) n[b] (%)	Placebo (N[a]=3558) n[b] (%)	Total (N[a]=7128) n[b] (%)
Safety population	3568 (99.9)	3558 (100.0)	7126 (100.0)
Participants excluded from safety population			
Mother not vaccinated	0	0	0
Participant not eligible - unblinded during study	2 (<0.1)	0	2 (<0.1)
mITT efficacy population	3568 (99.9)	3558 (100.0)	7126 (100.0)
Participants excluded from mITT efficacy population			
Mother not vaccinated	0	0	0
Participant not eligible - unblinded during study	2 (<0.1)	0	2 (<0.1)
Evaluable efficacy population	3495 (97.9)	3480 (97.8)	6975 (97.9)
Participants excluded from evaluable efficacy population			
Participant not eligible - unblinded during study	2 (<0.1)	0	2 (<0.1)
Infant not eligible for study	3 (<0.1)	4 (0.1)	7 (<0.1)
Mother not vaccinated as randomized	0	0	0
Mother had major protocol violations before delivery	27 (0.8)	19 (0.5)	46 (0.6)
Mother not vaccinated at least 14 days prior to delivery	44 (1.2)	56 (1.6)	100 (1.4)
Infant had major protocol violations	0	1 (<0.1)	1 (<0.1)

a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

The first interim efficacy analysis was conducted in April 2022, at which time 56 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth had accrued. The E-DMC reviewed the results and recommended continuation of the study. The second interim efficacy analysis was conducted on 28 October 2022. The analysis included 80 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth, of which 39 were severe MA-LRTI. The point estimates for VE against MA-LRTI due to RSV based on all cases accrued through the data cut-off date were in the range 51-57%. The lower

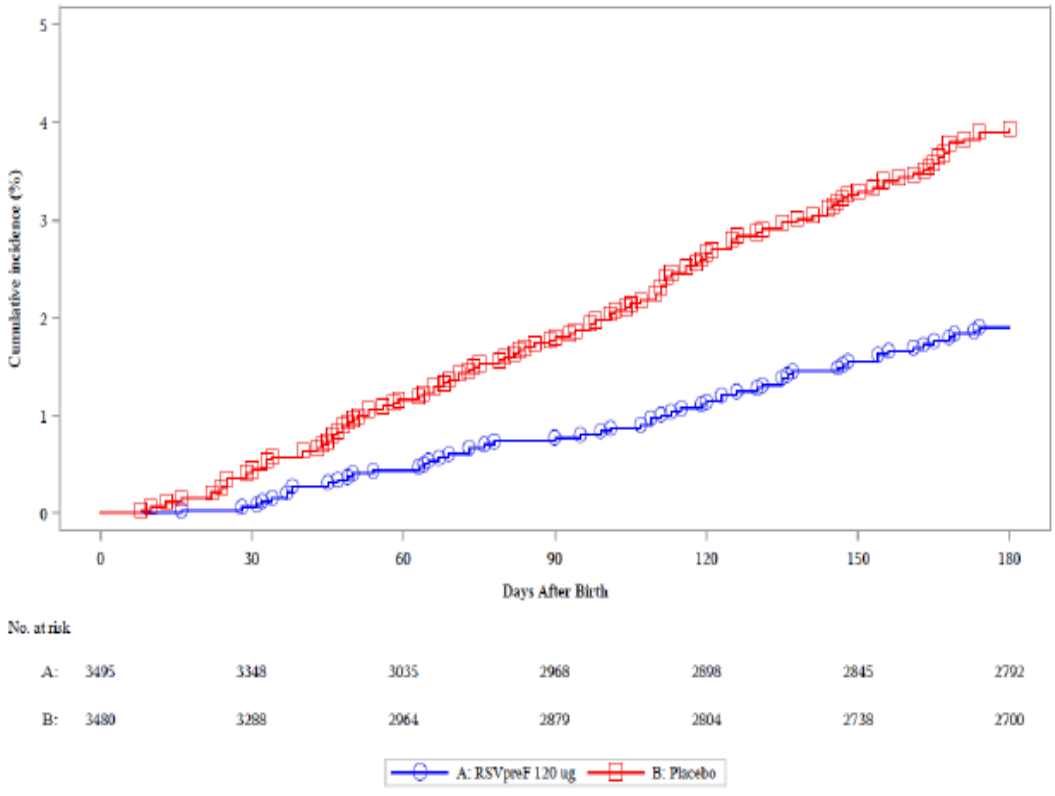
bounds of the CI were above the 20% pre-defined criterion for success except for cases in the first 90 days after birth (lower bound 14.7%). The E-DMC recommended stopping the study.

Table 25: RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)			
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)		
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (CI)	Nominal P-value[d]
90 Days after birth[c]	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)	0.0058
120 Days after birth[c]	35 (1.0)	81 (2.3)	56.8 (31.2, 73.5)	0.0012
150 Days after birth[c]	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9)	0.0017
180 Days after birth[c]	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)	0.0011

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations.
b. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
c. Confidence intervals are 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).
d. Unadjusted 1-sided nominal p-value for the null hypothesis that vaccine efficacy ≤20%. Statistical significance cannot be claimed for these analyses due to the planned testing strategy and the failure to meet the statistical success criterion at 90 days for this endpoint.

Figure 9: Kaplan-Meier Curves for RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 180 Days After Birth, Infant Participants – Evaluable Efficacy Population



Results for the mITT population were similar with 3 additional cases in the vaccine group before day 90 and one in the placebo group before day 150.

Palivizumab was given to 2 infants in the vaccine group and 10 in the placebo group. There were no cases of MA-LRTI due to RSV in the 2 infants given palivizumab in the vaccine group vs. 1 in the 10 in the placebo group up to day 180. No infants who received palivizumab were hospitalised.

Sensitivity analyses were performed to address missing or invalid swab results. When all positive RSV tests were considered, including non-NAAT tests, the results were similar to the primary analysis.

Table 26: MA-LRTIs Occurring Within 90, 120, 150 and 180 Days After Birth, with RSV-Positive Results - Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (CI)
90 Days after birth[c]	26 (0.7)	57 (1.6)	54.4 (10.9, 77.9)
120 Days after birth[c]	38 (1.1)	82 (2.4)	53.7 (27.2, 71.1)
150 Days after birth[c]	50 (1.4)	100 (2.9)	50.0 (25.5, 66.9)
180 Days after birth[c]	61 (1.7)	118 (3.4)	48.3 (25.7, 64.5)

Analyses including imputation of missing swab results are shown below. Under the missing-at-random assumption, 17.2% of the 90 day result imputations had a 99.5% CI lower bound > 20%.

Table 27: Sensitivity Analysis for Missing Lab Results RSV-positive MA-LRTI as Confirmed by the EAC Occurring Within 90, 120, 150, 180 Days After Birth – Infant Participants – Evaluable Efficacy Population

Efficacy Endpoint Time Intervals	Imputed Value Positive Rate Across all Imputations [RSVpreF:Placebo][a] (%)	Infection Rates Based on Existing and Imputed Values (/1000 participants) [RSVpreF:Placebo][b]	Number of VE (100-α[c])% CI LB>20%	Percentage of VE (100-α[c])% CI LB>20%	Average VE (%)
Within 90 days after birth	19.6:30.5[d]	134.4:296.3	86	17.2	57.3
	32.1:30.5	141.5:296.3	18	3.6	55.1
	53.5:30.5	151.2:296.3	1	0.2	52.0
	89.9:30.5	166.8:296.3	0	0	47.1
	99.7:30.5	171.0:296.3	0	0	45.7
Within 120 days after birth	17.5:30.5[d]	140.3:307.7	500	100	56.9
	32.6:30.5	148.4:307.7	498	99.6	54.4
	55.3:30.5	158.9:307.7	450	90	51.1
	90.1:30.5	174.9:307.7	117	23.4	46.2
	99.8:30.5	179.3:307.7	10	2	44.9
Within 150 days after birth	15.7:30.1[d]	149.1:301.8	500	100	53.0
	32.2:30.1	158.0:301.8	492	98.4	50.2
	56.6:30.1	170.6:301.8	335	67	46.2
	90.0:30.1	187.7:301.8	4	0.8	40.8
	99.8:30.1	192.7:301.8	0	0	39.2
Within 180 days after birth	16.9:30.4[d]	153.7:305.4	500	100	50.9
	33.8:30.4	163.1:305.4	492	98.4	47.9
	57.6:30.4	175.8:305.4	304	60.8	43.8
	91.0:30.4	193.6:305.4	1	0.2	38.2
	99.8:30.4	198.4:305.4	0	0	36.6

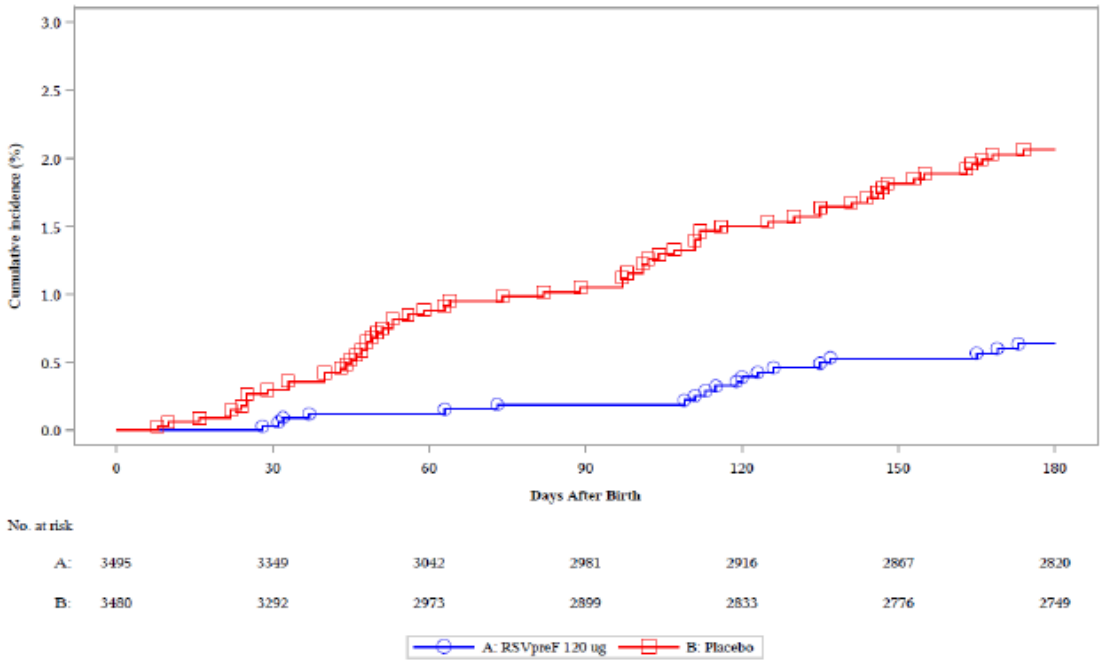
The point estimates for VE against severe MA-LRTI due to RSV based on all cases accrued through the data cut-off date were in the range 69-82%. The lower bounds of the CI were well above the 20% pre-defined criterion for success and all were above 40%. The primary analysis of efficacy for cases up to day 90 met the pre-defined success criterion. In the mITT population, there were 2 additional cases of severe RSV MA-LRTI in the vaccine group within 90 days of birth and one in the placebo group within 150 days of birth. All lower bounds of the CI were well above 20%. There were no cases of severe RSV in any infants who received palivizumab.

Table 28: Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (CI)
90 Days after birth[c]	6 (0.2)	33 (0.9)	81.8 (40.6, 96.3)
120 Days after birth[c]	12 (0.3)	46 (1.3)	73.9 (45.6, 88.8)
150 Days after birth[c]	16 (0.5)	55 (1.6)	70.9 (44.5, 85.9)
180 Days after birth[c]	19 (0.5)	62 (1.8)	69.4 (44.3, 84.1)

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations.
b. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
c. Confidence intervals are 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).

Figure 10: Kaplan-Meier Curves for Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 180 Days After Birth, Infant Participants – Evaluable Efficacy Population



Sensitivity analyses were performed to address missing or invalid swab results. When all positive RSV tests were considered, including non-NAAT tests, results were similar to the primary analysis.

Table 29: Severe MA-LRTIs Occurring Within 90, 120, 150, and 180 Days After Birth with RSV-Positive Results – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (CI)
90 Days after birth[c]	7 (0.2)	33 (0.9)	78.8 (34.7, 95.0)
120 Days after birth[c]	14 (0.4)	46 (1.3)	69.6 (38.9, 86.1)
150 Days after birth[c]	18 (0.5)	55 (1.6)	67.3 (39.1, 83.5)
180 Days after birth[c]	21 (0.6)	62 (1.8)	66.1 (39.7, 81.9)

Analyses that included imputation of missing swab results are summarised below. When close to 100% of missing results in the vaccine group were assumed to be positive, 100% of the imputed datasets gave CI lower bounds greater than 20%.

Table 30: Sensitivity Analysis for Missing Lab Results RSV-positive Severe MA-LRTI as Confirmed by the EAC Occurring Within 90, 120, 150, 180 Days After Birth – Infant Participants – Evaluable Efficacy Population

Efficacy Endpoint Time Intervals	Imputed Value Positive Rate Across all Imputations [RSVpreF:Placebo][a] (%)	Infection Rates Based on Existing and Imputed Values (/1000 participants) [RSVpreF:Placebo][b]	Number of VE (100-α[c])% CI LB>20%	Percentage of VE (100-α[c])% CI LB>20%	Average VE (%)
Within 90 days after birth	38.0:56.8[d]	107.7:499.0	500	100	81.5
	44.3:56.8	114.7:499.0	500	100	80.3
	55.4:56.8	124.9:499.0	500	100	78.6
	86.0:56.8	145.1:499.0	500	100	75.1
	99.7:56.8	152.4:499.0	500	100	73.9
Within 120 days after birth	33.0:56.2[d]	154.3:484.2	500	100	73.3
	43.0:56.2	163.0:484.2	500	100	71.8
	60.3:56.2	174.4:484.2	500	100	69.9
	90.8:56.2	190.6:484.2	500	100	67.1
	99.7:56.2	195.0:484.2	500	100	66.3
Within 150 days after birth	26.1:51.7[d]	169.0:478.5	500	100	70.0
	37.8:51.7	179.3:478.5	500	100	68.2
	60.6:51.7	194.1:478.5	500	100	65.6
	91.7:51.7	212.9:478.5	500	100	62.2
	99.8:51.7	217.7:478.5	500	100	61.4
Within 180 days after birth	23.5:50.3[d]	163.9:449.4	500	100	68.4
	38.2:50.3	174.7:449.4	500	100	66.3
	60.1:50.3	188.6:449.4	500	100	63.6
	91.3:50.3	206.4:449.4	500	100	60.2
	99.8:50.3	211.3:449.4	500	100	59.3

As of the cut-off date, there were 10 hospitalisations due to EAC-confirmed RSV in infants within 90 days after birth in the RSVpreF group and 31 in the placebo group in the evaluable efficacy population, corresponding to a VE of 67.7% (99.17% CI: 15.9, 89.5). There were 19 vs. 44 such cases within 180 days after birth, corresponding to a VE of 56.8% (99.17% CI: 10.1, 80.7) for RSVpreF. Additionally, there were 70 cases of investigator-reported RSV-positive MA-LRTI within 210 days after birth in the RSVpreF group and 127 in the placebo group in the evaluable efficacy population, corresponding to a

VE of 44.9% (99.17% CI: 17.9, 63.5) for RSVpreF. The observed VE within 240, 270, and 360 days after birth was consistent with the VE within 210 days after birth, with CI lower bounds >0%.

The table below shows the subgroup analyses of EAC-confirmed RSV-positive MA-LRTI cases in infants within 90 days after birth.

Table 31: RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth by Subgroups – Infant Participants – Evaluable Efficacy Population

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N[a] =3495)		Placebo (N[a]=3480)		
Time Interval	Subgroup Variable	Subgroup	n[b]	Number of Cases (%)	n[b]	Number of Cases (%)	Vaccine Efficacy[c] (%) (95% CI)
90 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	6 (0.7)	866	13 (1.5)	55.1 (-26.6, 86.0)
		≥28 weeks to <32 weeks	1030	4 (0.4)	1070	22 (2.1)	81.1 (44.4, 95.3)
		≥32 weeks to ≤36 weeks	1572	14 (0.9)	1539	21 (1.4)	34.7 (-34.6, 69.3)
		>36 weeks	3	0	5	0	NC
	Country	Argentina	412	7 (1.7)	406	20 (4.9)	65.5 (15.1, 87.7)
		Australia	11	0	13	0	NC
		Brazil	35	0	35	0	NC
		Canada	26	1 (3.8)	28	1 (3.6)	-7.7 (-8353.5, 98.6)
		Chile	83	2 (2.4)	83	2 (2.4)	0.0 (-1279.6, 92.8)
		Denmark	30	0	29	1 (3.4)	100.0 (-3670.0, 100.0)
		Spain	114	1 (0.9)	122	1 (0.8)	-7.0 (-8300.5, 98.6)
		Finland	75	0	71	1 (1.4)	100.0 (-3592.0, 100.0)
		Gambia	78	3 (3.8)	79	2 (2.5)	-51.9 (-1718.9, 82.6)
		Japan	214	0	213	7 (3.3)	100.0 (30.9, 100.0)
		Korea	7	0	3	0	NC
		Mexico	36	0	35	0	NC
		Netherlands	96	0	94	0	NC
		New Zealand	46	0	46	0	NC
		Philippines	32	0	34	0	NC
		Taiwan	120	0	124	0	NC
		United States	1619	2 (0.1)	1597	15 (0.9)	86.8 (43.4, 98.5)
		South Africa	461	8 (1.7)	468	6 (1.3)	-35.4 (-373.3, 58.8)
	Country subcategories	High income	2441	6 (0.2)	2423	28 (1.2)	78.7 (47.6, 92.8)
		Upper middle income	944	15 (1.6)	944	26 (2.8)	42.3 (-13.1, 71.6)
		Lower middle income	32	0	34	0	NC
		Low income	78	3 (3.8)	79	2 (2.5)	-51.9 (-1718.9, 82.6)

Table 31: RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth by Subgroups – Infant Participants – Evaluable Efficacy Population (cont'd)

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N[a] =3495)		Placebo (N[a]=3480)		
Time Interval	Subgroup Variable	Subgroup	n[b]	Number of Cases (%)	n[b]	Number of Cases (%)	Vaccine Efficacy[c] (%) (95% CI)
	Exclusive breastfeeding	Yes	936	10 (1.1)	931	13 (1.4)	23.5 (-88.9, 70.0)
		No	2435	14 (0.6)	2403	42 (1.7)	67.1 (38.6, 83.4)
	Duration of breastfeeding	<1 month	3362	24 (0.7)	3330	55 (1.7)	56.8 (29.0, 74.4)
		≥1 month to <6 months	2908	22 (0.8)	2864	47 (1.6)	53.9 (22.0, 73.5)
		≥6 months to <12 months	1829	14 (0.8)	1810	36 (2.0)	61.5 (26.9, 80.8)
		≥12 months to <18 months	724	10 (1.4)	714	21 (2.9)	53.0 (-4.2, 80.3)
		≥18 months to <24 months	136	0	127	2 (1.6)	100.0 (-397.2, 100.0)
		≥24 months	1	0	0	0	NC
	Maternal smoking	Smoker	104	0	78	0	NC
		Nonsmoker	3391	24 (0.7)	3401	56 (1.6)	57.0 (29.5, 74.5)
	Number of household members	0	1	0	1	0	NC
		1	54	0	73	0	NC
		2	829	3 (0.4)	878	9 (1.0)	64.7 (-41.5, 93.9)
		3	1076	9 (0.8)	1031	18 (1.7)	52.1 (-12.3, 81.0)
		4	675	7 (1.0)	650	9 (1.4)	25.1 (-126.0, 76.3)
		≥5	844	5 (0.6)	827	19 (2.3)	74.2 (28.6, 92.5)
	Maternal age at vaccination	<18 years	8	0	7	0	NC
		≥18 years	3487	24 (0.7)	3473	56 (1.6)	57.3 (30.0, 74.7)

As of the cut-off date, there were 392 investigator-reported all-cause MA-LRTI episodes within 180 days after birth in the RSVpreF group and 402 in the placebo group in the evaluable efficacy population, corresponding to a VE of 2.5% (99.17% CI: -17.9, 19.4). Within 360 days after birth, with 504 and 531 cases, VE was 5.1% (99.17% CI: -12.1, 19.6).

The table shows EAC-confirmed severe RSV MA-LRTI that occurred within 90 days of birth. The findings for cases up to 180 days gave a similar pattern. Most participating countries had no cases of severe RSV MA-LRTI. Total numbers are driven by Argentina and the US. However, for totals accrued from Day 120 to day 180 it seemed that there was a benefit for the vaccine against severe RSV MA-LRTI even in S. Africa (by day 180 there were 2 cases in the vaccine group and 10 in the placebo group [VE 79.7%, lower bound CI 42.7]).

Table 32: Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth by Subgroups – Infant Participants – Evaluable Efficacy Population

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N[a] =3495)		Placebo (N[a]=3480)		
Time Interval	Subgroup Variable	Subgroup	n[b]	Number of Cases (%)	n[b]	Number of Cases (%)	Vaccine Efficacy[c] (%) (95% CI)
90 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	4 (0.4)	866	11 (1.3)	64.6 (-19.4, 91.8)
		≥28 weeks to <32 weeks	1030	1 (<0.1)	1070	11 (1.0)	90.6 (35.0, 99.8)
		≥32 weeks to ≤36 weeks	1572	1 (<0.1)	1539	11 (0.7)	91.1 (38.8, 99.8)
		>36 weeks	3	0	5	0	NC
	Country	Argentina	412	2 (0.5)	406	13 (3.2)	84.8 (33.0, 98.3)
		Australia	11	0	13	0	NC
		Brazil	35	0	35	0	NC
		Canada	26	0	28	1 (3.6)	100.0 (-4100.0, 100.0)
		Chile	83	0	83	1 (1.2)	100.0 (-3800.0, 100.0)
		Denmark	30	0	29	0	NC
		Spain	114	1 (0.9)	122	1 (0.8)	-7.0 (-8300.5, 98.6)
		Finland	75	0	71	1 (1.4)	100.0 (-3592.0, 100.0)
		Gambia	78	0	79	0	NC
		Japan	214	0	213	3 (1.4)	100.0 (-140.9, 100.0)
		Korea	7	0	3	0	NC
		Mexico	36	0	35	0	NC
		Netherlands	96	0	94	0	NC
		New Zealand	46	0	46	0	NC
		Philippines	32	0	34	0	NC
		Taiwan	120	0	124	0	NC
		United States	1619	1 (<0.1)	1597	10 (0.6)	90.1 (30.7, 99.8)
		South Africa	461	2 (0.4)	468	3 (0.6)	32.3 (-490.8, 94.3)

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N[a] =3495)		Placebo (N[a]=3480)		
Time Interval	Subgroup Variable	Subgroup	n[b]	Number of Cases (%)	n[b]	Number of Cases (%)	Vaccine Efficacy[c] (%) (95% CI)
	Country subcategories	High income	2441	2 (<0.1)	2423	17 (0.7)	88.3 (50.8, 98.7)
		Upper middle income	944	4 (0.4)	944	16 (1.7)	75.0 (22.5, 93.9)
		Lower middle income	32	0	34	0	NC

	Low income	78	0	79	0	NC
Exclusive breastfeeding	Yes	936	3 (0.3)	931	7 (0.8)	57.4 (-86.7, 92.9)
	No	2435	3 (0.1)	2403	25 (1.0)	88.2 (61.2, 97.7)
Duration of breastfeeding	<1 month	3362	6 (0.2)	3330	32 (1.0)	81.4 (55.0, 93.7)
	≥1 month to <6 months	2908	6 (0.2)	2864	26 (0.9)	77.3 (43.5, 92.4)
	≥6 months to <12 months	1829	4 (0.2)	1810	19 (1.0)	79.2 (37.3, 94.8)
	≥12 months to <18 months	724	3 (0.4)	714	11 (1.5)	73.1 (-1.8, 95.2)
	≥18 months to <24 months	136	0	127	1 (0.8)	100.0 (-3541.9, 100.0)
	>24 months	1	0	0	0	NC
Maternal smoking	Smoker	104	0	78	0	NC
	Nonsmoker	3391	6 (0.2)	3401	33 (1.0)	81.8 (55.9, 93.8)
Number of household members	0	1	0	1	0	NC
	1	54	0	73	0	NC
	2	829	2 (0.2)	878	5 (0.6)	57.6 (-158.8, 96.0)
	3	1076	3 (0.3)	1031	10 (1.0)	71.3 (-11.6, 94.9)
	4	675	1 (0.1)	650	3 (0.5)	67.9 (-299.8, 99.4)
	≥5	844	0	827	14 (1.7)	100.0 (70.5, 100.0)
Maternal age at vaccination	<18 years	8	0	7	0	NC
	>18 years	3487	6 (0.2)	3473	33 (1.0)	81.9 (56.2, 93.8)

The tables below (modified by the assessor) depict vaccine efficacy by maternal gestational age at vaccination at 90/120/150/180 days after birth:

Table 33: Severe MA-LRTIs due to RSV by Maternal Gestational Age (table modified by assessor)

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N^a =3495)		Placebo (N^a=3480)		
Time Interval	**Subgroup Variable**	**Subgroup**	**n[b]**	**Number of Cases (%)**	**n[b]**	**Number of Cases (%)**	**Vaccine Efficacy[c] (%) (95% CI)**
90 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	4 (0.4)	866	11 (1.3)	64.6 (-19.4, 91.8)
		≥28 weeks to <32 weeks	1030	1 (<0.1)	1070	11 (1.0)	90.6 (35.0, 99.8)
		≥32 weeks to ≤36 weeks	1572	1 (<0.1)	1539	11 (0.7)	91.1 (38.8, 99.8)
		>36 weeks	3	0	5	0	NC
120 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	7 (0.8)	866	15 (1.7)	54.6 (-18.3, 84.3)
		≥28 weeks to <32 weeks	1030	2 (0.2)	1070	13 (1.2)	84.0 (29.4, 98.2)
		≥32 weeks to ≤36 weeks	1572	3 (0.2)	1539	18 (1.2)	83.7 (44.1, 96.9)
		>36 weeks	3	0	5	0	NC
150 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	10 (1.1)	866	17 (2.0)	42.8 (-32.4, 76.6)
		≥28 weeks to <32 weeks	1030	2 (0.2)	1070	16 (1.5)	87.0 (44.8, 98.6)
		≥32 weeks to ≤36 weeks	1572	4 (0.3)	1539	22 (1.4)	82.2 (47.6, 95.5)
		>36 weeks	3	0	5	0	NC
180 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	11 (1.2)	866	19 (2.2)	43.7 (-24.6, 75.8)
		≥28 weeks to <32 weeks	1030	2 (0.2)	1070	18 (1.7)	88.5 (51.8, 98.7)
		≥32 weeks to ≤36 weeks	1572	6 (0.4)	1539	25 (1.6)	76.5 (41.3, 92.1)
		>36 weeks	3	0	5	0	NC

Table 34: RSV-positive MA-LRTIs by Maternal Gestational Age (table modified by assessor)

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N^a =3495)		Placebo (N^a=3480)		
Time Interval	Subgroup Variable	Subgroup	n^b	Number of Cases (%)	n^b	Number of Cases (%)	Vaccine Efficacy[c] (%) (95% CI)
90 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	6 (0.7)	866	13 (1.5)	55.1 (-26.6, 86.0)
		≥28 weeks to <32 weeks	1030	4 (0.4)	1070	22 (2.1)	81.1 (44.4, 95.3)
		≥32 weeks to ≤36 weeks	1572	14 (0.9)	1539	21 (1.4)	34.7 (-34.6, 69.3)
		>36 weeks	3	0	5	0	NC
120 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	10 (1.1)	866	20 (2.3)	51.3 (-8.9, 79.7)
		≥28 weeks to <32 weeks	1030	7 (0.7)	1070	26 (2.4)	72.0 (33.8, 89.8)
		≥32 weeks to ≤36 weeks	1572	18 (1.1)	1539	35 (2.3)	49.7 (8.7, 73.2)
		>36 weeks	3	0	5	0	NC
150 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	17 (1.9)	866	23 (2.7)	28.1 (-40.7, 63.9)
		≥28 weeks to <32 weeks	1030	10 (1.0)	1070	31 (2.9)	66.5 (29.9, 85.3)
		≥32 weeks to ≤36 weeks	1572	20 (1.3)	1539	45 (2.9)	56.5 (24.8, 75.7)
		>36 weeks	3	0	5	0	NC
180 Days after birth	Maternal gestational age at vaccination	≥24 weeks to <28 weeks	890	22 (2.5)	866	27 (3.1)	20.7 (-44.6, 57.0)
		≥28 weeks to <32 weeks	1030	11 (1.1)	1070	35 (3.3)	67.4 (34.2, 85.0)
		≥32 weeks to ≤36 weeks	1572	24 (1.5)	1539	55 (3.6)	57.3 (29.8, 74.7)
		>36 weeks	3	0	5	0	NC

Among 6975 infants in the evaluable efficacy population at the cut-off date of 30 Sep 2022, 2034 (58.2%) in the RSVpreF group and 2032 (58.4%) in the placebo group had at least 1 all-cause MA-RTI (i.e. not necessarily LRTI) within 730 days after birth as reported by investigators. The EAC evaluated all such events within 180 days after birth to determine if the event met criteria for the primary endpoints and evaluated hospitalised or severe MA-LRTIs up to 730 days after birth.

Numbers of EAC-confirmed RSV-positive MA-RTI cases in infants within 180 days after birth were 157 in the RSVpreF group and 253 in the placebo group in the evaluable efficacy population, corresponding to a VE of 37.9% (95% CI: 24.0, 49.5).

Table 35: RSV-Positive MA-RTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
90 Days after birth	67 (1.9)	110 (3.2)	39.1 (16.7, 55.7)
120 Days after birth	98 (2.8)	160 (4.6)	38.7 (20.8, 52.9)
150 Days after birth	126 (3.6)	209 (6.0)	39.7 (24.4, 52.1)
180 Days after birth	157 (4.5)	253 (7.3)	37.9 (24.0, 49.5)

The majority of EAC-confirmed RSV MA-LRTI cases were due to RSV subgroup B. For EAC-confirmed MA-LRTI cases due to RSV subgroup B in infants within 180 days after birth, there were 38 cases in the RSVpreF group and 87 cases in the placebo group. These numbers give VE 56.3% (95% CI: 35.4, 71.0). For RSV A, there were 19 and 26 cases in respective groups (VE 26.9% [95% CI: -37.2, 61.8]).

Table 36: MA-LRTIs Confirmed by the EAC, Shown by RSV Subgroup A and Subgroup B, Occurring Within 180 Days After Birth – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)	
RSV Subgroup	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
A	19 (0.5)	26 (0.7)	26.9 (-37.2, 61.8)
B	38 (1.1)	87 (2.5)	56.3 (35.4, 71.0)

The next table shows EAC-confirmed severe MA-LRTI by RSV subgroup within 180 days after birth.

Table 37: Severe MA-LRTIs Confirmed by the EAC, Shown by RSV Subgroup A and Subgroup B, Occurring Within 180 Days After Birth – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)	
RSV Subgroup	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
A	7 (0.2)	14 (0.4)	50.0 (-32.4, 82.9)
B	11 (0.3)	44 (1.3)	75.0 (50.8, 88.4)

Numbers with EAC-confirmed MA-LRTI due to RSV with positive non-RSV pathogens within 180 days after birth were 27 in the RSVpreF group and 47 in the placebo group, for a corresponding VE of 42.6 (95% CI: 5.9, 65.6).

Numbers of RSV-positive MA-RTI cases in premature infants with onset within 180 days after birth were 9 in the RSVpreF group and 13 in the placebo group, for a corresponding VE of 41.1% (95% CI: -49.0, 77.8) for RSVpreF. Similar results were obtained at 360 days and 730 days after birth.

Table 38: MA-LRTI Due to RSV Occurring Within 730 Days After Birth in Premature Infants Born <37 Weeks of Gestational Age – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =168)	Placebo (N[a]=143)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
180 Days after birth	4 (2.4)	6 (4.2)	43.3 (-139.3, 88.2)
360 Days after birth	6 (3.6)	8 (5.6)	36.2 (-109.8, 81.7)
730 Days after birth	7 (4.2)	8 (5.6)	25.5 (-135.0, 77.0)

Table 39: Severe MA-LRTI Due to RSV, Confirmed by the EAC, Occurring Within 730 Days After Birth in Premature Infants Born <37 Weeks of Gestational Age – Infant Participants – Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a] =168)	Placebo (N[a]=143)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
180 Days after birth	4 (2.4)	3 (2.1)	-13.5 (-674.8, 80.8)
360 Days after birth	6 (3.6)	4 (2.8)	-27.7 (-515.1, 69.7)
730 Days after birth	7 (4.2)	4 (2.8)	-49.0 (-593.9, 62.1)

As of the data cut-off date of 02 Sep 2022 (for maternal efficacy), the number of all-cause MA-RTIs for maternal participants from vaccination up to 180 days after delivery was 246 in the RSVpreF group and 241 in the placebo group.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application.

Summary of efficacy for trial C3671013 (adults aged 60+ years)

Title: Efficacy Study RSV Season 1 Primary Analysis Report – A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults		
Study identifier	C3671013 EudraCT 2021-003696-31 (NCT05035212)	
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled efficacy study to assess the safety, immunogenicity and efficacy of bivalent RSVpreF in prevention of LRTI-RSV in adults 60 years of age and older during the first RSV season and the long-term immunogenicity and efficacy of RSVpreF across 2 RSV seasons.	
	Duration of main phase:	Aug 2021 to July 2022, covering first RSV season
Hypothesis	Superiority vs. placebo	
Treatment groups	RSVpreF 120 µg (60 µg RSV A and 60 µg RSV B)	Single dose administered to 17148 subjects
	Placebo	Single dose administered to 17136 subjects

Endpoints and definitions	Primary endpoints		VE, defined as the relative risk reduction of first-episode LRTI-RSV cases with ≥2 LRTI signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after vaccination) As above but based on cases with ≥3 LRTI signs/symptoms
	Key secondary Endpoint Secondary endpoint		VE, defined as the relative risk reduction of first-episode severe (sLRTI) RSV cases in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination). First episode RSV ARI
Database lock	8 July 2022		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Evaluable efficacy population			
Descriptive statistics and estimate variability	Treatment group	RSVpreF	Placebo	
	Number of subjects	16306	16308	
	LRTI-RSV cases with ≥2 LRTI signs/symptoms	11 (0.07%) [1 RSV A and 10 RSV B]	<33 (0.20%) [9 RSV A and 23 RSV B]	VE 66.7% [96.66% CI 28.8, 85.8]
	LRTI-RSV cases with ≥3 LRTI signs/symptoms	2 (0.01%) [1 RSV A and 1 RSV B]	14 (0.09%) [3 RSV A and 10 RSV B]	VE 85.7% [96.66% CI 32.0, 98.7]
	Secondary endpoint Severe RSV LRTI	RSVpreF awaited	Placebo awaited	
	First episode RSV ARI	22 (0.13%) VE 62.1% (95% CI 37.1, 77.9)	58 (0.36%)	
Notes	The above is taken from Efficacy Study RSV Season 1 Primary Analysis Report. Results for key and other secondary endpoints are to be provided in a supplementary CSR.			

Summary of efficacy for trial C3671008 (infants born to vaccinated mothers)

Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Infants Born to Mothers Vaccinated During Pregnancy				
Study identifier	C3671008 EudraCT 2019-002943-85 (NCT04424316)			
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled efficacy study to assess the safety and efficacy of bivalent RSVpreF in prevention of RSV medically attended LRTI (MA-LRTI) and severe MA-LRTI in infants born to vaccinated vs. unvaccinated mothers			
	Duration of main phase:		June 2020 to September 2022	
Hypothesis	Superiority vs. placebo			
Treatment groups	RSVpreF 120 µg (60 µg RSV A and 60 µg RSV B)		Single dose administered to 3682 pregnant women	
	Placebo		Single dose administered to 3676 pregnant women	
Endpoints and definitions	Primary endpoints in infants		VE, defined as the relative risk reduction of EAC-confirmed first-episode RSV MA-LRTI and severe MA-LRTI with onset at least 72 h after birth and occurring within day 90, 120, 150 or 180 after birth	
	Secondary Endpoint (major)		Hospitalisation due to RSV	
Database lock	30 September 2022			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Infant evaluable efficacy population			
Descriptive statistics and estimate variability	Treatment group	RSVpreF	Placebo	
	Number of subjects	3495	3480	
	RSV MA-LRTI 90 days 120 days 150 days 180 days	 24 (0.7%) 35 (1.0%) 47 (1.3%) 57 (1.6%)	 56 (1.6%) 81 (2.3%) 99 (2.8%) 117 (3.4%)	 VE 57.1% (14.7, 79.8) 56.8 (31.2, 73.5) 52.5 (27.8, 68.9) 51.3 (29.4, 66.8)

	Severe RSV MA-LRTI 90 days 120 days 150 days 180 days	 6 (0.2%) 12 (0.3%) 16 (0.5%) 19 (0.5%)	 33 (0.9%) 46 (1.3%) 55 (1.6%) 62 (1.8%)	 VE 81.8% (40.6, 96.3) 73.9 (45.6, 88.8) 70.9 (44.5, 85.9) 69.4 (44.3, 84.1)
	Secondary endpoint Hospitalisation due to RSV	RSVpreF Day 90 10 (0.3%) Day 120 15 (0.4%) Day 150 17 (0.5%) Day 180 19 (0.5%) VE was from 56.4% to 67.7%; all lower bounds of the 99.17% CI were above zero up to day 180		Placebo 31 (0.9%) 37 (1.1%) 39 (1.1%) 44 (1.3%)
Notes	Results in the mITT infant population were broadly comparable As in the older adults study, RSV B predominated. There was a numerical benefit of maternal vaccination for infant for RSV A cases and VE was shown for RSV B cases. Protection of infants against RSV MA-LRTI or severe MA-LRTI did not persist beyond 180 days after birth, reflecting depletion of maternal antibody			

Supportive studies

C3671001

This was a randomised and placebo-controlled first-in-human study with the RSVpreF antigen in healthy male and female subjects aged 18-85 years. RSVpreF doses were 60 µg (30 A and 30 B), 120 µg (60 A and 60 B) or 240 µg (120 A and 120 B) of the prefusion RSV F antigen, with or without $Al(OH)_3$. RSVpreF formulations were given with or without concomitant inactivated seasonal influenza vaccine (SIIV; Fluzone). The standard dose quadrivalent vaccine was used for subjects aged 18-49 years and trivalent Fluzone HD was used for those aged 65-85 years.

Sentinel Cohort

All Sentinel Cohort subjects (aged 18-85 years) received either one dose of RSVpreF with $Al(OH)_3$, RSVpreF without $Al(OH)_3$ or placebo. Initial subjects received 60 µg (i.e. 30 µg of each RSV A and B preF). An IRC reviewed safety over 14 days post-dose and recommended progression to the next dose as well as recommending initiation of that dose level in the Expanded Cohort.

Expanded Cohort

Subjects in each age group (18-49 years and 65-85 years) were randomised to one of 13 groups equally (across each dose level or placebo, with or without SIIV co-administration). At Visit 1, all Expanded Cohort subjects received 2 injections:

- One dose of RSVpreF with $Al(OH)_3$ or RSVpreF without $Al(OH)_3$ or placebo in the left deltoid muscle
- One dose of SIIV or placebo in the right deltoid muscle

At Visit 2, subjects previously given placebo received SIIV and subjects previously given SIIV received placebo in the deltoid muscle of the non-dominant arm.

At ~12 months, expanded cohort subjects from the initial 240 µg dose group who had received RSVpreF with or without $Al(OH)_3$ were invited to be revaccinated with the same dose and formulation as before. The SIIV or placebo assignment and the vaccination scheme was the same as for the first year of the study. The placebo group was revaccinated with placebo alone followed by SIIV alone. Thus, subjects received two injections at Visit 7 and one at Visit 8.
Data shown for the Sentinel and Expanded Cohort includes all subjects who did not receive SIIV with the first dose of vaccine. The figures below show that Month 1 NA responses to RSV A and RSV B preF trended slightly higher in the younger age group and the highest dose gave the largest increments but there was no advantage over the middle dose for the older subjects. NA against RSV B appeared slightly higher than against RSV A in both age groups. $Al(OH)_3$ did not notably enhance the immune response at any antigen dose in either age group.

Figure 11: RSV A-Neutralizing Titer GMTs and GMFRs at 1 month After Vaccination 1 (Age Group: 18 through 49 Years) – Sentinel and Expanded Cohorts – Evaluable RSV Immunogenicity Population

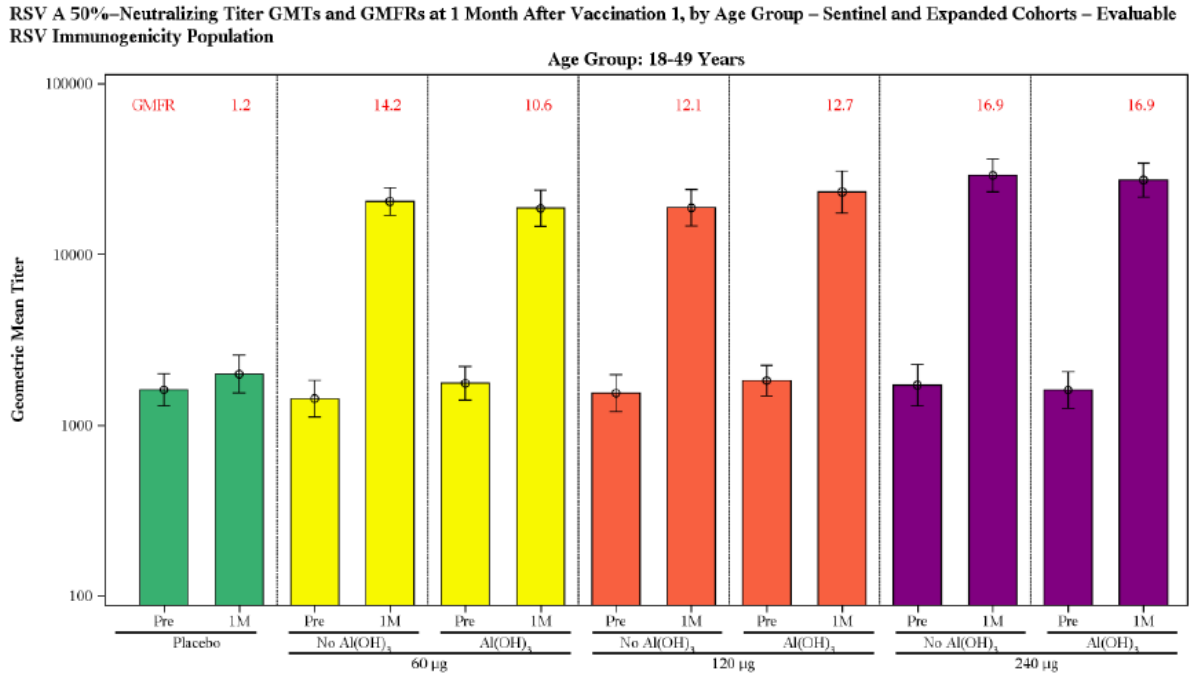


Figure 12: RSV A-Neutralizing Titer GMTs and GMFRs at 1 Month After Vaccination 1 (Age Group: 50 through 85 Years) – Sentinel and Expanded Cohorts – Evaluable RSV Immunogenicity Population

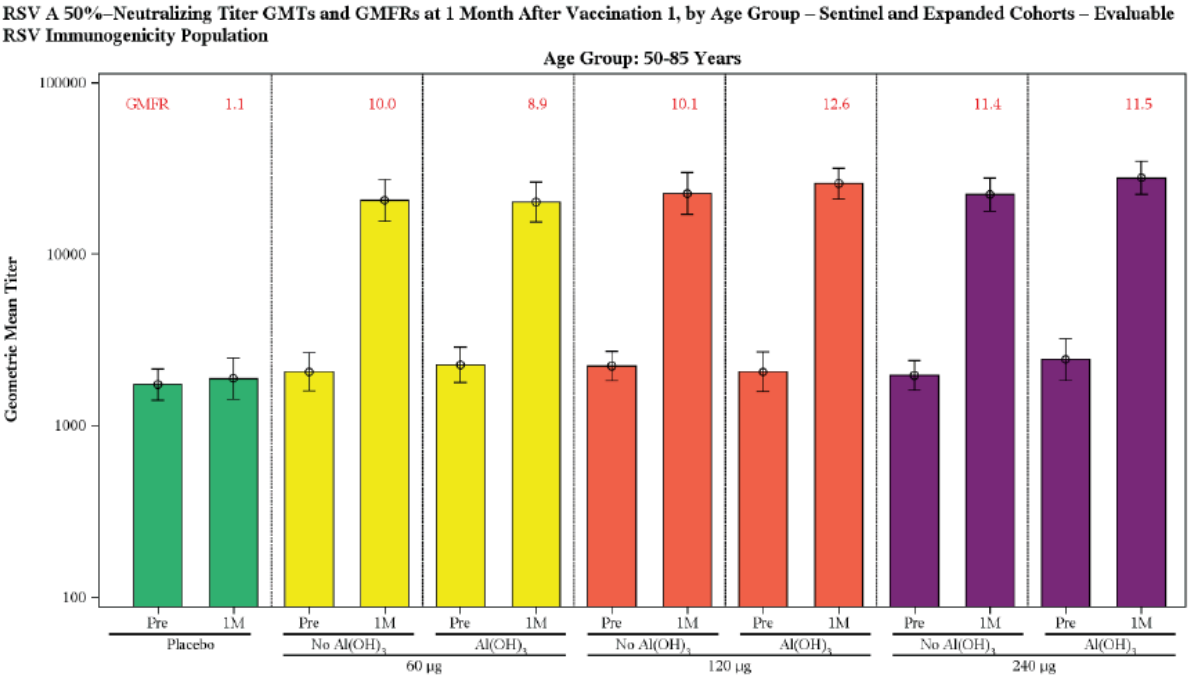


Figure 13: RSV B-Neutralizing Titer GMTs and GMFRs at 1 Month After Vaccination 1 (Age Group: 18 through 49Years) Sentinel and Expanded Cohorts – Evaluable RSV Immunogenicity Population

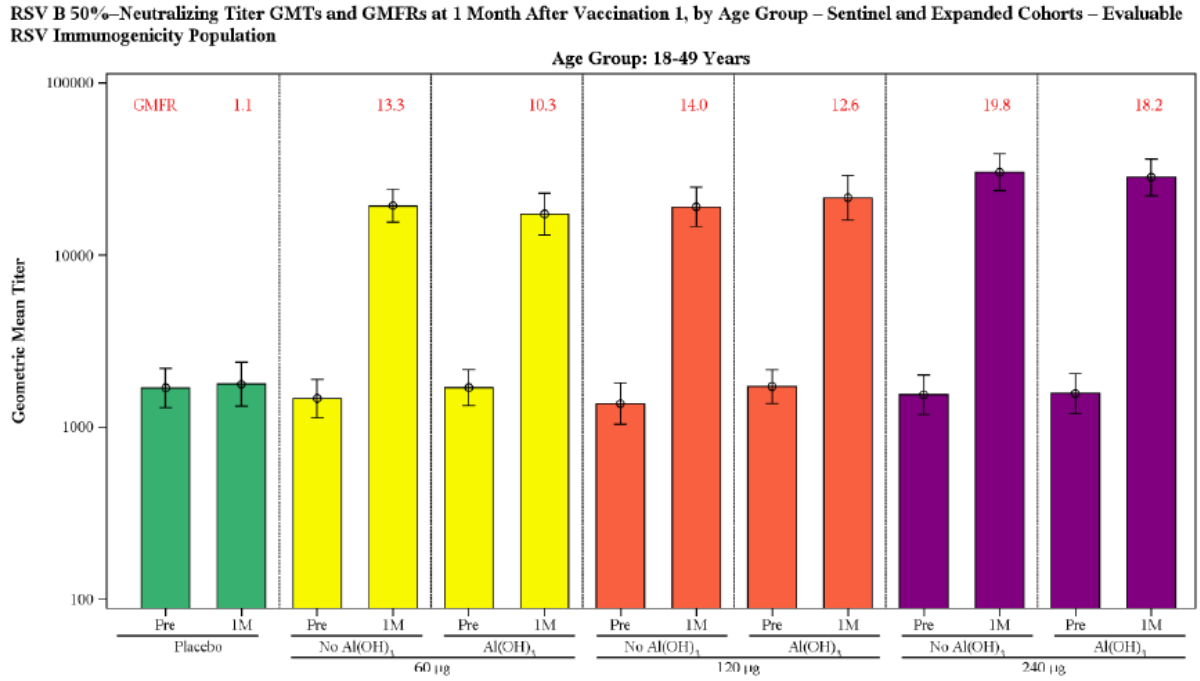
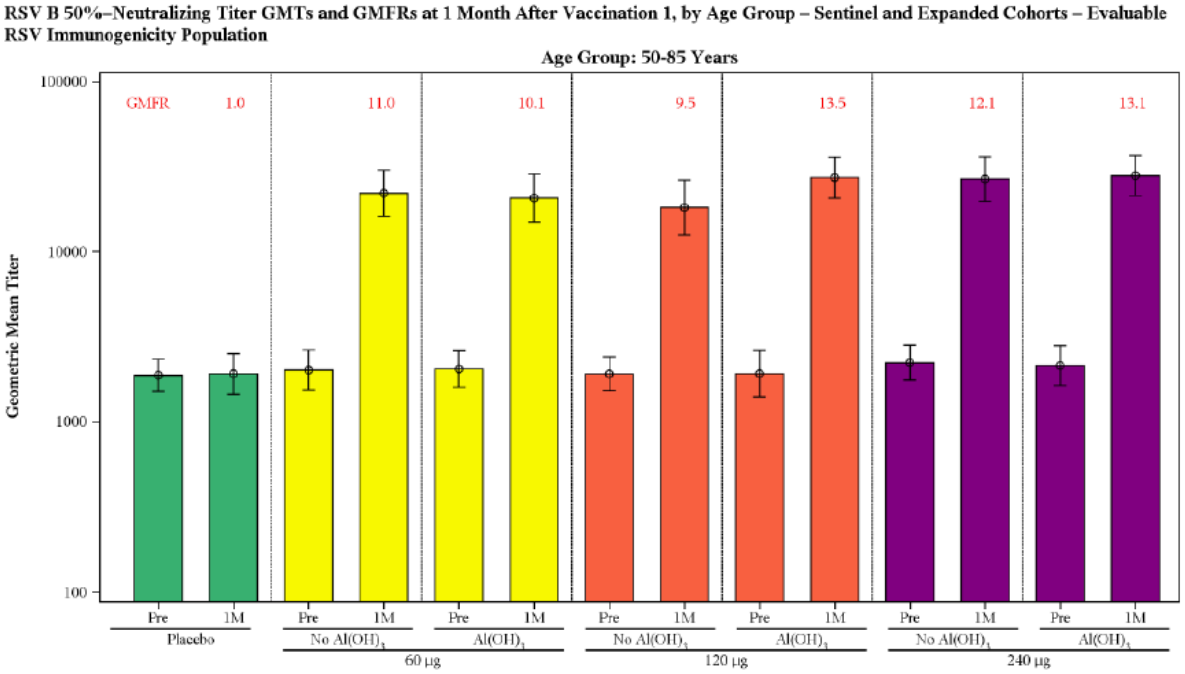


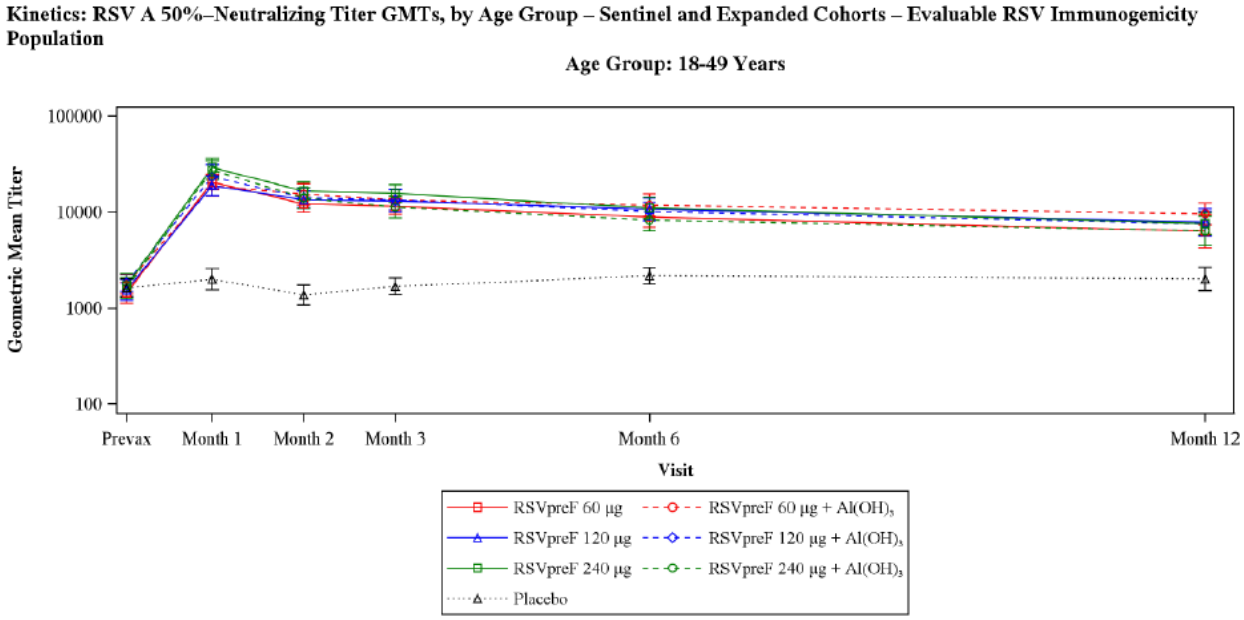
Figure 14: RSV B-Neutralizing Titer GMTs and GMFRs at 1 Month After Vaccination 1 (Age Group: 50 through 85 Years) – Sentinel and Expanded Cohorts – Evaluable RSV Immunogenicity Population



The GMRs across the 6 RSVpreF dose level and formulation groups for RSV A ranged from 0.78 to 1.02 in the 18-49 years group and from 0.76 to 1.12 in the 65-85 years group. For RSV B, the corresponding GMRs ranged from 0.74 to 1.11 and from 0.74 to 1.30.
While NA responses to RSVpreF with or without SIIV co-administration varied across dose level, formulation and age group, there were no notable differences observed on co-administration.

At all sampling times to month 12, the RSV A and RSV B NA GMTs were higher compared to baseline and were also higher than those for the placebo group regardless of age group or inclusion of $Al(OH)_3$. The same pattern was observed for those who received concomitant SIIV. An example of the graphical displays is shown below.

Figure 15: Kinetics: RSV A-Neutralizing Titer GMTs (Age Group: 18 through 49 Years) – Sentinel and Expanded Cohorts – Evaluable RSV Immunogenicity Population



In the Expanded Cohorts, the age group 65-85 years received HD trivalent SIIV that omitted the B/Phuket strain although the HAI GMTs and GMFRs for this strain were measured. There was a general trend to lower HAI responses to SIIV after concomitant administration with RSVpreF vs. SIIV alone although the differences were less pronounced in the older group of 50-85 years.

RSVpreF interference with immune responses to SIIV generally increased with the RSVpreF antigen level in subjects aged 18-49 years but this was not a consistent finding in the older subjects. The proportions with HAI titres ≥1:40 and with seroconversion (≥ 4-fold rise) at 1 month after SIIV were lower when it was given with RSVpreF vs. given alone.

Moreover, NA GMTs against H3N2 as well as proportions with HAI titres ≥1:40 and with seroconversion (≥ 4-fold rise) were generally lower after concomitant administration.

Table 40: HAI Antibody GMRs 1 Month After SIIV for RSVpreF With SIIV to SIIV Only, by Age Group – Expanded Cohort – Evaluable Influenza Immunogenicity Population Age Group: 18-49 Years

	Vaccine Group (as Randomized)						
	RSVpreF 60 µg + SIIV (N[a]=39)	RSVpreF 60 µg + Al(OH)3 + SIIV (N[a]=40)	RSVpreF 120 µg + SIIV (N[a]=40)	RSVpreF 120 µg + Al(OH)3 + SIIV (N[a]=39)	RSVpreF 240 µg + SIIV (N[a]=40)	RSVpreF 240 µg + Al(OH)3 + SIIV (N[a]=41)	Placebo + Placebo (N[a]=34)
Influenza Strain	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMT[c]
A-H1N1/ Michigan	0.61 (0.38, 0.96)	0.68 (0.44, 1.04)	0.49 (0.32, 0.77)	0.55 (0.33, 0.93)	0.45 (0.30, 0.69)	0.57 (0.37, 0.87)	127
A-H3N2/ Singapore	0.51 (0.33, 0.79)	0.53 (0.35, 0.82)	0.56 (0.34, 0.91)	0.49 (0.30, 0.79)	0.53 (0.35, 0.81)	0.63 (0.40, 0.99)	153
B1/ Colorado	0.74 (0.45, 1.23)	0.92 (0.54, 1.57)	0.58 (0.36, 0.95)	0.60 (0.36, 1.00)	0.49 (0.29, 0.81)	0.75 (0.47, 1.21)	32
B2/ Phuket	0.80 (0.51, 1.25)	0.77 (0.50, 1.19)	0.63 (0.42, 0.93)	0.62 (0.39, 0.96)	0.56 (0.36, 0.86)	0.72 (0.46, 1.11)	36

Table 41: HAI Antibody GMRs 1 Month After SIIV for RSVpreF With SIIV to SIIV Only, by Age Group – Expanded Cohort – Evaluable Influenza Immunogenicity Population Age Group: 65-85 Years

	Vaccine Group (as Randomized)						
	RSVpreF 60 µg + SIIV (N^a=38)	RSVpreF 60 µg + $Al(OH)_3$ + SIIV (N^a=40)	RSVpreF 120 µg + SIIV (N^a=38)	RSVpreF 120 µg + $Al(OH)_3$ + SIIV (N^a=40)	RSVpreF 240 µg + SIIV (N^a=40)	RSVpreF 240 µg + $Al(OH)_3$ + SIIV (N^a=41)	Placebo + Placebo (N^a=34)
Influenza Strain	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMR[b] (95% CI[b])	GMT[c]
A-H1N1/ Michigan	0.57 (0.34, 0.97)	0.59 (0.35, 0.99)	0.70 (0.43, 1.13)	0.75 (0.42, 1.31)	0.60 (0.36, 1.00)	0.69 (0.40, 1.21)	76
A-H3N2/ Singapore	0.89 (0.47, 1.68)	0.74 (0.38, 1.43)	1.32 (0.71, 2.45)	1.24 (0.65, 2.34)	0.74 (0.41, 1.36)	0.97 (0.49, 1.93)	106
B1/ Colorado	0.73 (0.42, 1.28)	0.85 (0.50, 1.47)	0.92 (0.52, 1.63)	0.98 (0.55, 1.75)	0.70 (0.40, 1.25)	0.79 (0.46, 1.36)	27
B2/ Phuket	0.78 (0.50, 1.22)	0.98 (0.59, 1.62)	1.25 (0.76, 2.07)	1.01 (0.62, 1.66)	0.73 (0.47, 1.13)	0.82 (0.51, 1.32)	13

Of the 267 consented subjects (134 in the younger age group and 133 in the older age group), 263 (98.5%) completed re-vaccination and 248 (92.9%) completed the study. At 1 month after revaccination, the NA GMFRs across the RSVpreF vaccine groups for RSV A ranged from 1.4 to 2.3 in the younger age group and from 1.4 to 2.2 in the older age group. Corresponding ranges for RSV B were 1.4 to 2.2 and 1.5 to 2.1.

The figures below show that the month 1 post-dose NA GMTs were lower after revaccination compared to initial vaccination in both age groups and for RSV A and B but they were higher than for placebo.

Figure 16: RSV A 50% - NT GMTs and GMFRs from After Vaccination 1 to After Vaccination 3 (Age Group: 18 through 49 Years) – Expanded Cohort for Revaccination – Evaluable RSV Immunogenicity Population

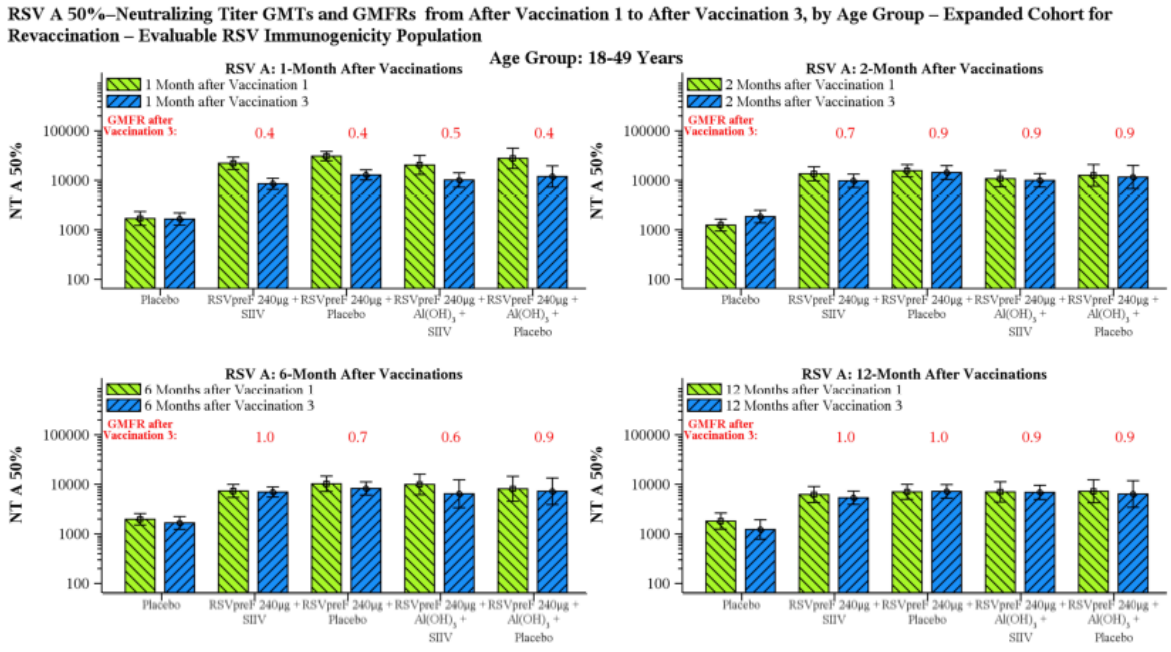


Figure 17: RSV A 50% - NT GMTs and GMFRs from After Vaccination 1 to After Vaccination 3 (Age Group: 65 through 85 Years) – Expanded Cohort for Revaccination – Evaluable RSV Immunogenicity Population

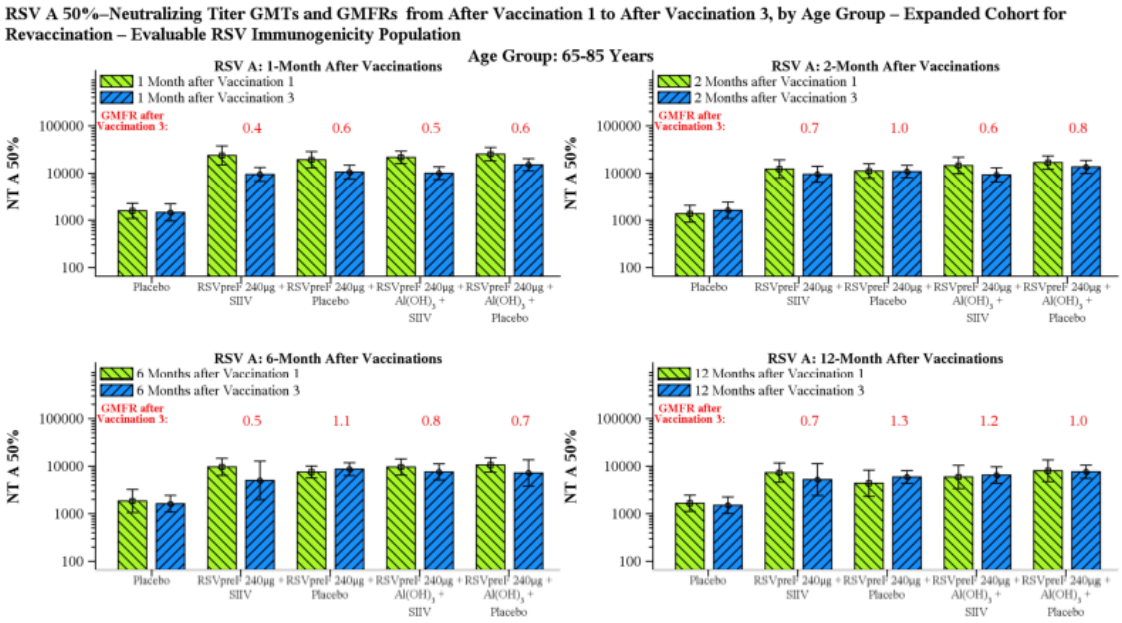


Figure 18: RSV B 50% - NT GMTs and GMFRs from After Vaccination 1 to After Vaccination 3 (Age Group: 18 through 49 Years) – Expanded Cohort for Revaccination – Evaluable RSV Immunogenicity Population

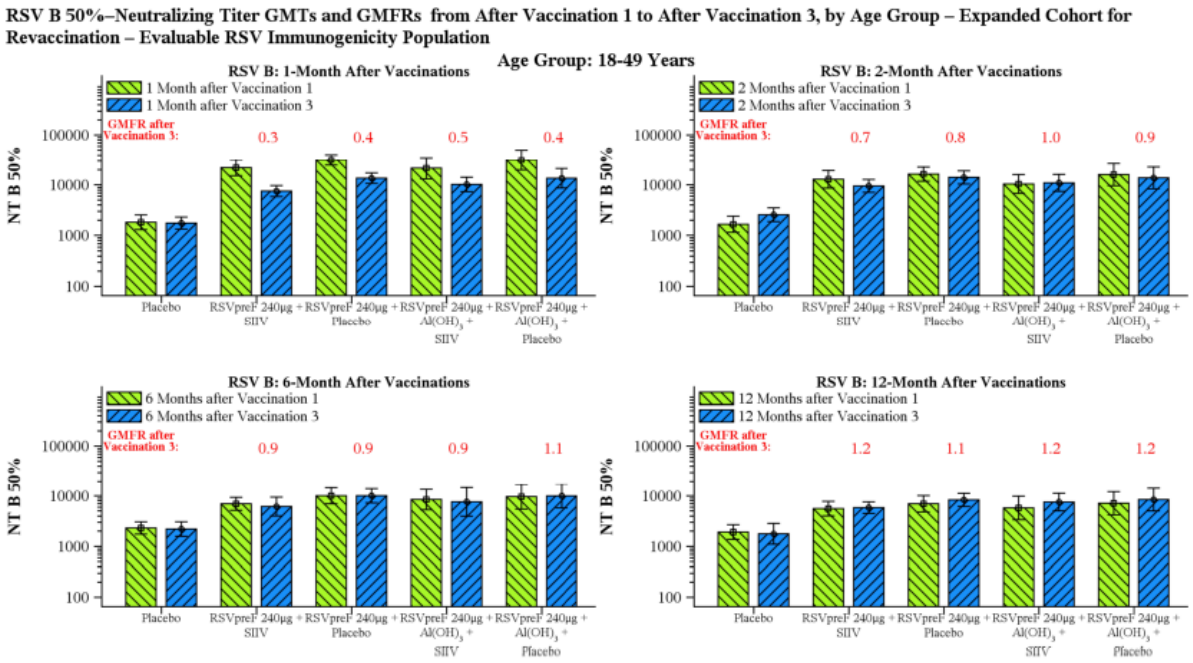
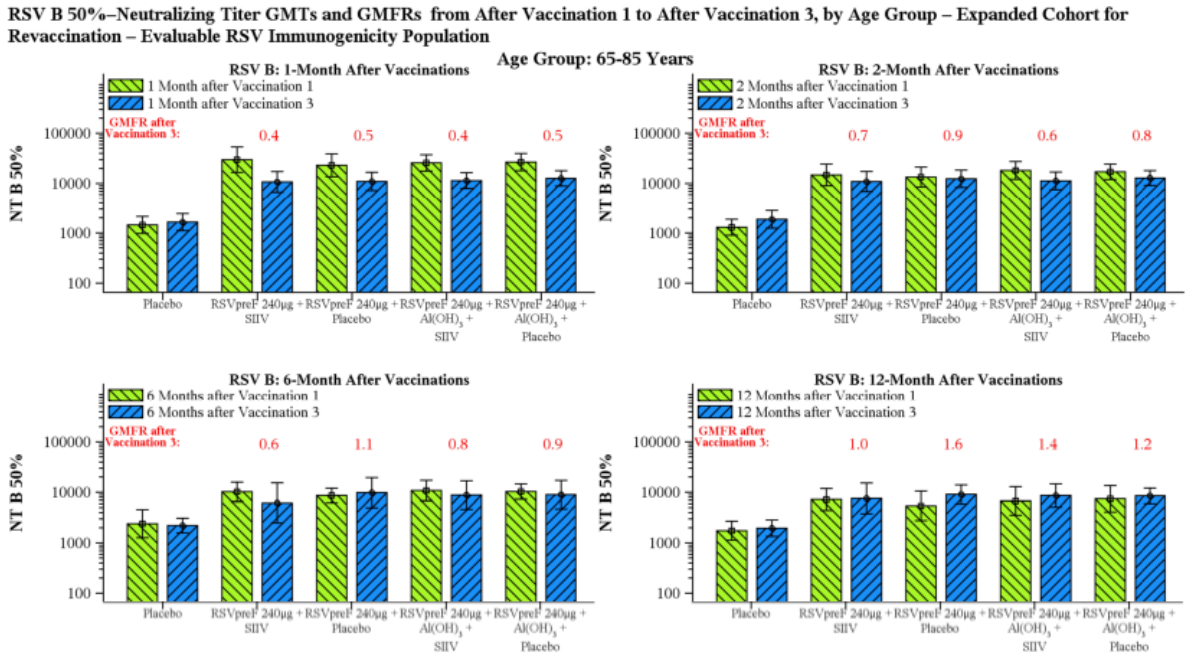
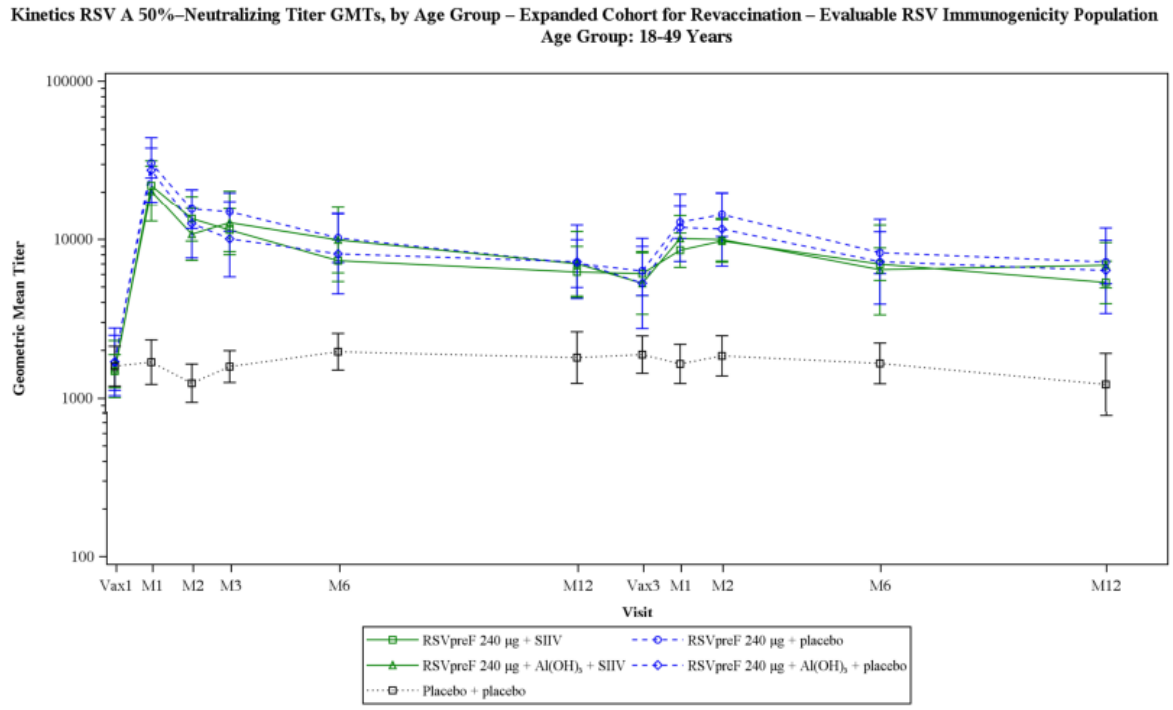


Figure 19: RSV B 50% - NT GMTs and GMFRs from After Vaccination 1 to After Vaccination 3 (Age Group: 65 through 85 Years) – Expanded Cohort for Revaccination – Evaluable RSV Immunogenicity Population



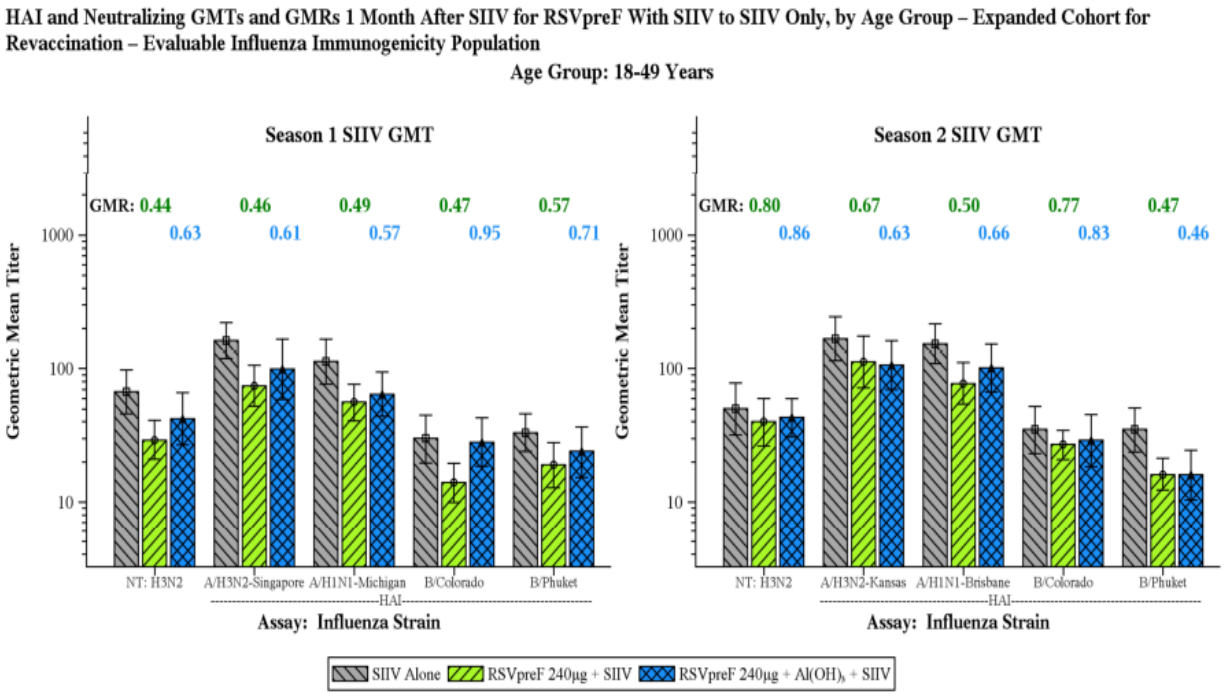
The figure below depicts a typical curve for NA titres over time.

Figure 20: Kinetics RSV A 50% - NT GMTs (Age Group: 18 through 49 Years) – Expanded Cohort for Revaccination – Evaluable RSV Immunogenicity Population



In general, RSVpreF interference with immune responses to SIIV was apparent in the younger age group but not in the older age group.

Figure 21: HAI and Neutralizing GMTs and GMRs 1 Month After SIIV for RSVpreF With SIIV to SIIV Only (Age Group: 18 through 49 Years) – Expanded Cohort for Revaccination – Evaluable Influenza Immunogenicity Population



C3671002

This study evaluated the RSVpreF antigen adjuvanted with $Al(OH)_3$ or $CpG/Al(OH)_3$ in subjects aged 65-85 years (mean age ~71 years). In Stage 1, there was randomisation of 254 subjects (250 vaccinated) to a single dose of placebo or to one of 7 RSV A and B preF formulations. These formulations included three dose levels (60 µg [i.e. 30 µg of each of RSV A and B preF], 120 µg [60 µg of each] and 240 µg [120 µg of each]) tested with $Al(OH)_3$ or $CpG/Al(OH)_3$ plus 240 µg [120 µg of each of RSVpreF A and B] without adjuvant.

The Month-0, Month-2 Cohort separately randomised 63 subjects to receive 2 doses of either 240 µg with $CpG/Al(OH)_3$ or placebo given 2 months apart. SIIV (Fluzone HD) was administered concomitantly except for the Month-0, Month-2 Cohort.

This study was terminated early (10 August 2020) after the sponsor's interim analysis review of data from the designated Primary Cohort. This showed no enhancement of immune responses to RSVpreF when adjuvanted with CpG compared to adjuvantation with $Al(OH)_3$ or no adjuvant. Also, there was no booster response to a second dose of RSVpreF with $CpG/Al(OH)_3$ when this was administered 2 months after the initial dose. Therefore, the planned revaccination stage (Stage 2) of this study at month 12 was not pursued.

To assess co-administration with SIIV, NA titres at month 1 were compared between the Month-0, Month-2 Cohort and the Primary Cohort that received RSVpreF 240 µg + $CpG/Al(OH)_3$. The GMRs were 1.14 and 1.27 for RSV A and RSV B 50% NA titres, respectively, with lower bounds of 95% CIs ≥0.75, indicating no important negative interference of SIIV on the anti-RSVpreF responses.

The HAI GMTs for A/H1N1, A/H3N2 and B/Phuket after SIIV were similar or slightly lower when given with RSVpreF compared to co-administration with placebo.

Figure 22: HAI and Neutralizing Antibody GMTs and GMFRs at 1 Month after Vaccination – Primary Cohort – Evaluable Immunogenicity Population – HAI: H1N1 A/Michigan

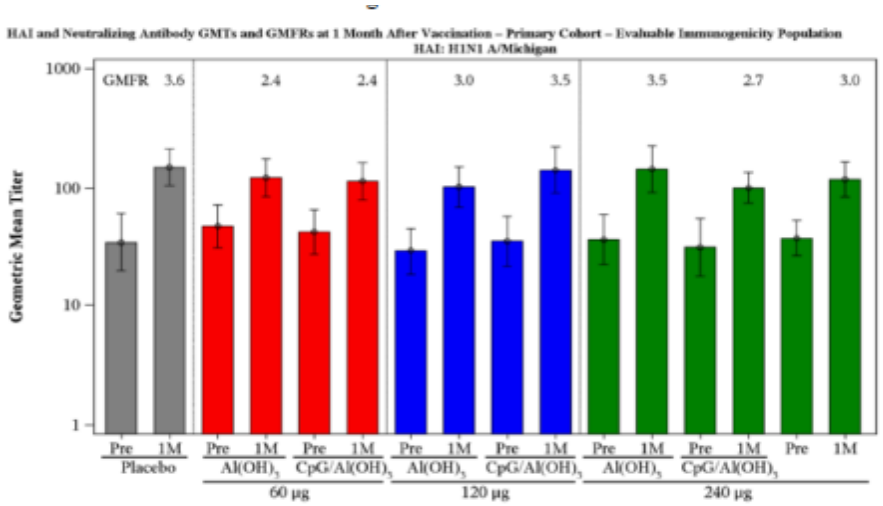


Figure 23: HAI and Neutralizing Antibody GMTs and GMFRs at 1 Month after Vaccination – Primary Cohort – Evaluable Immunogenicity Population – HAI: H3N2 A/Brisbane

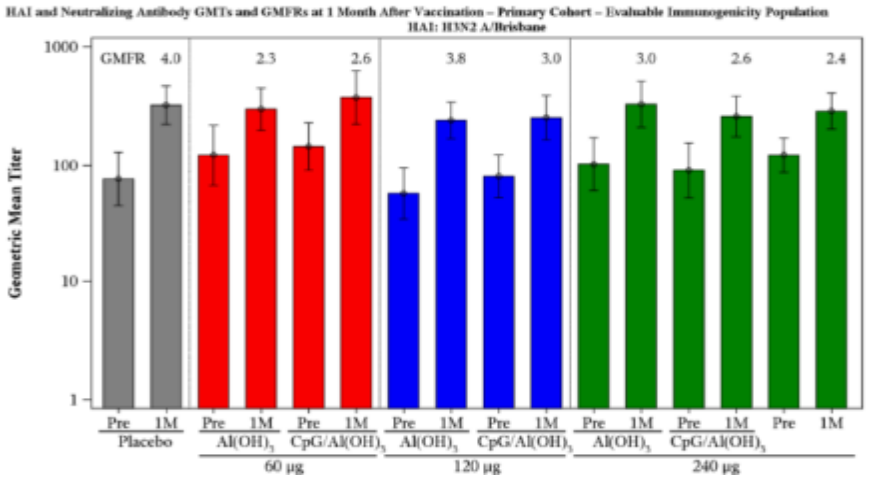
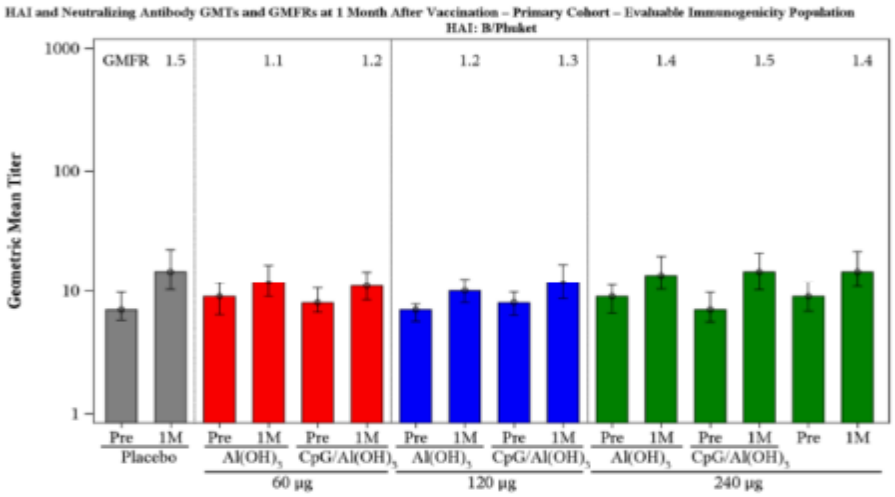


Figure 24: HAI and Neutralizing Antibody GMTs and GMFRs at 1 Month after Vaccination – Primary Cohort – Evaluable Immunogenicity Population – HAI: B/Phuket



C3671004

This was a randomised and placebo-controlled study to evaluate co-administration of RSVpreF vaccine (120 or 240 µg) and tetanus, diphtheria and acellular pertussis vaccine (Tdap; Boostrix) in healthy non-pregnant women aged 18-49 years. Participants were randomised in equal numbers to one of 5 treatment groups and all received 2 injections in accordance with their assignment as follows:

- RSVpreF 120 µg and Placebo (saline solution)
- RSVpreF 120 µg and Tdap
- RSVpreF 240 µg + $Al(OH)_3$ (0.4 mg/mL) and Placebo
- RSVpreF 240 µg + $Al(OH)_3$ (0.4 mg/mL) and Tdap
- Placebo and Tdap

Sera were obtained for determination of immune responses pre-vaccination and at one month post-vaccination. The NA responses to RSV A and RSV B were determined as well as the anti-D, anti-T, anti-PT and anti-FHA immune responses.

There were 709 women vaccinated, of which 97.5% completed the post-vaccination visit. All non-completers were lost to follow-up. The mean age of women was 35.6 years.

At pre-vaccination, >80% of subjects still had at least 0.1 IU/mL anti-D and almost all subjects still had at least 0.1 IU/mL anti-T. The primary analysis met the pre-defined criteria for concluding on non-inferior anti-D and anti-T responses when TdaP was given with RSVpreF vs. co-administration with placebo, i.e. the lower bounds of the 2-sided 95% CI for the differences in proportions reaching at least 0.1 IU/mL between combined RSVpreF/Tdap groups and the placebo/Tdap group were >-10%. As shown below, the actual lower bounds were within -5%.

Table 42: Difference in % of Subjects Achieving Anti-TTd or Anti-DTd Antibody Concentrations ≥0.1 IU/mL Between Combined RSVpreF/Tdap Groups and Placebo/Tdap Group – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)		
		RSVpreF/Tdap	Placebo/Tdap	Vaccine Comparison
Antibody	Time Point[a]	n[b]/N[c] (%) (95% CI)[d]	n[b]/N[c] (%) (95% CI)[d]	Diff[e] (95% CI)[f]
Anti-DTd	Before vaccination	220/272 (80.9) (75.7, 85.4)	110/134 (82.1) (74.5, 88.2)	
	1 Month after vaccination	265/272 (97.4) (94.8, 99.0)	133/134 (99.3) (95.9, 100.0)	-1.8 (-4.6, 1.7)
Anti-TTd	Before vaccination	264/272 (97.1) (94.3, 98.7)	133/134 (99.3) (95.9, 100.0)	
	1 Month after vaccination	272/272 (100.0) (98.7, 100.0)	134/134 (100.0) (97.3, 100.0)	0.0 (-1.4, 2.8)

Abbreviations: DTd = Diphtheria toxoid; LLOQ = lower limit of quantitation; TTd = Tetanus toxoid.
Note: RSVpreF/Tdap is the combination of RSVpreF 120 µg/Tdap and RSVpreF 240 µg + $Al(OH)_3$/Tdap groups. The LLOQ values for each antibody were: Anti-DTd = 0.037 IU/mL and Anti-TTd = 0.05 IU/mL. Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results ≥0.1 IU/mL.
c. N = number of subjects with valid and determinate assay results for the specified serotype at the specified time point. These values were used as the denominators for the percentage calculations.
d. Exact 2-sided CI, calculated using the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (RSVpreF/Tdap – Placebo/Tdap).
f. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions expressed as a percentage.

The next table shows the exploratory analysis of the percentages with anti-T or anti-D antibody concentrations at the higher level of ≥1.0 IU/mL for the combined RSVpreF/Tdap group and the placebo/Tdap group.

The percentage with anti-D ≥1.0 IU/mL before vaccination was higher in the combined RSVpreF/Tdap groups compared to the placebo/Tdap group (26.1% and 17.9%, respectively). The percentages with anti-T ≥1.0 IU/mL before vaccination were higher than for anti-D but they were comparable between the combined RSVpreF/Tdap groups and the placebo/Tdap group (59.9% and 62.7%).

As shown below, the proportion with at least 1.0 IU/mL anti-D at month 1 was considerably higher in the placebo group vs. the RSVpreF group with a difference of -25.4%.

In contrast, very similar percentages in each group achieved at least 1.0 IU/mL anti-T at month 1, with more than 97% reaching this level.

Table 43: Difference in % of Subjects Achieving Anti-TTd or Anti-DTd Antibody Concentrations ≥0.1 IU/mL Between Combined RSVpreF/Tdap Groups and Placebo/Tdap Group – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)		
		RSVpreF/Tdap	Placebo/Tdap	Vaccine Comparison
Antibody	Time Point[a]	n[b]/N[c] (%) (95% CI)[d]	n[b]/N[c] (%) (95% CI)[d]	Diff[e] (95% CI)[f]
Anti-DTd	Before vaccination	71/272 (26.1) (21.0, 31.7)	24/134 (17.9) (11.8, 25.5)	
	1 Month after vaccination	140/272 (51.5) (45.4, 57.5)	103/134 (76.9) (68.8, 83.7)	-25.4 (-34.2, -15.7)
Anti-TTd	Before vaccination	163/272 (59.9) (53.8, 65.8)	84/134 (62.7) (53.9, 70.9)	
	1 Month after vaccination	264/272 (97.1) (94.3, 98.7)	132/134 (98.5) (94.7, 99.8)	-1.4 (-4.5, 2.5)

Abbreviations: DTd = Diphtheria toxoid; LLOQ = lower limit of quantitation; TTd = Tetanus toxoid.
Note: RSVpreF/Tdap is the combination of RSVpreF 120 µg/Tdap and RSVpreF 240 µg + Al(OH)3/Tdap groups. The LLOQ values for each antibody were: Anti-DTd = 0.037 IU/mL and Anti-TTd = 0.05 IU/mL. Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. n = Number of subjects with valid and determinate assay results ≥1.0 IU/mL.
c. N = number of subjects with valid and determinate assay results for the specified serotype at the specified time point. These values were used as the denominators for the percentage calculations.
d. Exact 2-sided CI, calculated using the Clopper and Pearson method.
e. Difference in proportions, expressed as a percentage (RSVpreF/Tdap – Placebo/Tdap).
f. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions expressed as a percentage.

The observed percentage with anti-D ≥1.0 IU/mL was higher in the RSVpreF 120 µg/Tdap and RSVpreF 240 µg + Al(OH)$_3$/Tdap groups in comparison to the placebo/Tdap group before vaccination while percentages with anti-T ≥1.0 IU/mL before vaccination were similar across treatment groups.

Table 44: Difference in % of Subjects Achieving Anti-TTd or Anti-DTd Antibody Concentrations ≥0.1 IU/mL Between RSVpreF/Tdap Groups and Placebo/Tdap Group – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)				
		RSVpreF 120 µg/ Tdap		RSVpreF 240 µg + Al(OH)3/Tdap		Placebo/Tdap
Antibody	Time Point[a]	n[b]/N[c] (%) (95% CI)[d]	Diff[e] (95% CI)[f]	n[b]/N[c] (%) (95% CI)[d]	Diff[e] (95% CI)[f]	n[b]/N[c] (%) (95% CI)[d]
Anti-DTd	Before vaccination	33/135 (24.4) (17.5, 32.6)		38/137 (27.7) (20.4, 36.0)		24/134 (17.9) (11.8, 25.5)
	1 Month after vaccination	72/135 (53.3) (44.6, 62.0)	-23.5 (-34.3, -12.3)	68/137 (49.6) (41.0, 58.3)	-27.2 (-37.9, -15.9)	103/134 (76.9) (68.8, 83.7)
Anti-TTd	Before vaccination	83/135 (61.5) (52.7, 69.7)		80/137 (58.4) (49.7, 66.7)		84/134 (62.7) (53.9, 70.9)
	1 Month after vaccination	133/135 (98.5) (94.8, 99.8)	0.0 (-3.9, 4.0)	131/137 (95.6) (90.7, 98.4)	-2.9 (-7.9, 1.4)	132/134 (98.5) (94.7, 99.8)

At month 1, percentages with anti-D ≥1.0 IU/mL were 53.3%, 49.6% and 76.9% for the RSVpreF 120 µg/Tdap group, RSVpreF 240 µg + Al(OH)$_3$/Tdap group, and placebo/Tdap group, respectively. Nearly all participants in the RSVpreF 120 µg/Tdap group, RSVpreF 240 µg + Al(OH)$_3$/Tdap group and placebo/Tdap group achieved anti-T ≥1.0 IU/mL at 1 month after vaccination.

Non-inferiority was not shown for anti-PT, anti-FHA and anti-PRN immune responses since the lower bounds of the 2-sided 95% CIs for the GMC ratios of the combined RSVpreF/Tdap groups to the placebo/Tdap group did not exceed 0.67 (they ranged from 0.48 to 0.64).

Table 45: Antipertussis Component Antibody GMRs of Combined RSVpreF/Tdap Groups GMCs to Placebo/Tdap Group GMCs – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)		
		RSVpreF/Tdap	Placebo/Tdap	
Antipertussis Component	Time Point[a]	GMC[b] (n[c]) (95% CI)[d]	GMC[b] (n[c]) (95% CI)[d]	GMR[e] (95% CI)[f]
Anti-PT	Before vaccination	5.55 (272) (4.79, 6.43)	5.66 (134) (4.49, 7.14)	
	1 Month after vaccination	36.59 (272) (33.10, 40.46)	45.90 (134) (37.43, 56.29)	0.80 (0.64, 1.00)
Anti-FHA	Before vaccination	25.07 (272) (21.88, 28.72)	26.39 (134) (22.11, 31.50)	
	1 Month after vaccination	113.30 (272) (104.13, 123.28)	191.33 (134) (164.46, 222.59)	0.59 (0.50, 0.70)
Anti-PRN	Before vaccination	28.31 (272) (23.41, 34.24)	23.63 (134) (18.23, 30.63)	
	1 Month after vaccination	154.13 (272) (135.98, 174.70)	257.05 (134) (211.55, 312.34)	0.60 (0.48, 0.76)

Abbreviations: FHA = filamentous hemagglutinin; GMC = geometric mean concentration; GMR = geometric mean ratios; LLOQ = lower limit of quantitation; PRN = pertactin; PT = pertussis toxin.
Note: RSVpreF/Tdap is the combination of RSVpreF 120 µg/Tdap and RSVpreF 240 µg + $Al(OH)_3$/Tdap groups. The LLOQ values for each antibody were: Anti-PT = 0.9 EU/mL, Anti-FHA = 2.9 EU/mL, and Anti-PRN = 3.0 EU/mL. Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. GMCs were calculated using all subjects with available data collected within the specified window for the specified blood draw.
c. n = Number of subjects with valid and determinate assay results for the specified serotype at the specified time point.
d. CIs were back transformations of CIs based on the Student t distribution for the mean logarithm of the titers.
e. GMRs were calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units. GMRs were calculated using combined RSVpreF/Tdap as a numerator and Placebo/Tdap as a denominator.
f. CIs were back transformations of CIs based on the Student t distribution for the mean difference of logarithm of the titers.

The GMRs for anti-PT, anti-FHA and anti-PRN antibodies were all <1 for the comparisons between the RSVpreF 120 µg/Tdap group and RSVpreF 240 µg + $Al(OH)_3$/Tdap group vs. placebo/TdaP.

The observed anti-PT, anti-FHA, and anti-PRN antibody GMCs were lower for the RSVpreF 120 µg/Tdap and RSVpreF 240 µg + $Al(OH)_3$/Tdap groups vs. the placebo/Tdap group. The GMFRs ranged from 4.16 to 6.50 for the 2 RSVpreF groups, while GMFRs for the placebo/Tdap group ranged from 7.14 to 10.22 at 1 month after vaccination.

The primary comparison between immune responses to RSVpreF (RSV A and B) when administered concomitantly with Tdap compared to RSVpreF given alone (RSVpreF/placebo) met the predefined threshold for non-inferiority since the lower bounds of the 2-sided 95% CIs for the GMT ratios (RSVpreF/Tdap groups vs. RSVpreF/placebo groups) were >0.5 and actually exceeded 0.67.

The observed RSV A and RSV B NA_{50} GMTs and the NA_{90} GMTs were each similar for the combined RSVpreF/Tdap groups and the combined RSVpreF/placebo groups before vaccination.

The RSV A and RSV B NA_{50} GMRs for the combined RSVpreF/Tdap groups and the combined RSVpreF/placebo groups were 0.97 and 0.96, respectively, at 1 month after vaccination. The lower bound values of the 2-sided 95% CIs for the RSV A and RSV B NA_{50} GMRs were 0.84 and 0.81, respectively. The RSV A and RSV B NA_{90} GMRs for the combined RSVpreF/Tdap groups and the combined RSVpreF/placebo groups were 0.94 and 0.91, respectively, at 1 month after vaccination. The lower bound values of the 2-sided 95% CIs for the RSV A and RSV B NA_{90} GMRs were 0.82 and 0.78, respectively.

Table 46: RSV Neutralizing Titer GMRs at all Time Points for Combined RSVpreF/Tdap Groups GMTs to Combined RSVpreF/Placebo Group GMTs – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)		
		RSVpreF/Tdap	RSVpreF/Placebo	
RSV Subgroup	Time Point[a]	GMT[b] (n[c]) (95% CI)[d]	GMT[b] (n[c]) (95% CI)[d]	GMR[e] (95% CI)[f]
A - 50%	Before vaccination	1582.6 (272) (1450.3, 1726.9)	1560.6 (271) (1419.4, 1715.8)	
	1 Month after vaccination	22339.0 (272) (20362.3, 24507.6)	22980.1 (270) (20371.3, 25922.9)	0.97 (0.84, 1.13)
B - 50%	Before vaccination	1470.2 (272) (1343.6, 1608.7)	1417.3 (271) (1284.8, 1563.5)	
	1 Month after vaccination	21509.7 (272) (19279.4, 23997.9)	22486.0 (271) (19696.2, 25671.0)	0.96 (0.81, 1.14)
A - 90%	Before vaccination	254.7 (272) (235.0, 276.1)	255.3 (271) (232.9, 279.8)	
	1 Month after vaccination	3315.4 (272) (3030.5, 3627.1)	3527.7 (271) (3160.2, 3937.9)	0.94 (0.82, 1.08)
B - 90%	Before vaccination	234.8 (272) (214.4, 257.2)	228.8 (271) (206.8, 253.2)	
RSV Subgroup	Time Point[a]	GMT[b] (n[c]) (95% CI)[d]	GMT[b] (n[c]) (95% CI)[d]	GMR[e] (95% CI)[f]
	1 Month after vaccination	3457.9 (272) (3095.8, 3862.3)	3779.1 (271) (3338.4, 4278.0)	0.91 (0.78, 1.08)

Abbreviations: GMR = geometric mean ratios; GMT = geometric mean titer; LLOQ = lower limit of quantitation.
Note: RSVpreF/Tdap is the combination of RSVpreF 120 µg/Tdap and RSVpreF 240 µg + $Al(OH)_3$/Tdap groups. RSVpreF/Placebo is the combination of RSVpreF 120 µg/Placebo and RSVpreF 240 µg + $Al(OH)_3$/Placebo groups. The LLOQ values for each neutralization titer were: A-50% = 50, A-90% = 50, B-50% = 70, and B-90% = 55. Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. GMTs were calculated using all subjects with available data collected within the specified window for the specified blood draw.
c. n = Number of subjects with valid and determinate assay results for the specified serotype at the specified time point.
d. CIs were back transformations of CIs based on the Student t distribution for the mean logarithm of the titers.
e. GMRs were calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units. GMRs were calculated using combined RSVpreF/Tdap as a numerator and combined RSVpreF/Placebo as a denominator.
f. CIs were back transformations of CIs based on the Student t distribution for the mean difference of logarithm of the titers.

As in the primary analysis, the results for RSV A and B suggested no important negative effect of TdaP. Furthermore, the observed RSV A and RSV B NA GMFRs ranged from 12.73 to 16.41 across all the RSVpreF formulations, with the greatest response in the RSVpreF 240 µg + $Al(OH)_3$/placebo group.

C3671014

This was a lot-to-lot consistency study in healthy adults aged 18 to ≤49 years. Participants received one of three lots of RSVpreF (120 µg) or placebo and sera were obtained at pre-vaccination and at one month post-vaccination. The primary immunogenicity objective was as follows:

Table 47: The primary immunogenicity objective

Objectives	Estimands	Endpoints
Primary Immunogenicity Section 5.1		
To demonstrate that the immune responses induced by 3 RSVpreF lots (Groups 1, 2, and 3) 1 month after vaccination are equivalent.	• The ratio of neutralizing GMTs obtained 1 month after vaccination for every pair of RSVpreF lots (Group 1/Group 2, Group 1/Group 3, Group 2/Group 3) for RSV A and RSV B neutralization assays, in participants receiving 1 dose of study intervention and in compliance with the key protocol criteria (evaluable participants).	• RSV A and RSV B NTs.

This study was conducted at 17 sites in the United States. For the evaluable immunogenicity population, RSV A and RSV B NA_{50} GMTs were substantially increased from pre- to post-vaccination for each of the 3 RSVpreF lots and this increase was consistent across lots but there was a negligible change in the placebo group. Lot consistency across the 3 RSVpreF lots was achieved in the evaluable immunogenicity population based on a 1.5-fold equivalence margin for both RSV A and RSV B antigens.

Subgroup analyses by sex showed that the ratio of GMTs (GMRs) for RSV A and RSV B at 1 month after vaccination were similar for females and males in the evaluable immunogenicity population and mITT population.

For the evaluable immunogenicity population, the GMFRs for RSV A and RSV B NTs were similar for all 3 RSVpreF lots and ranged from 14.0 to 14.6 for RSV A and 14.2 to 15.1 for RSV B. GMFRs were close to 1 in the placebo group, indicating negligible change from baseline.

For the evaluable immunogenicity population, GMCs of RSVpreF-binding IgG for RSV A and B were substantially increased from before vaccination to 1 month post-vaccination for each of the 3 RSVpreF lots and this increase was consistent across lots. The GMC change from baseline was negligible in the placebo group. The GMFRs of RSVpreF-binding IgG for RSV A and RSV B were similar for all 3 RSVpreF lots and ranged from 15.8 to 16.7 for RSV A and 15.9 to 16.4 for RSV B. GMFRs were close to 1 in the placebo group, indicating negligible change from baseline.

2.6.6. Discussion on clinical efficacy

The applicant sought two indications for use, with final wording as follows:

- Passive protection against lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age following maternal immunisation during pregnancy. See sections 4.2 and 5.1.
- Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

The vaccine is given to adults aged from 60 years or to pregnant individuals with no mention of age, so it includes by default pregnant adolescents. Regardless of age and gender/pregnancy status the same formulation and single dose regimen (120 µg unadjuvanted) applies.

Design and conduct of clinical studies

Selection of doses from immunogenicity data

Immune responses in adults, including older adults

The clinical development programme commenced with an exploration of three dose levels of RSV A and RSV B PreF (30 µg of each, 60 µg of each or 120 µg of each; referred to as 60 µg, 120 µg or 240 µg doses, respectively) administered with and without aluminium hydroxide as adjuvant. In this RSV-experienced population, a single dose was administered with exploration of a second dose in the 240 µg dose groups after 12 months. The primary readout was NA_{50} titres against RSV A and RSV B; the applicant also presented the total NA_{50} titres. The approach taken was appropriate.

Immune responses in pregnant women

Immune responses in pregnant women were explored in the Phase 2b study C3671003, which enrolled only pregnant women, all of whom were aged 18+ years and at 24-36 weeks gestation when vaccinated. The study compared 120 and 240 µg RSVpreF doses, each with and without aluminium hydroxide, with placebo. This design allowed evaluation of the possibility that in pregnant women a higher dose and/or adjuvanted formulation might improve on the immune responses elicited with the selected formulation for older adults (120 µg unadjuvanted) with an acceptable safety profile.

Transfer of neutralizing antibody across the placenta

The Phase 2b study C3671003 described anti-RSV NA titres in infants at birth (cord blood) and at months 1, 2, 4 and 6 after birth. The applicant calculated the transfer ratios based on titres at delivery. The data were then taken into account when selecting the dose for pregnant women.

Concomitant administrations

The FIH study C3671001 included an exploration of co-administration with influenza vaccine depending on age 18-49 years (standard unadjuvanted QIV) or 65-85 years (HD trivalent vaccine). Additional data on co-administration with influenza vaccine came from C3671002 in subjects aged 65-85 years. Study C3671004 in non-pregnant women aged 18-49 years assessed co-administration of the selected RSVpreF formulation with TdaP.

Support for a potentially efficacious dose from the human challenge study

Using a RSV A strain, the study enrolled adults <50 years who received a nasal challenge at 4 weeks after receipt of RSVpreF 120 µg unadjuvanted or placebo. In this RSV-experienced population, it was expected that not all subjects in the placebo group would develop symptomatic infections. The data were analysed using a range of definitions of symptomatic RSV disease and also counting cases with detectable or quantifiable RSV in the various calculations of vaccine efficacy.

Phase 3 efficacy study in adults aged from 60 years

This was the single pivotal vaccine efficacy study to support use in subjects aged from 60 years. The study sites covered N. and S. America, two EU countries, S. Africa and Japan. There was stratification at site-based randomisation with an aim to recruit at least 6,000 in each of the sub-groups 60-69 and 70-79 years and at least 800 aged 80+ years. There was also an aim to recruit at least 10% with stable chronic cardiopulmonary conditions but those with unstable conditions or known to be immunosuppressed were excluded. Generally, the approach taken was acceptable.

The protocol pre-defined acceptable clinical definitions for RSV-LRTI, RSV severe LRTI (sLRTI) and RSV acute respiratory infection (ARI) and required RT-PCR confirmation for RSV. Nevertheless, as these are composite endpoints, a descriptive comparison of the different lower respiratory symptoms/signs leading to RSV-confirmed (severe) LRTI between groups was provided. For the primary efficacy endpoint, only LRTI-RSV with initial symptom onset date between Day 15 (i.e. 14 days after vaccination) and the end of the first RSV season was included in the evaluable efficacy population analysis. Also, only cases with symptom onset prior to 1 year after the vaccination were included as cases in the first RSV season. If the symptom onset is after 1 year, the case was to be counted as being in Season 2, even if it occurred before the study surveillance window during Season 2. The applicant explained that there was no subject with symptom onset after one-year post-vaccination but still within RSV Season 1. Any LRTI-RSV case with a symptom onset date from Day 1 (the day of vaccination) was included in the analysis of cases in the mITT population.

Regarding the respiratory illness visit, which was triggered after the participant experienced 1 or more of the ARI symptoms, it is stated in the protocol that this visit might be conducted as a telephone visit or a clinic or home visit and would occur optimally within 7 days after the onset of the illness. It is unclear how confirmation of respiratory illness and an adequate clinical assessment of the participant (including the collection of temperature, respiratory rate, and oxygen saturation) might have been possible via a telephone visit. The applicant explained that there was no external adjudication committee. In addition, it might have been possible that some subjects could have presented/been taken by relatives directly to a local healthcare facility. There was no exhaustive trawling for cases and there was reliance on subject reporting, supported by the case ascertainment methods put in place. While this situation is perhaps not entirely optimal, the study was double-blind in nature.

This randomised, double blind, placebo-controlled study was designed to estimate the absolute vaccine efficacy of RSVpreF using a case-driven primary analysis based on RSV-LRTI meeting the primary case definitions that required ≥2 or ≥3 of the listed symptoms to be present.

There was a plan for sequential testing of hypotheses such that if the lower bound of the adjusted CI around the point estimate of vaccine efficacy was >20% for RSV-LRTI with ≥2 symptoms, then efficacy was to be estimated for RSV-LRTI with ≥3 symptoms. If the lower bound of the adjusted CI around the point estimate of vaccine efficacy for RSV-LRTI with ≥3 symptoms was >20%, efficacy was to be calculated for severe RSV-LRTI, which was designated as a key secondary endpoint and had the same criterion for concluding on efficacy. Vaccine efficacy against RSV-ARI was a planned secondary analysis but this endpoint was not included in the confirmatory testing strategy. Therefore, the analysis of ARI-RSV was descriptive and prevention of ARI-RSV cannot be claimed in the indication.

The primary analysis method was VE based on the case count ratio using the conditional exact test based on the binomial distribution of the number of cases in the RSVpreF group, given the total number of cases in both groups, without adjustment for prognostic factors and the calculation assumes equal person-time follow-up. The following sensitivity analyses were pre-planned: 1) To assess the

impact of different person-time follow-up between groups, 2) To assess the assumption that the risk of illness is constant over time (Cox regression). The Cox regression relies on the assumption of proportional hazards, i.e. that the relative hazards are constant over time.

The sample size calculation was based on conducting the primary analysis when at least 59 cases of RSV-LRTI with ≥2 symptoms had accrued in the efficacy evaluable population. It was calculated that ~30,000 subjects would be needed to provide 59 such cases, which would then give 90% power to demonstrate that the lower bound of the adjusted CI around the point estimate of vaccine efficacy was >20% assuming that the observed efficacy was at least 70%. However, there was also a planned interim analysis when at least 29 evaluable first-episode LRTI-RSV cases with ≥2 symptoms had been accrued. Moreover, the interim analysis was to estimate efficacy against RSV-LRTI with ≥3 symptoms if at least 15 cases had accrued and against RSV-sLRTI if 12 cases had accrued. Pocock-adjusted CIs were planned to be applied. For 44 cases at interim, the two-sided Type I error would be 0.0334. The Pocock-adjusted CIs have a confidence level of 96.66% (=100%-3.34%) which should be correct at an information fraction of approximately 0.75. The information fraction at interim for the second and third endpoint is unknown as the final analysis is based on the number of events of the first endpoint or the end of season 1.

According to the statistical analysis plan, at the interim analysis the DMC could recommend stopping the study for success (other than completing follow-up of recruited subjects) or could recommend continuing the study until the target number of 59 cases of RSV-LRTI with ≥2 symptoms had accrued. There was no plan or criteria set for possibly stopping the study for futility at the time of the interim analysis. While this would have been appropriate, since there was no preliminary assessment of efficacy in a prior study, the results of the interim analysis (see below) were favourable.

Phase 3 efficacy study in infants born to vaccinated mothers

The Phase 2b study C3671003 evaluated efficacy against RSV in infants as an exploratory endpoint and there were very few cases accrued, with no comment possible. Therefore, C3671008 stands alone to provide the evidence of vaccine efficacy against RSV disease in infants born to vaccinated mothers.

In this randomised, double blind and placebo-controlled study, eligible women were to be between 24 and 36 weeks of gestation based on LMP and the earliest ultrasound conducted with an uncomplicated and natural singleton pregnancy. For purposes of providing a population expected to be adherent to study procedures, these women were to be attending antenatal care with planned delivery in a healthcare facility. This plan was to ensure sample and data collection was as complete as possible. In line with the co-administration data, any TdaP administrations were to be at least 14 days prior to or after RSVpreF and it seems a 7-day window would have applied in case of influenza vaccination.

The protocol defined the infant efficacy endpoints in detail, which were acceptable. It should be noted that these endpoints all involved medically-attended illnesses, defined by any contact with a healthcare professional. By definition, it could happen that severe MA-LRTI cases occur with minimal difference to non-severe MA-LRTI.

A descriptive comparison of the different lower respiratory symptoms/signs leading to RSV-confirmed MA-RTI, MA-LRTI and severe MA-LRTI between groups was provided as requested (analysis of cases within 180 days of birth). For severe MA-LRTI cases in both the placebo and RSV-PreF group, the most frequent symptoms were SpO_2 <93% (61.3% and 68.4%, respectively) and fast breathing (50.0% and 52.6%, respectively). For MA-LRTI cases, the most frequent symptoms were due to fast breathing (64.1% and 57.9%, respectively), chest wall indrawing (44.4% and 40.4%, respectively) or SpO_2

<95% (52.1% and 29.8%, respectively). The applicant further clarified that all cases were PCR-confirmed, that cases could have had more than one symptom and that for almost all symptoms the number of cases with the symptom in the RSVpreF group was less than in the placebo group.

As the definitions of MA-LRTI and severe MA-LRTI are based on MA-RTI and additional conditions, the unlikely case could occur that a severe MA-LRTI event is not considered a MA-LRTI event. The applicant confirmed that any adjudicated severe MA-LRTI case due to RSV was also a MA-LRTI case. Active surveillance commenced with weekly contacts from 72 h after birth and continued until month 6, after which the frequency of contact was reduced to approximately monthly. Care-givers were also able to initiate contact with study staff in case of intervening onset of illnesses potentially meeting the criteria.

An EAC adjudicated all RSV-positive MA-RTI cases through the active follow-up period including all cases occurring up to 180 days after birth.

There were multiple primary efficacy objectives applied to infant RSV cases with parallel primary efficacy endpoints of MA-LRTI and severe MA-LRTI for which there was a Bonferroni multiplicity adjustment procedure. Success of the study required that the lower bounds of the adjusted CIs around the point estimates of vaccine efficacy for either or both endpoints were >20%. Furthermore, for each of these primary endpoints, there was sequential testing for vaccine efficacy based on cases that occurred up to day 90, day 120, day 150 and day 180 after birth. That is, testing for efficacy beyond day 90 required that efficacy was shown based on cases with onset before day 90, and so on for each sequential time point.

A simple 1:1 randomisation between RSVpreF or placebo for study-eligible pregnant women was performed. The randomisation was not stratified for any prognostic variables. In this case-driven study, based on several assumptions regarding accrual and on 60% vaccine efficacy, 6,900 pregnant women were to be enrolled to provide 124 cases of RSV MA-LRTI in their infants with onset within 90 days of birth ensuring power by the exact binomial test of at least 90%. However, the sample size/power calculations did not consider the two possible interim analyses with possible stopping for futility or efficacy.

The primary efficacy analysis was conducted in the evaluable efficacy infant set, which was confined to those born at least 14 days after maternal vaccination and excluded any infants who received an anti-RSV monoclonal antibody. The analysis was repeated using data from the mITT efficacy infant population consisting of all those born to vaccinated maternal participants. This plan was considered acceptable. Intercurrent events include the infant receiving palivizumab or another monoclonal antibody targeting RSV and the infant receiving transfusions of more than 20 mL/kg of any blood products at ≤180 days of age. The applicant planned to use the hypothetical strategy for estimating the vaccine efficacy but seems to have excluded all participants with an intercurrent event similar to a complete case analysis instead of imputing for these participants ("All post discontinuation or post violation observations will be censored"). In a sensitivity analysis, the impact of palivizumab administration was analysed using a composite strategy, i.e. the endpoint analysed was occurrence of either MA-LRTI due to RSV (as defined for the main analysis) or receipt of palivizumab.

Where MA-LRTI and severe MA-LRTI visits had no accompanying valid central RT-PCR or local NAAT test results, positive or negative results were imputed. Based on a blinded review of data at the end of February 2022, approximately 22% of all swabs from MA-LRTI events with valid central laboratory results proved to be RSV-positive so the minority of the missing results was expected to be truly RSV-

positive. For missing RSV swab results which are imputed by multiple imputation under different assumptions, Rubin´s Rules were applied to pool parameter estimates and to derive confidence intervals for RSV positive MA-LRTI and RSV positive severe MA-LRTI.

In a further sensitivity analysis, any test indicating positivity for RSV was to be accepted and used to define MA-LRTI cases if qualified by clinical symptoms. Examples of positive swab results counted in this analysis were local non-NAAT tests, central laboratory PCR tests from samples taken outside the protocol-specified window and centrally-tested swabs that exceeded the documented stability testing duration but were positive.

Interim analyses were planned to assess efficacy and safety after at least 43 cases and/or after at least 62 cases of MA-LRTI due to RSV within 90 days of birth had accrued and results could be used for internal business decisions regarding study planning, stopping for futility or stopping for early success. Only cases that had been fully adjudicated prior to taking a data snapshot were to be included in an interim analysis. The analysis of efficacy was to use an O'Brien-Fleming alpha spending rule based on the fraction of cases of MA-LRTI due to RSV within 90 days available. The exact number of cases at each interim analysis was not fixed and could be decided based on operational reasons. The first interim analysis took place when 56 MA-LRTI cases had accrued through 90 days and the second after 80 RSV-positive MA-LRTI cases within 90 days after birth. In April 2022, an E-DMC reviewed results of the first interim analysis when 56 MA-LRTI cases had accrued through 90 days and recommended continuation of the study.

Testing of the primary endpoints at the interim analysis was to follow the sequence of interval-specific tests. Secondary endpoints were not planned to be tested at the interim analyses. Futility was to be assessed using conditional power.

The alpha levels used at interim and final analyses depends on the exact fraction of cases available at the interim analysis. The first interim analysis was performed after 56 RSV-positive MA-LRTI cases within 90 days after birth and the second interim analysis after 80 RSV-positive MA-LRTI cases within 90 days after birth. It can be followed that the first interim analysis has a 2-sided alpha of 0.0017. The second interim analysis has a 2-sided alpha of 0.010. Using a Bonferroni split, this would lead to 99.5% CIs (i.e. 1-0.0100/2). Nevertheless, it is not allowed to split the nominal alpha at an interim analysis for the two parallel primary endpoints, but a separate group sequential design at 2.5% two-sided significance level each would be needed. The proposed procedure does not conform with the closed testing principle. The applicant claims that the proposed design could control the type I error rate due to the inherent conservatism of the exact binomial test. Starting with a procedure based on the normal approximation is a useful strategy, but then the precise error rates for that design have to be derived by exact calculation. Furthermore, there is no specific case target for the additional primary endpoint of severe MA-LRTI and the same information fraction at interim as for MA-LRTI has to be assumed.

As the proposed design by the applicant was not shown to control type I error rate, the confidence levels of a design which comes closest to what is proposed, but controls the type I error, would be more adequate: A Bonferroni split needs to be performed between the endpoints and then the O'Brien Fleming spending functions applied for each endpoint. Assuming the same information fraction for each endpoint at interim, the first interim analysis with information fraction 56/124 has a 2-sided alpha of 0.0004 for each endpoint and the second interim analysis with information fraction 80/124 has a 2-sided alpha of 0.0036 for each endpoint leading to 99.64% CIs.

It is claimed that since MA-LRTI through 180 days was inspected at the first interim analysis in April 2022 with a 2-sided alpha of 0.0017, the analysis of the primary endpoints at 120 days and later after a successful interim analysis can use a 2-sided alpha of 0.05 - 0.0017 = 0.0483, to be split between the endpoints using the Bonferroni correction (1-0.0483/2=0.97585). This is not the correct nominal significance level and especially does not apply in case of a second interim analysis. A naive strategy of testing other endpoints at full remaining level α whenever the primary endpoint(s) are significant and the trial stops does not maintain the overall type I error rate at level α (Hung *et al*. (*J. Biopharm. Stat.* 2007; **17**:1201–1210)).

The applicant recalculated the confidence intervals for both primary endpoints using 99.64% CIs: as no case target for RSV-positive severe MA-LRTI was specified the same information fraction at interim for RSV-positive severe MA-LRTI as for RSV-positive MA-LRTI is assumed. When assuming minimum information fractions of 0.39 and 0.47 (currently 45% and 65% are used), the CI lower bounds are all above 20% confirming the robustness of results.

The confidence level of 99.17% for the secondary endpoints was derived by splitting half of the two-sided 5% significance level again for the three secondary endpoints (1-0.05/6= 0.9916667). The secondary endpoints have to be tested sequentially, at 90 days, 120 days, 150 days, 180 days, and 360 days for hospitalisation due to RSV and all-cause MA-LRTI and at 210 days, 240 days, 270 days, and 360 days for MA-LRTI due to RSV. However, the secondary endpoints were not planned to be tested at the interim analysis and the ad-hoc adjustment applied by the applicant is not correct. A naive strategy of testing the secondary endpoint family at level α or level α/2 whenever the primary endpoint(s) are significant does not maintain the FWER at level α (Hung *et al*. (*J. Biopharm. Stat.* 2007; **17**:1201–1210). The simulation provided was considered inadequate. Therefore, the overall type I error rate is still not controlled and there is an alpha inflation. As the analysis of all secondary endpoints is considered descriptive, 95% CIs were requested and presented by the applicant.

Efficacy data and additional analyses

Selection of doses from immunogenicity data

Immune responses in adults, including older adults

The FIH study C3671001 suggested that there was no major advantage for the highest dose over the middle dose in either age sub-group (18-49 or 50-85 years; median age in the latter was ~71 years). While titres against RSV B were slightly higher than against RSV A, neither was significantly improved by addition of aluminium hydroxide. The study supported progression with the unadjuvanted 120 µg dose in adults regardless of age. Omission of an adjuvant was further supported by the results of study C3671002 in older adults, which compared two adjuvanted formulations with no adjuvant. This study also reported on CMI, again suggesting no benefit of adjuvantation.

At month 12, NA titres were still higher in the vaccinated groups vs. the placebo recipients. Administration of a further dose of 240 µg resulted in very modest increments in NA in both age subgroups, suggesting that repeat vaccination at one year might not lead to any major enhancement of protection. It remains to be determined if/when a further dose of vaccine may be potentially useful.

Immune responses in pregnant women

The effect of pregnancy on immune responses was not determined in a direct comparison between pregnant and non-pregnant women of comparable ages within a single study. C3671003 enrolled ~115

pregnant adult women per dose group, most of whom were recruited in the US. All doses and formulations of RSVpreF induced RSV A and RSV B NA_{50} increments from baseline with higher GMTs in the RSVpreF group vs. the placebo group from 2 weeks post-dose (peak titres) until 6 months after delivery. Whereas there was some suggestion of an effect of adjuvant in the higher dose group for peak titres, there was no appreciable difference between the 120 µg and 240 µg doses. Furthermore, at one-month post-dose and at delivery, there was not a consistent advantage for the higher dose or for adjuvantation. Furthermore, there was no consistent trend in terms of peak GMTs according to gestational age at time of maternal vaccination. Generally, the findings suggested that 120 µg unadjuvanted could suffice.

The actual anti-RSV A and RSV B NA_{50} GMTs in pregnant women mostly resident in the US who received 120 µg unadjuvanted RSVpreF in this study peaked at week 2 with values of 31871 and 39152, respectively. At one month, the respective GMTs were 24149 and 34397. In non-pregnant female subjects in the US aged 18-49 years enrolled into C3671004 and given any of the four RSVpreF formulations alone, the pre-vaccination NA_{50} GMTs for RSV A and RSV B were very similar to those in the pregnant women (1582 vs. 1574 in pregnant women for RSV A and 1470 vs. 1756 in pregnant women for RSV B). The month 1 NA_{50} GMTs in non-pregnant women were 22339 and 21509, respectively. These month 1 GMTs are also very similar to those reported from the lot consistency study C3671014 in US male and female adults aged 18-49 years. While cross-study comparisons must be viewed with caution, the data suggest that there is not a negative effect of pregnancy on the magnitude of immune response to RSVpreF.

No immunogenicity data have been reported from pregnant adolescents, although subjects aged from 16 years received RSVpreF in C3671008 (and subjects from 14 years received placebo).
With slightly higher immune responses in the younger vs. older adults in the FIH study, and with almost everyone RSV-experienced by the age of 2 years, there is no concern on grounds of efficacy over using the selected adult dose in pregnant adolescents. Therefore, the applicant's indication for use in pregnant individuals without specifying a lower age for use could be acceptable.

Transfer of neutralizing antibody across the placenta

In C3671003, the median gestational age of infants at birth was 39 weeks (range 31-42 weeks). The statistical analysis plan and table footnotes for C3671003 do not actually specify how the transfer ratio was calculated. However, the statistical analysis plan for C3671008 specifies that the transfer ratios are based on NA_{50} titres in infants and their mothers at the time of delivery. Assuming this also applied in C3671003, the transfer ratios were in the range 1.3 to 1.9 and were broadly similar for NA_{50} against RSV A and B as well as between the four RSVpreF groups and the placebo group (i.e. transfer ratio for naturally acquired maternal antibody). The anti-RSV A and B NA_{50} GMTs in infants at birth were broadly comparable across the four RSVpreF groups and >10-fold the GMTs for infants born to unvaccinated mothers. There were at least 8-fold differences for corresponding GMTs at one month of age and at least 5-fold differences at 6 months of age.

With the majority of mothers enrolled in the US, it is not possible to conclude on transfer ratios by hemisphere. When examined by gestation duration at vaccination across the range 27-36 weeks, there was no consistent trend regarding transfer ratios. The relatively few data on infants born within 14 days of maternal vaccination did suggest lower transfer ratios but the transfer ratios for those born <30 or >30 days from time of maternal vaccination in the 120 µg unadjuvanted group and placebo group suggested higher transfer ratios for those born within 30 days.

At month 6 the GMTs for RSV A and B for infants born to mothers who had received 120 µg unadjuvanted RSVpreF (1529 and 1609, respectively) were ~7-fold those for infants born to mothers assigned to placebo (233 and 221, respectively). In the infants born to mothers given 120 µg unadjuvanted RSVpreF, these month 6 GMTs of 1529 and 1609 resembled the pre-vaccination GMTs of their RSV-experienced mothers (1574 and 1756, respectively). As mentioned above, while there was some suggestion of an effect of adjuvant in the higher dose group for peak titres in pregnant women, this did not translate into higher GMTs in their infants. These findings supported selection of the 120 µg unadjuvanted dose for pregnant women.

Concomitant administrations

In the FIH study, there was no consistent negative effect of co-administration of 240 µg RSVpreF with seasonal influenza vaccines on the immune responses to RSVpreF. However, co-administration gave a general trend to lower HAI titres especially in the younger age subgroup, noting that the two age subgroups received different seasonal influenza vaccines. Additional data for HD seasonal influenza vaccine in subjects aged 65-85 years in C3671002 suggested no major effect of RSVpreF co-administration on HAI titres in this age range.

To further investigate co-administration with seasonal influenza vaccines, the applicant conducted a Phase 3 study C3671006 in ~1400 healthy Australian adults aged 65+ years who received RSVpreF + SIIV together or in a staggered fashion. Data from this study were provided at day 91 and indicated a consistent numerical reduction in GMTs for NA against RSV A and B as well as for HAI titres on co-administration of RSVPreF with an adjuvanted quadrivalent inactivated seasonal influenza vaccine although all the lower bounds of the 95% CI around the GMT ratios exceeded 0.67. Overall, there is no reason to preclude co-administration of RSVpreF with SIIV but section 4.5 needs to be re-worded to reflect the evidence provided.

In non-pregnant women aged 18-49 years, co-administration with Tdap was initially analysed using data from the combined RSVpreF groups (i.e. 240 µg adjuvanted and 120 µg unadjuvanted RSVpreF combined) vs. the placebo group. The data for the combined RSVpreF groups and for the selected RSVpreF formulation group compared to respective groups that received concomitant Tdap indicated no negative effect on anti-RSV A and B NA based on the pre-defined non-inferiority criteria.

For anti-T and anti-D, the majority of subjects already had >0.1 IU/mL prior to vaccination, which somewhat limits any conclusion based on results that showed the pre-defined non-inferiority criteria were met. For proportions with >1.0 IU/mL anti-D, there was an imbalance between groups at pre-vaccination with 26% and 18% in the RSVpreF and placebo groups, respectively. At post-vaccination, the proportions were 51% vs. 77%, which raises some potential that RSVpreF exerts negative interference on the anti-D response.

Furthermore, the comparison of proportions with at least 1.0 IU/mL anti-D made between the selected RSVpreF formulation (120 µg) and the placebo group (Tdap alone) suggested a negative effect of co-administration (from 24% to 53% in the co-administration group vs. 17.9% to 77% in the Tdap alone group). The GMCs and RCDs are not included in the CSR.

Using the combined results from RSVpreF groups, non-inferiority was not shown for anti-PT, anti-FHA and anti-PRN immune responses since the lower bounds of the 2-sided 95% CIs for the GMC ratios of the combined RSVpreF/Tdap groups to the placebo/Tdap group did not exceed 0.67 (they ranged from 0.48 to 0.64). When the comparison was made between the selected RSVpreF formulation and Tdap alone, the lower bounds of the CIs were 0.68 for anti-PT, 0.52 for anti-FHA and 0.45 for anti-PRN. In

the Phase 3 study C3671008 at least 2 weeks was to elapse between administration of RSVpreF and Tdap. Section 4.5 of the SmPC should advise that at least 2 weeks elapse between administrations of RSVpreF and TdaP.

Selection of a potentially efficacious dose from the human challenge study

Of the 31 subjects challenged per group and applying various definitions of symptomatic infection as well as considering those with detectable or quantifiable RSV as cases in different analyses, <60% in the placebo group were counted as cases in the different calculations of vaccine efficacy.

Regardless of the case definition applied, the estimates of RSVpreF efficacy were from 86.7% to 100% and the lower bounds of the 95% CI around these estimates all fell above 53%. Correspondingly, prior vaccination was shown to reduce viral loads in nasal washes (based on qRT-PCR) and to reduce the overall symptom scores.

In these UK residents, selected for having pre-study NA titres in the lowest quartile, the pre-vaccination and pre-challenge (i.e. one month post-vaccination) RSV A NA_{50} GMTs were lower than those recorded in pregnant women in C3671003 (mostly enrolled in the US) while the RSV B GMTs were only slightly lower. The same pattern applied when comparing NA_{50} GMTs between these UK subjects and the younger cohort of male and non-pregnant female US subjects in the same age range who received the 120 µg unadjuvanted formulation in C3671001.

In the older cohort in C3671001 (50-85 years; again, US only), the pre-vaccination NA_{50} GMTs were higher than in the younger cohort while the GMTs at one month in the group that received the 120 µg unadjuvanted formulation were very similar to those in the younger cohort in the same study. In these older US subjects, the month one post-vaccination RSV A NA_{50} GMT was higher than for UK subjects but the RSV B NA_{50} GMTs were broadly comparable.

Generally, the data on vaccine efficacy against symptomatic infections in adults 18-50 years gives support to the selection of the 120 µg RSVpreF formulation for pregnant women and for older adults.

An interesting observation from the RSV A and B NA_{50} GMTs in these UK adults is that the GMTs dropped from pre-challenge to day 12 and onwards post-challenge, so exposure to the challenge strain did not further augment the systemic humoral response. In contrast, challenge with RSV A did result in increases in GMTs for RSV A and B in the placebo group at day 12, followed by a decline thereafter. However, the day 12 GMTs in the placebo group were still lower (~10%) than the day 12 GMTs in the vaccinated group.

Phase 3 efficacy study in adults aged from 60 years

By mid-July 2022, more than 34,000 subjects had been randomised and treated and 94% were still being followed in the study. Most of the withdrawals were due to the subject and there were no important differences in rates or reasons for withdrawal between the vaccine and placebo groups. The majority (>22,000; ~60%) was enrolled in N. America, followed by ~8000 (~21%) in Argentina. Only ~1000 (~3%) were enrolled in S. Africa. While the majority was aged 60-69 years (~21,000), ~11,000 were aged 70-79 years and >900 subjects in each group (~6%) was 80+ years. Just over half had at least one of the pre-specified significant underlying conditions.

Although 213 (0.6%) subjects somehow managed to enrol at more than one site, and so received more than one dose of assigned treatment, these subjects were balanced between the two groups and

were removed from the primary analysis population. Other important protocol deviations were also balanced between treatment groups, noting that those who received assigned treatment that had not been stored adequately were removed from the primary analysis population. The poor protocol adherence at site 1227 did not affect the analyses of efficacy since no cases were reported from this site. Ultimately, 95% of randomised subjects in each group were eligible for the evaluable efficacy population.

The latest version of the SAP (version 4) was dated on 22 Jul 2022 and thus after the cut-off dates for the study report.

The applicant states that the data snapshot for the 13 July 2022 data cut-off occurred on 05 August 2022, i.e. after the SAP amendment and the SAP change was not informed by study results.

The planned interim efficacy analysis was conducted when 44 first-episode LRTI-RSV cases with ≥2 symptoms had accrued in the first RSV season through the surveillance cut-off date of 08 July 2022. At this time, the mean surveillance duration was 206 days in both treatment groups. All study participants remained in blinded follow-up after the interim analysis. Based on this analysis, vaccine efficacy was 66.7% with a lower bound of the 96.66% CI >28%. The graphical display of cases indicates that the benefit of RSVpreF was apparent very shortly after commencement of active surveillance and, based on available follow-up data, was maintained at one year.

The majority of cases was due to RSV B and the study was not powered for efficacy analyses by subtype. Nevertheless, using the standard method of calculating vaccine efficacy, the point estimates and 96.66% CI were 88.9 (10.6, 99.8) for RSV A and 56.5 (-0.7, 82.8) for RSV B. The inconsistency in results for the RSV A and RSV B subgroups for LRTI-RSV cases with ≥2 symptoms was not observed for LRTI-RSV cases with ≥3 symptoms or ARI. Therefore, the numerical differences on point estimate of subgroup A and subgroup B for LRTI-RSV cases with ≥2 symptoms at interim analysis were attributed to the small case numbers.

In the evaluable efficacy population there were 45 participants with 46 episodes of LRTI-RSV cases with ≥2 symptoms reported after vaccination (Day 1). Therefore, one participant experienced, 2 episodes within one RSV season. The applicant explained that the participant who experienced two LRTI episodes within one RSV season was in the placebo group and had an ongoing medical history of asthma and allergic rhinitis. The two episodes were divided by a symptom free period of 8 days, which by definition in the SAP specifies them as two different episodes. However, it is agreed that this might represent a single episode of a respiratory illness.

There were 16 first-episode RSV-LRTI cases with ≥3 symptoms, reported as the first episode from Day 15 (1 episode was reported before Day 15), using the same cut-off date, so the interim analysis of that endpoint was conducted at the same time as for RSV-LRTI cases with ≥2 symptoms. With only 2/16 cases in the RSVpreF group, vaccine efficacy was 85.7% and the lower bound of the 96.66% CI was 32%. Of the 16 cases, 11 were due to RSV B, with vaccine efficacy at 90% (96.66% CI 21.8, 99.8). For RSV A, it can only be observed that 3 of the 4 cases occurred in the placebo group. The benefit of vaccination for this endpoint was apparent from ~day 45 post-vaccination onwards and was maintained using all available one-year follow-up data.

The exploration of vaccine efficacy against RSV-LRTI in subgroups gave point estimates (noting that the CIs were wide or very wide and the lower bound was >0 only for Whites, which accounted for the majority of the study population) that suggested no important effect of gender and no decrease in

efficacy with increasing age. The point estimate for vaccine efficacy was <0 only for Black or African American subjects.

Overall, the interim analysis demonstrated that RSVpreF is efficacious in preventing RSV-LRTI from day 15 post-vaccination onwards. The number of cases of severe RSV-LRTI accrued as of the cut-off date was <12 so no analysis was conducted and no claim for prevention of severe cases is made by the applicant. In any case, efficacy against severe RSV-LRTI can only be determined from the proportion of breakthrough cases of RSV-LRTI in the vaccine (total 11) and placebo (total 33) groups that met the criteria for classification as severe. The higher the vaccine efficacy, the less likely it is that any severe cases will occur in vaccinated individuals. Moreover, the shorter median duration per episode (10.5 days among vaccine breakthrough cases compared to 15.5 days for placebo group cases) points to some amelioration effect in the vaccine group. The applicant provided the planned analysis of vaccine efficacy against the secondary endpoint of severe RSV-LRTI. There were only two severe LRTI-RSV cases, both in the Placebo group. Due to the low number of cases, the estimated VE of 100% is not robust and no meaningful conclusion on VE against severe cases can be drawn.

Having reached the success criteria for the primary analyses of RSV-LRTI, the applicant analysed the secondary endpoint of RSV-ARI. With 22 RSVpreF vs. 58 placebo group cases, the point estimate of vaccine efficacy was 62% and the lower bound of the 95% CI was 37%, which supports a conclusion that RSVpreF also has an effect on preventing any RSV ARI cases. The results by RSV subtype supported an effect on RSV ARI due to RSV A or B although, again, for RSV A this is based on the numerical difference in small numbers. However, this was a secondary analysis for which the study was not powered and for which there is no evidence that Type 1 error was controlled.

Follow-up of the study population was ongoing at the time of filing the MAA. In the responses at day 91, the applicant provided data for the end of season 1 (EOS1) analysis. There were 15 first-episode LRTI-RSV cases with ≥2 symptoms in the RSVpreF group and 43 in the placebo group in the evaluable efficacy population that occurred from Day 15, corresponding to a VE of 65.1% (95% CI: 35.9%, 82.0%) for RSVpreF based on the risk ratio. For RSV A, VE for LRTI-RSV with ≥2 symptoms was 81.3% (95% CI: 34.5%, 96.5%) based on 3 cases in the RSVpreF group and 16 cases in the placebo group. For RSV B, VE for LRTI-RSV with ≥2 symptoms was 53.8% (95% CI: 5.2%, 78.8%) based on 12 cases in the RSVpreF group and 26 cases in the placebo group.

Through the EOS1, there were 2 first-episode LRTI-RSV cases with ≥3 symptoms in the RSVpreF group and 18 in the placebo group in the evaluable efficacy population that occurred from Day 15, corresponding to a VE of 88.9% (95% CI: 53.6%, 98.7%) for RSVpreF based on risk ratio. For RSV A, VE for LRTI-RSV with ≥3 symptoms was 80.0% (95% CI: -78.5%, 99.6%) based on 1 case in the RSVpreF group and 5 cases in the placebo group. For RSV B, VE for LRTI-RSV with ≥3 symptoms was 91.7% (95% CI: 43.7%, 99.8%) based on 1 case in the RSVpreF group and 12 cases in the placebo group.

It was concluded that the VE estimated from the EOS1 analysis was similar to VE at interim analysis for both LRTI-RSV with ≥2 symptoms and ≥3 symptoms.

In addition, the applicant provided the immunogenicity subset results. The immunogenicity subset included participants enrolled only from the US and Japan and sera were not obtained from a randomly selected subset. In the RSVpreF group, geometric mean fold rises (GMFRs) of neutralizing titres (NTs) for RSV A, RSV B, and combined RSV A/B were 11.6, 12.7, and 12.1, respectively. GMFRs were close to 1 in the placebo group, indicating negligible change from baseline.

For subgroup analyses by sex, GMFRs of NTs for RSV A, RSV B, and combined RSV A/B trended higher for females (range: 14.1 to 14.8) than males (range: 10.4 to 11.7). For age group, race and prespecified significant conditions, neutralizing antibody GMTs and GMFRs for RSV A, RSV B and

combined RSV A/B were generally similar to those observed in the main analyses and did not identify any clinically meaningful differences between subgroups (for those with enough participants for the analysis). At baseline and 1-month after vaccination time points, GMTs were lower for participants who were Non-Hispanic/Non-Latino versus Hispanic/Latino and for Japanese versus US subjects.

When also viewed in light of the subgroup analyses of efficacy, there were no concerns raised by the immunogenicity data reported overall or by subgroup.

Phase 3 efficacy study in infants born to vaccinated mothers

The results reported in the CSR of December 2022 reflect the second interim efficacy analysis, which was conducted following the predicted end of the fourth RSV season and included 80 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth, of which 39 were severe MA-LRTI.

The results led the E-DMC to recommend stopping the study because the success criterion was met for one of the two primary efficacy endpoints. At the time of data cut-off, >75% of the 7392 pregnant women had completed the study and almost 80% of their infants had completed at least to month 6.

Only cases that had been fully adjudicated prior to taking a data snapshot were included in an interim analysis.

Enrolment for maternal participants was completed on 03 Oct 2022, i.e. after the data cut-off on 30 Sep 2022 used for the second interim analysis. The participants already vaccinated and randomised were still followed-up for study completion after the decision to stop study recruitment. The applicant provided the final results of analyses including all participants recruited and randomised.

Just over half of the adolescent and adult females (aged from 14-47 years) had been vaccinated between weeks 24 and 32 and ~45% between weeks 32-36. In this global study, the majority was White and Caucasian, reflecting the fact that the majority was enrolled in the US. Most infants were born at term (≥93.7% born at ≥37 weeks to <42 weeks) while most of the pre-term infants were near-term at birth (≥4.4% were ≥34 to <37 weeks GA). Less than 2% were excluded from the primary analysis because they were born less than 2 weeks after maternal vaccination. For maternal participants, non-study vaccines most commonly received in the antenatal period were Tdap-containing vaccines (48.5%), inactivated influenza vaccines (28.6%) and SARS-CoV-2 vaccines (25.1%).

Of the 80 cases of RSV MA-LRTI with onset within 90 days of birth, 24 occurred in infants born to mothers given RSVpreF and 56 to mothers given placebo, giving a point estimate of vaccine efficacy at 57.1% and 99.5% CI 14.7, 79.8. Thus, the pre-defined lower bound criterion for success (>20%) was not met even though the lower bound was compatible with a conclusion of superiority for maternal vaccination vs. no vaccination. Although it was understood from the protocol that testing at sequential time points would not occur if the pre-defined criterion for success was not met at the prior time point, the CSR shows sequential analyses. The point estimate of vaccine efficacy remained >50% at days 120, 150 and 180 although there was a small decline to 51.3% at day 180 and the lower bounds of the 97.58% CI were from 28-31%. A time-trend of decreasing VE is observed in the point estimates of the different observation times. The graphical display showed separation of the curves from ~2 weeks after birth onwards. Results for the mITT population were similar.

As confidence levels of 99.5% were wrongly calculated, the applicant recalculated the confidence intervals for both primary endpoints using 99.64% CIs. Concerning the fulfilment of success criteria not much changes, MA-LRTI has a lower bound of the 99.64% CI less than 20% for 90d, but higher for 120d, 150d and 180d, all lower bounds are higher than 0%. For the severe MA-LRTI endpoint, the success criterion of a lower bound of the CI greater than 20% was met for all time-points with this wider CI.

Since the overall type I error rate was not controlled for the RSV-positive MA-LRTI endpoint at the later time-points, it cannot be guaranteed that observed data are not chance results. For MA-LRTI due to RSV within 210, 240, 270 and 360 days after birth, the statistical criterion for success for this endpoint (a CI lower bound >0%) was met using 99.17% CIs.

When all positive RSV tests were considered, including non-NAAT tests, the results were similar to the primary analysis, i.e. success criterion not met at day 90 but met thereafter. After imputation of swab results using the missing-at-random assumption, 17.2% of the 90-day result imputations had a 99.5% CI lower bound >20%. Using Rubin´s Rules to derive estimates and confidence intervals with multiple imputation under the MAR assumption, the lower bounds of the CIs for the RSV positive MA-LRTI endpoint are higher due to the higher number of events. Even the LB at 90 days is >20% for both the 95% and the 99.5% confidence levels, but slightly less than 20% for the 99.64% confidence level. With multiple imputation under MNAR, the lower bounds of the CIs are still >0%, but the LBs of the 99.64% CIs get below 20% almost right away with higher vaccine group positivity rates. For missing RSV swab results which are imputed by multiple imputation, robustness of results was shown for the RSV positive severe MA-LRTI endpoint.

Of the 80 cases of RSV MA-LRTI with onset within 90 days, 39 (6 in infants born to vaccinated mothers and 33 in those born to unvaccinated mothers) met the criteria for severe cases. Vaccine efficacy against severe RSV MA-LRTI fell from 81.8% at day 90 to 69.4% at day 180 but the lower bounds of the 99.5% and 97.58% CIs were >40% at each time point and the 99.64% CIs were >30% at each time point till day 180. Results were similar for the mITT population. When all positive RSV tests were considered, including non-NAAT tests, results were similar to the primary analysis. The analyses based on imputations of missing swab results also supported the primary analysis.

At Day 129, the applicant proposed a revised indication for prevention of lower respiratory tract disease caused by RSV in infants from birth through the first RSV season, which is based on numbers of cases accrued beyond day 180. For severe MA-LRTI the endpoints beyond 180 days were only exploratory study endpoints. The secondary endpoints MA-LRTI beyond 180d were not planned to be tested at an interim analysis according to protocol or SAP. Study RTI visits were performed until at least 6 months after delivery for MA-RTIs of any severity, and from 6 months through study completion for MA-RTI events that resulted in hospitalisation or met severe criteria. After Visit 3 at month 6, the study schedule mentions only a visit or telephone contact at 12, 18 and 24 months; there is no indication how cases occurring after the end of active surveillance at month 6 was captured. Maternal antibody was not expected to persist in infants beyond 3-6 months. To claim protection from birth through the first season of RSV in the EU, where the disease is strongly seasonal in nature, the data would have to cover an infant born in ~April of year 1 to the end of the Year 1/year 2 season the following April, i.e. over ~365 days. Therefore, it was not agreed that a claim can be made in section 4.1 that such a duration of protection is achieved.

The subgroup analyses must be viewed with caution due to small or very small denominators in many cases. There appeared to be at least a numerical benefit for RSVpreF for RSV MA-LRTI regardless of maternal vaccination between weeks 24-28, 28-32 or 32-36 weeks of gestation. However, VE for infants born to mothers given the vaccine in the period 24-28 weeks of gestation was substantially lower compared to those immunised after week 28. This information should not preclude use before 28 weeks but the data have been described in section 5.1.

When viewed by country, the largest proportion of pregnant women was enrolled in the US, where 17 cases accrued (2 RSV Pre F) by day 90, giving a point estimate of vaccine efficacy against RSV MA-LRTI at 86.8% (95% CI 43.4, 98.5). There were no cases recorded in several participating countries before day 90, possibly reflecting the success of COVID-19 restrictions and parental caution. Whereas similar numbers were enrolled in Argentina and S. Africa, vaccine efficacy by day 90 was shown only in

Argentina (65.5%; 15.1, 87.7) and there was no apparent benefit in S. Africa (with 8 cases in the vaccine group and 6 cases in the placebo group). Moreover, these day 90 data led to a clear picture of vaccine efficacy shown only in the upper income countries.

However, as time passed and cases accumulated, a numerical benefit for infants born to vaccinated mothers began to emerge in several countries with no or very few cases at earlier time points and case rates were lower vs. placebo group infants even in S. Africa. Also, breastfeeding did not seem to have an important effect on vaccine efficacy. When efficacy against RSV A and B was evaluated separately, the majority of cases were due to RSV B, in keeping with C3671013 in older adults. For cumulative cases up to day 180, efficacy against RSV MA-LRTI was ~27% for RSV A (19 vs. 26 cases) and ~56% for RSV B (38 vs. 87 cases). However, efficacy against severe RSV MA-LRTI was 50% for RSV A (7 vs. 14 cases) and 75% for RSV B (11 vs. 44 cases).

The RSV A subgroup has a consistently lower VE compared to the RSV B subgroup for both MA-LRTI and severe MA-LRTI. In addition, in infants born to RSVPreF vaccinated mothers (in study -003) 50% neutralizing GMTs at birth were lower against RSV-A (GMT (95% CI) of 22904 (18639; 28148)) compared to RSV-B (GMT (95% CI) of 30195 (24309; 37506)). Nevertheless, point estimates are directionally favorable for both RSV subgroups and in the absence of a threshold of protection differences in neutralizing titers against RSV A and B are difficult to interpret clinically. It should be noted that the RSV subgroup was not determined for all cases that met the clinical criteria and were laboratory-confirmed. It cannot be ruled out that some bias could have occurred in reporting of subtypes depending on the assay performance (e.g. if subtyping required a minimum amount of virus to be present and viral load was more likely to be higher in infants born to mothers given placebo).

With even fewer cases of severe RSV MA-LRTI recorded, even greater caution is required when viewing the subgroup analyses. However, a similar pattern emerged, with a numerical benefit evident even in S. Africa especially from D120 onwards.

2.6.7. Conclusions on the clinical efficacy

The final indication wordings proposed by the applicant are acceptable to the CHMP.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Population 60+ years of age

In Study C3671013, 17,215 participants received RSVpreF 120 µg and 17,069 received placebo. As of the cut-off date, 13,273 (77.1%) and 13,122 (76.9%) in respective groups had completed the 6-month safety follow-up visit. Analyses of reactogenicity were based on the e-diary subset safety population (3,630 RSVpreF: 3,539 placebo), consisting of all participants included in the reactogenicity subset who received the study intervention and with at least 1 day of e-diary data transferred.

Pregnant women

Among pregnant individuals, 4144 received any dose level/formulation of RSVpreF and 3797 received RSVpreF 120 µg. The median follow-up time after vaccination was 8.13 months (range: 0-20) and ≥6 months follow-up safety data were available for 3637 (87.8%).

There were 3682 live infants born to mothers who received RSVpreF 120 µg. The median follow-up time after birth was 11.70 months (range: 0-24.3) and ≥6 months follow-up safety data were available for 3069 (83.4%).

2.6.8.2. Adverse events

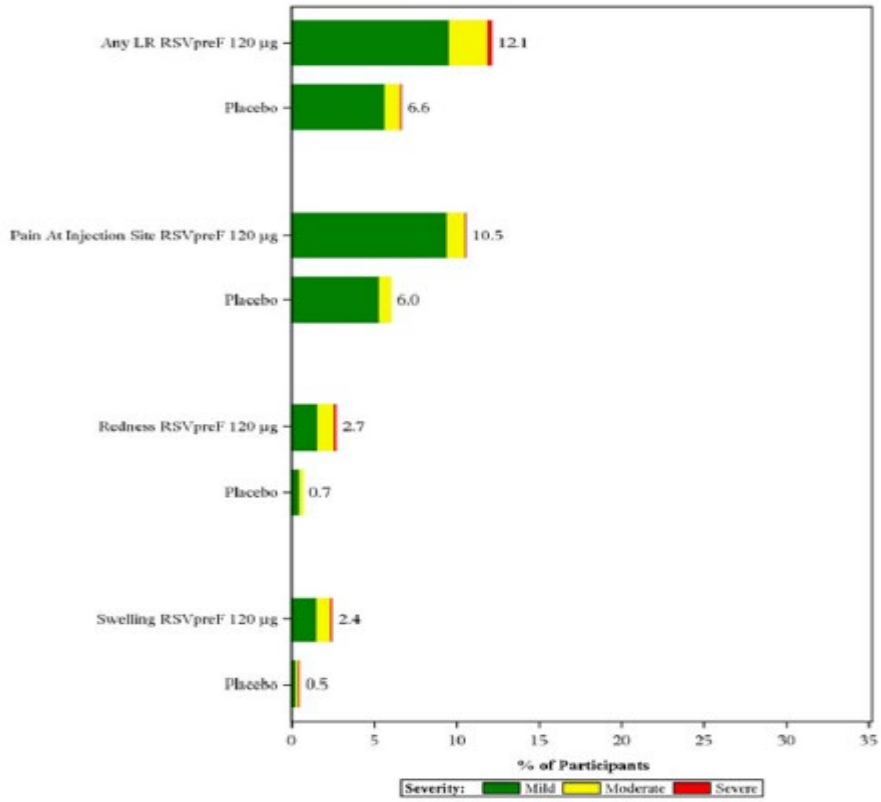
Adverse events within 7 days after vaccination

Older Adults

The proportion that reported local reactions within 7 days after vaccination was higher in the RSVpreF group (12.1%) compared to the placebo group (6.6%). The most frequently reported local reaction in both groups was pain at the injection site, reported by 10.5% in the RSVpreF group and 6.0% in the placebo group. Most local reactions were mild or moderate in severity. A total of 8 (0.2%) and 2 (<0.1%) participants in the RSVpreF and placebo groups, respectively, reported severe local reactions.

Observations generally suggested no clinically meaningful differences by subgroup. Any local reaction was reported by 15.7% of females vs. 8.8% of males in the RSVpreF group whereas rates in the placebo group were 6.4% vs. 6.9%, respectively. The reporting rates were higher for females than males in the RSVpreF group for each type of local reaction.

Figure 25: Local Reactions, by Maximum Severity, Within 7 Days After Vaccination – E-Diary Subset Safety Population

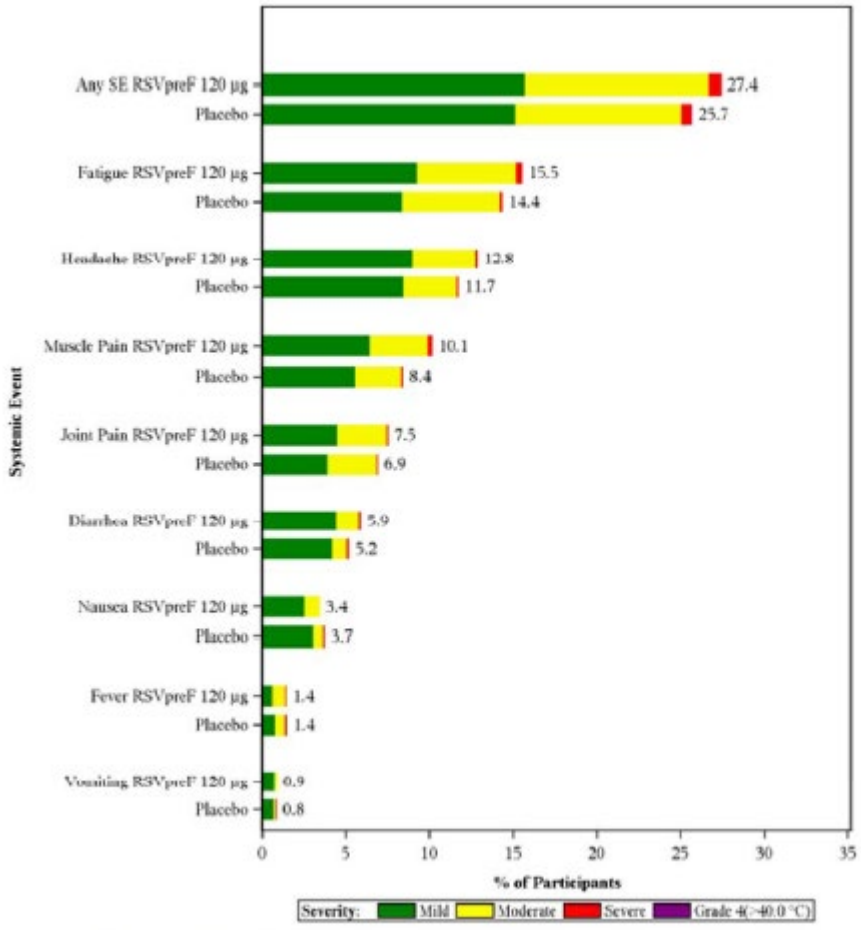


The proportions that reported systemic reactions within 7 days after vaccination were similar in the RSVpreF (27.4%) and placebo (25.7%) groups. The most frequently reported was fatigue (15.5% in the RSVpreF group and 14.4% in the placebo group). Most systemic reactions were mild or moderate in severity. The proportions with severe systemic reactions were similar in the RSVpreF (0.7%) and placebo (0.6%) groups. The most frequently reported severe systemic reaction in both groups was fatigue (≤0.3% across both groups).

The incidence of fever was low (1.4% of participants in each group) and most reports of fever were mild (≥38.0°C to 38.4°C) or moderate (>38.4°C to 38.9°C) in severity.

The reporting rate for any systemic event was higher for females (32.6%) than males (22.7%) in the RSVpreF group. This pattern was also observed in the placebo group (29.8% of females vs. 21.6% of males). Results for each type of systemic reaction were similar for the RSVpreF and placebo groups.

Figure 26: Systemic Events, by Maximum Severity, Within 7 Days After Vaccination – E-Diary Subset Safety Population



Pregnant individuals

For any dose level/formulation of RSVpreF, the proportions reporting local reactions within 7 days after vaccination were 43.3% in the pooled RSVpreF group vs. 10.5% in the placebo group. The most frequently reported local reaction in both groups was injection site pain (41.5% in the pooled RSVpreF group and 10.2% in the placebo group). Most local reactions were mild or moderate in severity. There were 14 (0.3%) participants in the pooled RSVpreF group and none in the placebo group that reported severe local reactions.

The safety profile of RSVpreF 120 µg in pregnant women was similar to that observed in pregnant women who received any dose level/formulation of RSVpreF. Also, reporting rates were comparable between pregnant and non-pregnant women.

Table 48: Local Reactions, by Maximum Severity, Within 7 Days After Vaccination from eDiary or Adverse Events CRF - All Maternal and All Female Participants - Safety Population

	All Maternal Participants			All Female Participants		
Local Reaction	Pooled RSVpreF[a] (N[b]=4122) n[c] (%) (95% CI)[d]	RSVpreF 120 µg (N[b]=3777) n[c] (%) (95% CI)[d]	Placebo (N[b]=3756) n[c] (%) (95% CI)[d]	Pooled RSVpreF[a] (N[b]=5522) n[c] (%) (95% CI)[d]	RSVpreF 120 µg (N[b]=4576) n[c] (%) (95% CI)[d]	Placebo (N[b]=4066) n[c] (%) (95% CI)[d]
Redness[e]						
Any	286 (6.9) (6.2, 7.8)	270 (7.1) (6.3, 8.0)	9 (0.2) (0.1, 0.5)	388 (7.0) (6.4, 7.7)	337 (7.4) (6.6, 8.2)	12 (0.3) (0.2, 0.5)
Mild	195 (4.7) (4.1, 5.4)	185 (4.9) (4.2, 5.6)	4 (0.1) (0.0, 0.3)	259 (4.7) (4.1, 5.3)	227 (5.0) (4.3, 5.6)	7 (0.2) (0.1, 0.4)
Moderate	85 (2.1) (1.7, 2.5)	79 (2.1) (1.7, 2.6)	5 (0.1) (0.0, 0.3)	117 (2.1) (1.8, 2.5)	99 (2.2) (1.8, 2.6)	5 (0.1) (0.0, 0.3)
Severe	6 (0.1) (0.1, 0.3)	6 (0.2) (0.1, 0.3)	0 (0.0, 0.1)	12 (0.2) (0.1, 0.4)	11 (0.2) (0.1, 0.4)	0 (0.0, 0.1)
Grade 4	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)
Swelling[e]						
Any	248 (6.0) (5.3, 6.8)	231 (6.1) (5.4, 6.9)	8 (0.2) (0.1, 0.4)	364 (6.6) (6.0, 7.3)	301 (6.6) (5.9, 7.3)	10 (0.2) (0.1, 0.5)
Mild	166 (4.0) (3.4, 4.7)	154 (4.1) (3.5, 4.8)	5 (0.1) (0.0, 0.3)	227 (4.1) (3.6, 4.7)	194 (4.2) (3.7, 4.9)	6 (0.1) (0.1, 0.3)
Moderate	78 (1.9) (1.5, 2.4)	73 (1.9) (1.5, 2.4)	3 (<0.1) (0.0, 0.2)	131 (2.4) (2.0, 2.8)	103 (2.3) (1.8, 2.7)	4 (<0.1) (0.0, 0.3)
Severe	4 (<0.1) (0.0, 0.2)	4 (0.1) (0.0, 0.3)	0 (0.0, 0.1)	6 (0.1) (0.0, 0.2)	4 (<0.1) (0.0, 0.2)	0 (0.0, 0.1)
Grade 4	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)
Pain at injection site[f]						
Any	1711 (41.5) (40.0, 43.0)	1521 (40.3) (38.7, 41.9)	384 (10.2) (9.3, 11.2)	2422 (43.9) (42.5, 45.2)	1864 (40.7) (39.3, 42.2)	446 (11.0) (10.0, 12.0)
Mild	1493 (36.2) (34.8, 37.7)	1345 (35.6) (34.1, 37.2)	352 (9.4) (8.5, 10.3)	2036 (36.9) (35.6, 38.2)	1623 (35.5) (34.1, 36.9)	407 (10.0) (9.1, 11.0)
Moderate	211 (5.1) (4.5, 5.8)	172 (4.6) (3.9, 5.3)	32 (0.9) (0.6, 1.2)	376 (6.8) (6.2, 7.5)	236 (5.2) (4.5, 5.8)	39 (1.0) (0.7, 1.3)
Severe	7 (0.2) (0.1, 0.3)	4 (0.1) (0.0, 0.3)	0 (0.0, 0.1)	10 (0.2) (0.1, 0.3)	5 (0.1) (0.0, 0.3)	0 (0.0, 0.1)
Grade 4	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)
Any local reaction[g]						
Any	1785 (43.3) (41.8, 44.8)	1593 (42.2) (40.6, 43.8)	394 (10.5) (9.5, 11.5)	2517 (45.6) (44.3, 46.9)	1951 (42.6) (41.2, 44.1)	457 (11.2) (10.3, 12.3)
Mild	1471 (35.7) (34.2, 37.2)	1324 (35.1) (33.5, 36.6)	358 (9.5) (8.6, 10.5)	2000 (36.2) (34.9, 37.5)	1596 (34.9) (33.5, 36.3)	413 (10.2) (9.2, 11.1)
Moderate	300 (7.3) (6.5, 8.1)	258 (6.8) (6.0, 7.7)	36 (1.0) (0.7, 1.3)	495 (9.0) (8.2, 9.7)	339 (7.4) (6.7, 8.2)	44 (1.1) (0.8, 1.5)
Severe	14 (0.3) (0.2, 0.6)	11 (0.3) (0.1, 0.5)	0 (0.0, 0.1)	22 (0.4) (0.2, 0.6)	16 (0.3) (0.2, 0.6)	0 (0.0, 0.1)
Grade 4	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)

For those who received any dose level/formulation of RSVpreF, the reporting rates for systemic reactions within 7 days after vaccination were 65.0% in the pooled RSVpreF group and 60.1% in the placebo group. The most frequently reported systemic reaction was fatigue (46.3% in the pooled RSVpreF group and 43.9% in the placebo group), but it should be noted that fatigue was reported at similar rates in both groups before and after vaccination in C3671008. Most systemic reactions were mild or moderate in severity while proportions with severe systemic reactions were similar in the pooled RSVpreF (2.4%) and placebo (2.4%) groups. The incidence of fever was low and similar for both groups (≤2.9%) and most reports were ≤38.9°C. Muscle pain was reported more frequently in the RSVpreF group (27.5%) compared to the placebo group (17.0%), as was headache (31.2% vs. 27.5%). The safety profile of RSVpreF 120 µg was similar to that observed in those who received any dose level/formulation of RSVpreF.

Overview of Adverse Events by Category

Older Adults

The proportions reporting any AEs within 1 month after vaccination were similar in the RSVpreF (9.0%) and the placebo (8.5%) groups. Most AEs were mild or moderate in severity and severe AEs were reported in ≤0.4% in both groups. AEs assessed as related by the investigator were reported in 1.4% of the RSVpreF group and 1.0% of the placebo group. SAEs, AEs leading to death, life-threatening AEs, AEs leading to withdrawal, immediate AEs and NDCMCs were reported in ≤0.6% across both groups.

For most subgroups, results in the RSVpreF and placebo groups suggested no clinically meaningful differences across subgroups. In the RSVpreF group the proportion reporting SAEs was higher for those ≥80 years (1.3%) than 60-69 years (0.5%) and 70-79 years (0.7%) whereas in the placebo group SAE reporting was similar by age subgroup (range: 0.4% - 0.6%). No SAEs were assessed as related in those aged ≥80 years in either group.

Table 49: Adverse Events, by Category, Reported From Vaccination Through the 1-Month Follow-Up Visit – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=17215)		Placebo (N[a]=17069)	
Adverse Event Category	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any Event	1544 (9.0)	(8.5, 9.4)	1453 (8.5)	(8.1, 8.9)
Serious	103 (0.6)	(0.5, 0.7)	81 (0.5)	(0.4, 0.6)
AE leading to death	11 (<0.1)	(0.0, 0.1)	8 (<0.1)	(0.0, 0.1)
Severe	65 (0.4)	(0.3, 0.5)	51 (0.3)	(0.2, 0.4)
Life-threatening	24 (0.1)	(0.1, 0.2)	19 (0.1)	(0.1, 0.2)
Related	239 (1.4)	(1.2, 1.6)	163 (1.0)	(0.8, 1.1)
AE leading to withdrawal	3 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Immediate AE[d]	37 (0.2)	(0.2, 0.3)	31 (0.2)	(0.1, 0.3)
Newly diagnosed chronic medical condition (NDCMC)	81 (0.5)	(0.4, 0.6)	83 (0.5)	(0.4, 0.6)

For AEs reported from vaccination through the data cut-off date, the proportions reporting any AEs were similar for the RSVpreF group (13.0%) and placebo group (12.8%). Most AEs were mild or moderate in both groups (≤1.4% reported as severe). AEs assessed as related by the investigator were reported in 1.4% of the RSVpreF group and 1.0% of the placebo group. Across both groups, SAEs and NDCMCs were reported in ≤2.3% and ≤1.8%, respectively; AEs leading to deaths, life-threatening AEs, AEs leading to withdrawal and immediate AEs were reported in ≤0.6% each.

As of the data cut-off (14 July 2022), NDCMCs reported after vaccination were balanced for the RSVpreF and placebo groups (1.7% vs. 1.8% overall); none of the events in the RSVpreF group and 1 in the placebo group were assessed as related. NDCMCs were most frequently reported (0.3% in each group) in the SOCs of Metabolism and nutrition disorders and Musculoskeletal and connective tissue disorders.

Table 50: Adverse Events, by Category, Reported From Vaccination Through Data Cut-off (14Jul2022) – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=17215)		Placebo (N[a]=17069)	
Adverse Event Category	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any Event	2234 (13.0)	(12.5, 13.5)	2181 (12.8)	(12.3, 13.3)
Serious	396 (2.3)	(2.1, 2.5)	387 (2.3)	(2.0, 2.5)
AE leading to death	52 (0.3)	(0.2, 0.4)	49 (0.3)	(0.2, 0.4)
Severe	246 (1.4)	(1.3, 1.6)	218 (1.3)	(1.1, 1.5)
Life-threatening	101 (0.6)	(0.5, 0.7)	103 (0.6)	(0.5, 0.7)
Related	240 (1.4)	(1.2, 1.6)	164 (1.0)	(0.8, 1.1)
AE leading to withdrawal	10 (<0.1)	(0.0, 0.1)	6 (<0.1)	(0.0, 0.1)
Immediate AE[d]	37 (0.2)	(0.2, 0.3)	31 (0.2)	(0.1, 0.3)
Newly diagnosed chronic medical condition (NDCMC)	301 (1.7)	(1.6, 2.0)	313 (1.8)	(1.6, 2.0)

ADRs identified in C3671013 through the one month follow-up visit are shown below.

Table 51: Related Adverse Events Reported From Vaccination Through 1-Month Follow-Up Visit, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=17215)		Placebo (N[a]=17069)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any AE	239 (1.4)	(1.2, 1.6)	163 (1.0)	(0.8, 1.1)
General disorders and administration site conditions	176 (1.0)	(0.9, 1.2)	95 (0.6)	(0.5, 0.7)
Injection site pain	77 (0.4)	(0.4, 0.6)	39 (0.2)	(0.2, 0.3)
Injection site erythema	31 (0.2)	(0.1, 0.3)	5 (<0.1)	(0.0, 0.1)
Injection site swelling	22 (0.1)	(0.1, 0.2)	4 (<0.1)	(0.0, 0.1)
Fatigue	15 (<0.1)	(0.0, 0.1)	23 (0.1)	(0.1, 0.2)
Pyrexia	15 (<0.1)	(0.0, 0.1)	9 (<0.1)	(0.0, 0.1)
Influenza like illness	11 (<0.1)	(0.0, 0.1)	10 (<0.1)	(0.0, 0.1)
Injection site pruritus	9 (<0.1)	(0.0, 0.1)	3 (<0.1)	(0.0, 0.1)
Injection site induration	5 (<0.1)	(0.0, 0.1)	0	(0.0, 0.0)
Injection site joint pain	4 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Injection site warmth	4 (<0.1)	(0.0, 0.1)	1 (<0.1)	(0.0, 0.0)
Chills	3 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Injection site bruising	3 (<0.1)	(0.0, 0.1)	0	(0.0, 0.0)
Injection site reaction	3 (<0.1)	(0.0, 0.1)	0	(0.0, 0.0)
Malaise	3 (<0.1)	(0.0, 0.1)	0	(0.0, 0.0)
Peripheral swelling	3 (<0.1)	(0.0, 0.1)	0	(0.0, 0.0)
Asthenia	2 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Axillary pain	2 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Injection site inflammation	2 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Chest discomfort	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)

Injection site haematoma	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Injection site haemorrhage	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Injection site hypersensitivity	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Injection site hypoaesthesia	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Injection site nodule	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Injection site oedema	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Injection site plaque	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Injection site rash	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Pain	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Swelling face	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Feeling abnormal	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Injection site paraesthesia	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Injection site scab	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Nervous system disorders	40 (0.2)	(0.2, 0.3)	35 (0.2)	(0.1, 0.3)
Headache	32 (0.2)	(0.1, 0.3)	29 (0.2)	(0.1, 0.2)
Dizziness	2 (<0.1)	(0.0, 0.0)	3 (<0.1)	(0.0, 0.1)
Dysaesthesia	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Guillain-Barre syndrome	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Head discomfort	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Hypoaesthesia	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Lethargy	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Miller Fisher syndrome	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Dysgeusia	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Paraesthesia	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Musculoskeletal and connective tissue disorders	24 (0.1)	(0.1, 0.2)	15 (<0.1)	(0.0, 0.1)
Myalgia	14 (<0.1)	(0.0, 0.1)	9 (<0.1)	(0.0, 0.1)
Pain in extremity	5 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Arthralgia	3 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Musculoskeletal stiffness	2 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Musculoskeletal pain	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Polymyalgia rheumatica	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Gastrointestinal disorders	12 (<0.1)	(0.0, 0.1)	19 (0.1)	(0.1, 0.2)
Diarrhoea	5 (<0.1)	(0.0, 0.1)	8 (<0.1)	(0.0, 0.1)
Vomiting	5 (<0.1)	(0.0, 0.1)	4 (<0.1)	(0.0, 0.1)
Nausea	2 (<0.1)	(0.0, 0.0)	10 (<0.1)	(0.0, 0.1)
Flatulence	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Paraesthesia oral	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Abdominal discomfort	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Respiratory, thoracic and mediastinal disorders	12 (<0.1)	(0.0, 0.1)	17 (<0.1)	(0.1, 0.2)
Rhinorrhoea	4 (<0.1)	(0.0, 0.1)	7 (<0.1)	(0.0, 0.1)
Oropharyngeal pain	3 (<0.1)	(0.0, 0.1)	5 (<0.1)	(0.0, 0.1)
Cough	2 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Asthma	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Dyspnoea exertional	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Nasal congestion	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Pharyngeal paraesthesia	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Chronic obstructive pulmonary disease	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Dysphonia	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Productive cough	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Infections and infestations	5 (<0.1)	(0.0, 0.1)	7 (<0.1)	(0.0, 0.1)
Upper respiratory tract infection	2 (<0.1)	(0.0, 0.0)	3 (<0.1)	(0.0, 0.1)
Injection site cellulitis	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Nasopharyngitis	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Pharyngitis	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Herpes zoster	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Viral infection	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)

System Organ Class Preferred Term	Vaccine Group (as Administered) RSVpreF 120 µg (N[a]=17215) n[b] (%)	(95% CI[c])	Placebo (N[a]=17069) n[b] (%)	(95% CI[c])
Viral upper respiratory tract infection	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Blood and lymphatic system disorders	4 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Lymphadenopathy	3 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Thrombocytosis	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Skin and subcutaneous tissue disorders	3 (<0.1)	(0.0, 0.1)	5 (<0.1)	(0.0, 0.1)
Eczema	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Hyperhidrosis	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Urticaria	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Macule	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Pruritus	0	(0.0, 0.0)	2 (<0.1)	(0.0, 0.0)
Psoriasis	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Rash	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Vascular disorders	3 (<0.1)	(0.0, 0.1)	0	(0.0, 0.0)
Flushing	2 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Hypotension	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Cardiac disorders	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Tachycardia	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Ear and labyrinth disorders	1 (<0.1)	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Vertigo positional	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Ear congestion	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Immune system disorders	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Hypersensitivity	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Metabolism and nutrition disorders	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Hyperglycaemia	1 (<0.1)	(0.0, 0.0)	0	(0.0, 0.0)
Eye disorders	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Dry eye	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Investigations	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)
Body temperature increased	0	(0.0, 0.0)	1 (<0.1)	(0.0, 0.0)

Pregnant individuals

For any dose level/formulation of RSVpreF, the proportions reporting any AEs within 1 month after vaccination were similar in the pooled RSVpreF (15.0%) and the placebo (13.5%) groups. AEs assessed as related by the investigator were reported in 0.4% of the pooled RSVpreF group and 0.2% of the placebo group. Most AEs were mild or moderate in severity; severe AEs were reported by similar proportions in the RSVpreF (1.7%) and placebo (1.3%) groups. SAEs were reported in 4.0% of the pooled RSVpreF group and 3.7% of the placebo group. AEs leading to deaths, life-threatening AEs, AEs leading to withdrawal and immediate AEs were reported in ≤0.5% across both groups.
For those who received RSVpreF 120 µg, the safety profile was similar to that for any dose level/formulation of RSVpreF.

For those who received any dose level/formulation of RSVpreF, the proportions reporting any AEs from vaccination through the data cut-off date were slightly higher in the pooled RSVpreF (30.7%) and the placebo (27.8%) groups. AEs assessed as related by the investigator were reported in 0.4% of the pooled RSVpreF group and 0.2% of the placebo group. Most AEs were mild or moderate in severity; severe AEs were reported by similar proportion in the RSVpreF (5.7%) and placebo (5.5%) groups. SAEs were reported in 15.8% of the pooled RSVpreF group and 15.1% of the placebo group. AEs leading to deaths, life-threatening AEs and AEs leading to withdrawal were reported in ≤1.6% in both groups.

Table 52: Adverse Events by Category Reported Within 1 Month After Vaccination - All Maternal and All Female Participants - Safety Population

	All Maternal Participants			All Female Participants		
	Pooled RSVpreF[a] (N^b=4144)	RSVpreF 120 µg (N^b=3792)	Placebo (N^b=3792)	Pooled RSVpreF[a] (N^b=5547)	RSVpreF 120 µg (N^b=4596)	Placebo (N^b=4104)
Adverse Event Category	n^c (%) (95% CI)[d]	n^c (%) (95% CI)[d]	n^c (%) (95% CI)[d]	n^c (%) (95% CI)[d]	n^c (%) (95% CI)[d]	n^c (%) (95% CI)[d]
Any event	622 (15.0) (13.9, 16.1)	533 (14.0) (12.9, 15.2)	512 (13.5) (12.4, 14.6)	754 (13.6) (12.7, 14.5)	591 (12.9) (11.9, 13.9)	537 (13.1) (12.1, 14.2)
Serious	164 (4.0) (3.4, 4.6)	155 (4.1) (3.5, 4.8)	140 (3.7) (3.1, 4.3)	165 (3.0) (2.5, 3.5)	155 (3.4) (2.9, 3.9)	140 (3.4) (2.9, 4.0)
Immediate[e]	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	2 (<0.1) (0.0, 0.1)	2 (<0.1) (0.0, 0.2)	1 (<0.1) (0.0, 0.1)
Severe	71 (1.7) (1.3, 2.2)	65 (1.7) (1.3, 2.2)	50 (1.3) (1.0, 1.7)	83 (1.5) (1.2, 1.9)	72 (1.6) (1.2, 2.0)	51 (1.2) (0.9, 1.6)
Life-threatening	22 (0.5) (0.3, 0.8)	21 (0.6) (0.3, 0.8)	11 (0.3) (0.1, 0.5)	22 (0.4) (0.2, 0.6)	21 (0.5) (0.3, 0.7)	11 (0.3) (0.1, 0.5)
Related	16 (0.4) (0.2, 0.6)	16 (0.4) (0.2, 0.7)	6 (0.2) (0.1, 0.3)	32 (0.6) (0.4, 0.8)	25 (0.5) (0.4, 0.8)	6 (0.1) (0.1, 0.3)
AE leading to withdrawal	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)
Death[f]	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)

ADRs identified for pregnant individuals in C3671008 within one month of vaccination are shown below. Most occurred after vaccination and before delivery.

Table 53: Related Adverse Events Reported Within 1 Month After Vaccination, by System Organ Class and Preferred Term – Maternal Participants – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N^a=3682)		Placebo (N^a=3675)	
System Organ Class Preferred Term	n^b (%)	(95% CI)[c]	n^b (%)	(95% CI)[c]
Any Event	15 (0.4)	(0.2, 0.7)	6 (0.2)	(0.1, 0.4)
Blood and lymphatic system disorders	2 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Lymphadenopathy	2 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Gastrointestinal disorders	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Nausea	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
General disorders and administration site conditions	4 (0.1)	(0.0, 0.3)	4 (0.1)	(0.0, 0.3)
Axillary pain	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Fatigue	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
Injection site bruising	2 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Injection site pruritus	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Injection site reaction	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Malaise	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Infections and infestations	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Pharyngitis	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Investigations	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Body temperature increased	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)

Musculoskeletal and connective tissue disorders	2 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Pain in extremity	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Systemic lupus erythematosus	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Nervous system disorders	2 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Dizziness	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Paraesthesia	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Pregnancy, puerperium and perinatal conditions	2 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
Eclampsia	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Premature labour	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Premature separation of placenta	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Skin and subcutaneous tissue disorders	2 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Rash	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Urticaria	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)

Among pregnant individuals who received any dose level/formulation of RSVpreF, the median interval between vaccination and delivery was similar between the pooled RSVpreF and placebo groups (55.0 days). Most (70.9% in the RSVpreF group and 70.4% in the placebo group) had a vaginal delivery and the median GA at delivery was 39.14 weeks for both groups. Overall, the majority of pregnancies in both groups (99.8%) resulted in full-term live births. The incidence of still births (also reported interchangeably as fetal deaths in C3671008) was 0.2% in the pooled RSVpreF and placebo groups.

Infants born to vaccinated mothers

In C3671008, for each category of AE reported within 1 month after birth, proportions were similar for infants born to mothers in the RSVpreF 120 µg and placebo groups. The proportions with any AE reported within 1 month after birth were 37.1% in the RSVpreF group and 34.5% in the placebo group. Most AEs were mild or moderate in severity across both groups; severe AEs were reported in ≤4.5%. No ADRs were identified in infant participants born to vaccinated mothers in C3671008.

Table 54: Number (%) of Participants Reporting Adverse Events by Category Within 1 Month After Birth – Infant Participants – Safety Population

	Maternal Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Any event	1324 (37.1)	(35.5, 38.7)	1229 (34.5)	(33.0, 36.1)
Serious	553 (15.5)	(14.3, 16.7)	541 (15.2)	(14.0, 16.4)
Severe	161 (4.5)	(3.9, 5.2)	134 (3.8)	(3.2, 4.4)
Life-threatening	34 (1.0)	(0.7, 1.3)	34 (1.0)	(0.7, 1.3)
Related	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
AESIs	298 (8.4)	(7.5, 9.3)	257 (7.2)	(6.4, 8.1)
Congenital Anomalies	172 (4.8)	(4.1, 5.6)	210 (5.9)	(5.2, 6.7)
NDCMCs	6 (0.2)	(0.1, 0.4)	6 (0.2)	(0.1, 0.4)
AE leading to withdrawal	0	(0.0, 0.1)	0	(0.0, 0.1)

Among infants born to mothers who received any dose level/formulation of RSVpreF, the proportions experiencing any AEs from birth through the data cut-off date were 44.8% in the pooled RSVpreF group and 40.7% in the placebo group.

AEs assessed as related by the investigator were similar between RSVpreF and placebo groups (<0.1%). Most AEs were mild or moderate in severity; severe AEs were similar in the RSVpreF (5.5%)

and placebo (4.6%) groups. SAEs were reported in 19.5% of the pooled RSVpreF group and 18.0% of the placebo group. AEs leading to deaths, life-threatening AEs, AEs leading to withdrawal were reported in ≤1.3% across both groups. Congenital anomalies were reported in ≤7.1% across both groups. Developmental delays were reported at a similar frequency in the RSVpreF and placebo groups (0.3%).

As of the data cut-off date, there were 10 (0.2%) fetal demises (including stillbirths) in the RSVpreF any dose level/formulation group and 9 (0.2%) in the placebo group. None of the fetal demises was assessed by the investigator as related to study intervention. The incidence rate of fetal demises in maternal participants who received RSVpreF any dose level or formulation was consistent with or lower than estimated background rates.

Congenital anomalies were reported at a similar frequency in the RSVpreF and placebo groups (6.3%). Developmental delays were reported in <0.1% of the pooled RSVpreF group and 0% of the placebo group.

Serious adverse events and deaths

Older Adult Population

From vaccination through the 1-month follow-up visit, for the RSVpreF and placebo groups there were few severe AEs (0.4% vs. 0.3%) or life-threatening AEs (0.1% vs. 0.1%) reported. Those assessed as related included 2 severe events (viral infection in placebo group, SAE of Miller Fisher syndrome in RSVpreF group) and 1 life-threatening event (SAE of GBS in the RSVpreF group); see below. No additional AEs of GBS or Miller Fisher syndrome were reported in the study as of the data cut-off date.

As of the data cut-off (14 July 2022), AEs leading to death were reported in 52 (0.3%) RSVpreF recipients and 49 (0.3%) placebo recipients. None of these deaths was assessed as related to study intervention. The primary causes of death most frequently reported were in the SOC of Cardiac disorders for participants in the RSVpreF (20 [0.1%]) and placebo (19 [0.1%]) groups.

The proportions with SAEs reported from vaccination through the 6-month follow-up visit were similar in the RSVpreF (1.9%) and placebo (1.7%) groups. The most frequently reported for RSVpreF were in SOCs of Infections and infestations, Cardiac disorders, and Neoplasms benign, malignant and unspecified (0.4%, 0.3%, and 0.3%, respectively), which were reported similarly in the placebo group (0.3% in each SOC). By PT, all SAEs were reported in <0.1% of participants in either group.

From vaccination through the data cut-off date of 14 July 2022, SAEs were reported in 2.3% of participants in each group. The most frequently reported SOCs in the RSVpreF group were Cardiac disorders and Infections and infestations (0.5% each), which were reported similarly in the placebo group (0.5% and 0.4%, respectively). By PT, all SAEs were reported in <0.1% of participants in either group. The most frequently reported SAEs by PT in the RSVpreF group were Coronary artery disease, Acute myocardial infarction, Atrial fibrillation, and Ischaemic stroke (11 participants each), which were reported similarly in the placebo group.

Three participants in the RSVpreF group and none in the placebo group had SAEs (GBS, Miller Fisher syndrome, and Hypersensitivity) assessed as related by the investigator.

The case of hypersensitivity (allergic reaction; moderate severity) had onset on the day of vaccination and it resolved after 5 days.

The case of GBS (life-threatening) had onset 7 days after vaccination and it was resolving as of the data cut-off date (177 days after vaccination).

The case of Miller Fisher syndrome had onset 8 days after vaccination and it resolved after 92 days.

For age subgroups, in the RSVpreF group the proportions reporting SAEs were higher for those ≥80 years (1.3%) than 60-69 years (0.5%) and 70-79 years (0.7%), whereas in the placebo group SAE reporting was similar by age subgroup (range: 0.4% - 0.6%). No SAEs were assessed as related in those aged ≥80 years in either group.

Pregnant individuals
Among maternal participants who received any dose level/formulation of RSVpreF, the proportions reporting any SAEs from vaccination through the data cut-off date were similar in the pooled RSVpreF (15.8%) and placebo (15.1%) groups. SAEs that were most frequently reported for the pooled RSVpreF and placebo groups were in the SOC of Pregnancy, puerperium and perinatal conditions (11.6% vs. 11.1%). By PT, the most frequently reported AEs for the pooled RSVpreF and placebo groups were pre-eclampsia (1.8% vs. 1.5%), fetal distress syndrome (1.7% vs. 1.6%), arrested labour (1.0% vs. 1.2%), gestational hypertension (1.0% vs. 1.0%), and premature delivery (0.7% vs. 0.6%).

As of the data cut-off date, there was 1 death of a maternal participant in the RSVpreF group in the Philippines due to postpartum haemorrhage and hypovolaemic shock, which was reported from delivery to 1 month after delivery. The death was assessed by the investigator as not related to study intervention.

There was 1 additional death of a 48 year old non-pregnant female participant in the pooled safety database who received RSVpreF 120 µg in C3671001. The cause of death was toxicity to various agents (combined toxic effects of quetiapine and amlodipine use) and was considered not related to study intervention.

Infants born to vaccinated mothers
Among infants born to mothers who received any dose level/formulation of RSVpreF, the proportions with SAEs through the data cut-off date were similar in the pooled RSVpreF (19.5%) and placebo (18.0%) groups. SAEs were most frequently reported in the SOCs of Respiratory, thoracic and mediastinal disorders (4.4% vs. 4.2%), Pregnancy, puerperium and perinatal conditions (3.7% vs. 3.5%) and Infections and infestations (3.1% versus 2.5%). Congenital, familial and genetic disorders were reported at a similar frequency in the pooled RSVpreF group (6.2%) and in the placebo group (5.7%). By PT, the most frequently reported SAEs were jaundice (1.9% vs. 1.8%), premature baby (1.4% vs. 1.2%), respiratory distress (1.2% vs. 1.2%) and hyperbilirubinaemia (1.2% vs. 1.1%).

AEs leading to death were reported in 5 (0.1%) infants born to mothers who received RSVpreF any dose level/formulation and 12 (0.3%) infants whose mothers received placebo. None of these deaths was assessed as related to study intervention.

Laboratory findings

Clinical laboratory evaluations were not performed systematically in the Phase 3 trial. Any clinical laboratory values of concern that came to the attention of the investigator were to be reported as AEs.

Safety in special populations

See above regarding safety in subjects aged from 60 years, pregnant individuals and their infants.

Adverse Events of Special Interest

Study C3671008
In Study C3671008, AESIs for infant participants included low birth weight baby, premature baby, developmental delay, and a positive SARS-CoV-2 test (PCR or antigen-based); these AESIs were collected throughout the study. The AESI of low birth weight baby was reported for infant participants at a similar frequency for the RSVpreF and placebo groups (5.1% [95% CI: 4.4, 5.8] versus 4.3% [95% CI: 3.7, 5.0], respectively). Premature baby was also reported at a similar frequency for the RSVpreF and placebo groups (5.7% [95% CI: 4.9, 6.5] versus 4.7% [95% CI: 4.1, 5.5], respectively). The AESI of developmental delay was reported at a similar frequency in the RSVpreF and placebo groups (0.3%).

Study C3671003
In Study C3671003, AESI for infant participants included congenital anomalies and developmental delay. There were no AESI of developmental delay reported throughout the study. Most AESI of congenital anomalies were mild and those of at least moderate severity were reported in a similar frequency across all groups. None of these events were considered related to maternal vaccination with investigational product.

Other Observations Related to Safety – Birth Outcomes
Among infant participants born to mothers who received any dose level/formulation of RSVpreF, most infants in the pooled RSVpreF and placebo groups were born at term (≥37 weeks to <42 weeks). No meaningful differences were detected between the RSVpreF and placebo groups with respect to GA at birth, Apgar scores, or birthweight.

Immunological events

Hypersensitivity is reported as an immune system disorder in the older population with a frequency of <1/10,000. It is not described or listed to have occurred in the pregnant population. Narratives are provided for the cases of hypersensitivity, Guillain-Barré and Miller Fisher syndrome. In the case of MFS, the investigator attributed causality to the vaccine due to the clinical presentation and the temporal relationship to administration of the vaccine. The Company did not agree with this assessment stating that the participant's underlying type 2 diabetes mellitus could have been responsible for the clinical presentation. However, given her presentation of ataxia, diplopia and loss of consciousness and as there is no data presented indicating abnormal glucose control, the causality assessment of the independent investigator is understood.

Hypersensitivity reaction

The participant experienced a hypersensitivity reaction approximately 8 hours after receiving the study intervention. She had a medical history of penicillin and vitamin B12 allergy. On 30 Nov 2021 (Day 1), approximately 8 hours after receiving study treatment, she experienced acute shortness of breath and chest pain, which resulted in syncope with loss of consciousness and bladder relaxation. She was transferred to a primary care centre and given oxygen supplementation and dexamethasone 8 mg intravenously. When stable, she was transferred to a hospital where examination, ECG and CT of thorax, cervical spine and brain were normal. On 01 Dec 2021 (Day 2), laboratory results showed normal levels of troponin, serum creatine phosphokinase-MB, and D-dimer. On 04 Dec 2021 (Day 5), she was discharged with a diagnosis of allergic drug reaction.

Guillain-Barré Syndrome

A 66-year-old, white, non-Hispanic/non-Latino male, received study intervention on 11 Jan 2022 (Day 1) and had onset of Guillain-Barré syndrome (GBS) on 18 Jan 2022. On 17 Jan 2022 (Day 7), he was hospitalised for non–ST-elevation myocardial infarction and had immediate angioplasty. He was treated with ticagrelor and started on ubidecarenone and Curcuma longa rhizome as supplementation therapy. On 18 Jan 2022 (Day 8), the event of myocardial infarction resolved and he was discharged on aspirin. He had lower back pain and bilateral lower extremity (BLE) weakness on 24 Jan 2022 (Day 14). On 16 Feb 2022 (Day 37), he had a fall because of difficulty in walking and was hospitalised for lower extremity weakness and ataxia. He was discharged on 19 Feb 2022 (Day 40) with a walker but on 24 Feb 2022 (Day 45), he was unable to walk and was re-hospitalised for worsening of lower extremity weakness and ataxia. After neurological exam, LP and nerve conduction study he was diagnosed with GBS, with an onset date of 18 Jan 2022 (Day 8). He received intravenous immunoglobulin therapy.

On 24 May 2022 (Day 134), he attended clinic in a wheelchair. He was noted to have gradually improved skin sensation and the ability to lift his legs and kick, but he was still unable to stand on his own. On 14 Jul 2022 (Day 185), he was able to walk with 2 canes. The event of GBS was resolving at the time of the last available report.

Miller Fisher syndrome

A 66-year-old, Asian, non-Hispanic/non-Latino female, received study intervention on 28 Oct 2021 (Day 1). On 07 Nov 2021 (Day 11), she had ataxic gait, which resolved on the same day. On 15 Nov 2021 (Day 19), she was brought to a hospital with severe fatigue and unstable movements and she developed diplopia and difficulty with her gait.

On 18 Nov 2021 (Day 22), she was admitted to a second hospital with paraesthesia in both her palms and in the soles of her feet, diplopia and ataxic gait. On 19 Nov 2021 (Day 23), she was confirmed by an ophthalmologist to have ophthalmoplegia, eyelid ptosis, oculomotor nerve paralysis and abducens nerve paralysis, with a possibility of myasthenia gravis or Graves' eye disease. On 29 Nov 2021 (Day 33), myasthenia gravis or Graves' eye disease was ruled out. On 06 Dec 2021 (Day 40), the diplopia was resolved and her gait, speech and consciousness had improved, except for the paraesthesia in the soles of her feet. On 07 Dec 2021 (Day 41), based on the information and clinical course, the neurologist made a retrospective diagnosis of MFS or Guillain-Barré syndrome (GBS). On 24 Dec 2021 (Day 58), she was discharged from the hospital with paraesthesia persisting in the soles of her feet. On 04 Feb 2022 (Day 100), the participant’s paraesthesia in the soles of her feet also resolved. The participant was ongoing in the study, with the last reported visit on 21 Apr 2022 (Day 176).

In the opinion of the investigator, there was a reasonable possibility that the MFS was related to the study intervention but not related to concomitant medications or clinical trial procedures. The investigator came to this conclusion as the participant’s symptom of malaise started on Day 9 and developed into double vision on Day 21, which had a time course typical for vaccine-related GBS. Also, since she did not have any background of immune-related disease, the investigator assessed a positive causality between the study intervention and MFS. Per Pfizer’s assessment, there was not enough evidence to attribute a causal association between MFS and the study intervention, and the underlying medical conditions of the participant could not be ruled out.

Safety related to drug-drug interactions and other interactions

In a co-administration study (C3671001) in healthy male and non-pregnant female participants 18-85 years of age, RSVpreF was safe and well-tolerated when administered alone or with SIIV, with no

major differences observed across all dose levels and formulations. Likewise, in a co-administration study (C3671004) in healthy non-pregnant women 18-49 years of age, both formulations of RSVpreF were safe and well tolerated when administered alone or with Tdap.

Discontinuation due to AES

Older Adult Population
AEs leading to withdrawal from the study through the data cut-off date were similar in the RSVpreF and placebo groups: 10 (<0.1%) and 6 (<0.1%) participants, respectively. By PT, for both groups all events were reported in 1 participant each except for Depression (3 participants in the RSVpreF group). None of the events was assessed as related.

Pregnant population
As of the data cut-off date, 1 maternal participant in the placebo group withdrew from the study due to the AE of premature delivery.

Infant Participants
As of the data cut-off date, 1 infant participant whose mother received placebo was discontinued from the study due to severe AEs of atrial septal defect, patent ductus arteriosus, and lung disorder; and life-threatening events of hypoxia and neonatal respiratory distress syndrome. None of the AEs was assessed as related to study intervention.

Post marketing experience

There are no post marketing data available.

2.6.9. Discussion on clinical safety

The pooled safety database consists of 17,215 treated older participants of which 6-month follow-up is available for approximately 77%. Local reaction and systemic event data were collected for 7 days after study vaccination in a subset of 7,160 participants. For all participants, adverse events were collected for 1 month after study vaccination and serious adverse events were collected throughout study participation.

In the pregnant population the pooled safety analysis is based on 4,144 maternal exposures, 3797 at the therapeutic dose, and 88% had completed 6 months follow-up at the time of data cut-off.

The most common adverse reactions reported within the first 30 days included injection site reaction, redness and swelling. Whilst the local reactions experienced by both groups was similar, a higher percentage of pregnant woman experienced local reactions.

The incidence of systemic reactions was also higher in the pregnant population. The most frequently reported systemic event in both groups was fatigue which occurred with a similar frequency in both treated and placebo groups. The incidence of fever was low and occurred at a similar frequency in both the placebo group and vaccinated participants. The applicant was asked to provide details concerning prophylactic antipyretics administered to determine whether administration may have affected the incidence of pyrexia in either group. In response to the list of questions the applicant provided details of analgesic/anti-pyrectic use in the maternal population which was slightly greater than use in the

placebo group as women who received the vaccine experienced more myalgia. Muscle pain and headache were more frequently reported in the RSVpreF group compared to placebo in the maternal population and are listed in section 4.8 of the SmPC.

The SmPC lists hypersensitivity reactions as occurring with a frequency of very rare in the older population. Further detail about the case of hypersensitivity reaction is provided in the participants' narratives. Guillain-Barré syndrome and Miller Fisher syndrome occurred in two participants in the older population. It is not clear how these adverse reactions are listed in the SmPC, it is not clear whether they have been included in the immune system disorders/hypersensitivity disorders whereas these reactions would by convention be considered nervous system disorders. The applicant has been asked to update section 4.8 with these adverse reactions.

The rationale for the frequency and content of the adverse reactions listed in section 4.8 of the SmPC was not clear. Further justification was requested form the applicant in particular for not including adverse reactions listed as occurring at a greater frequency in participants who received the vaccine. For example, in the older population the frequency of musculoskeletal disorders is higher (25 %) in subjects who received the vaccine than those who received placebo (15%), whilst myalgia is listed as an adverse reaction in the maternal population it is not listed as an adverse reaction in the older population. The applicant in response to the list of questions provided the rationale for inclusion of adverse reactions in the Table of ADRs in Section 4.8 of the SmPC. The risk ratio for myalgia in the older population was not significantly different to that for the older population who received placebo and therefore it was not listed in section 4.8.

Further discussion was also needed with regard to premature labour, systemic lupus erythematosus and eclampsia, as there were noted as related SAEs. The applicant provided in their response narratives and justification for not considering these events as related and therefore not listing them in the product information.

Most adverse reactions and events were of mild to moderate intensity.

The safety profile was similar in participants who received any dose level or formulation of RSVpreF.

The frequency of some adverse events was higher in pregnant women and this is reflected in the SmPC.

The safety of the fetus of a maternal participant were reported for the maternal participant. The risk of fetal death (0.2%) was consistent or lower than the estimated background rates. Congenital abnormalities were reported at a similar frequency in the active and placebo treated groups. Developmental delays were reported at a similar frequency across both groups.

The risk of preterm delivery was similar in the RSVpreF and placebo groups. However, there was a slightly higher number of preterm births reported in the vaccinated group in mothers from the upper middle-income group. The number of preterm infants involved is small. Overall the difference in preterm birth in mothers in the vaccinated and placebo groups was not statistically significant.

The number of extremely preterm infants remains low at 1 in both vaccinated and placebo groups. The number of extremely and very low birth weight infants was slightly greater in the placebo group and the total number of low-birth weight infants comparable in both groups.

In study C3671008, AESIs for infant participants included low birth weight baby, premature baby, developmental delay and a positive SARS-CoV-2 test (PCR or antigen-based); these AESIs were collected throughout the study. The AESI of low-birth weight baby was reported for infant participants with a slightly higher frequency for the RSVpreF vs placebo groups (5.1% versus 4.3%). Premature baby was also reported at a slightly higher frequency for the RSVpreF and placebo groups (5.7% versus 4.7 %). The AESI of developmental delay was reported in two infants in each group (<0.1%).

For both AESIs low birth weight as well as premature baby the applicant was asked to provide further information on severity (e.g. proportions of diverging weight and age at birth).

The applicant provided the requested data and clarified that the higher numbers in the RSV group vs the placebo group mainly come from imbalances observed in upper-middle income countries (7.5% vs 4.1%). As numbers in high and low-income countries were comparable, there was no increase in mortality in preterm births and the overall incidence of preterm births was lower than the background rates in all countries where the study was conducted, no further concerns are raised.

Over ninety three percent of pregnancies resulted in a full-term infant. Seventy percent of deliveries were vaginal which is in keeping with expected vaginal delivery rates. Low birth weight was reported at a similar frequency for infant participants. There is data on average birthweights, low Apgar score at birth and rate of admission to NICU provided by the applicant with no increase in incidence in infants born to vaccinated mothers.

However, the number of preterm deliveries and low birth weight should continue to be monitored in the planned post authorisation studies. Data including potential risk factors for preterm delivery should be collected in the studies.

The number of infant deaths to 24 months was higher in the placebo group.

In study 003 (phase 2 b) there were higher numbers of congenital anomalies of at least moderate severity in 9.6% (RSV) compared to the 6% placebo group. Except 3 cases of ankyloglossia congenital in RSV group vs 1 in placebo, all other AE of congenital anomalies were single cases. None of these events were considered related to maternal vaccination with investigational product. The applicant was asked to provide summary tables for all cases of congenital anomalies based on severity, as well as expected background incidence of the respective anomalies. The applicant provided the requested data in their responses. For all cases of congenital anomalies, a summary table based on severity was provided. There was no obvious difference in rates of SAEs of congenital anomalies between the RSVpreF and the placebo group.

2.6.10. Conclusions on the clinical safety

Overall, the CHMP is of the opinion that RSVpreF was well tolerated in the older population and in pregnant women and infants. Adverse reactions reported in the clinical trials in the older and pregnant populations are reflected in the proposed SmPC. There are no major safety objections.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 0.3:

Table 55: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Guillain-Barré syndrome
Missing information	Use in immunocompromised pregnant women and high-risk pregnancies Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old

Having considered the data in the safety specifications, the CHMP agrees that the safety concerns listed by the applicant are appropriate.

2.7.2. Pharmacovigilance plan

Routine Pharmacovigilance Activities

The description of routine pharmacovigilance activities is acceptable to the CHMP.

Summary of additional PhV activities

Table 56: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
Post-marketing safety study of respiratory syncytial virus vaccine among older adults in the United States (C3671031) Planned	To evaluate the risk of GBS, other immune-mediated demyelinating conditions and polyneuropathies following RSVpreF administration among older adults	Guillain-Barré syndrome	Submission of final study protocol to the FDA Submission of final study report to the FDA	30 November 2023 31 May 2030
Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in pregnant women and their offspring in a real world setting in Europe (C3671026) Planned	To evaluate the safety of RSVpreF in all pregnant women and their offspring including immunocompromised pregnant women and high-risk pregnancies	Use in immunocompromised pregnant women and high-risk pregnancies Guillain-Barré syndrome	Submission of study protocol Submission of final study report	31 Mar 2024 30 Sep 2029
Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe (C3671038) Planned	To evaluate the safety of RSVpreF in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older	Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old Guillain-Barré syndrome	Submission of study protocol Submission of final study report	31 Mar 2024 30 Sep 2029

The PhV plan includes 3 category 3 PASSs as follows:

1. **Study C3671031** entitled *Post-marketing safety study of respiratory syncytial virus bivalent stabilised prefusion F vaccine (RSVpreF) among older adults in the United States*

   The applicant proposes to further evaluate whether RSVpreF is associated with an increased risk of GBS and other immune-mediated demyelinating conditions among older adults in the US in a non-interventional, retrospective cohort study among US Medicare beneficiaries. Two study designs commonly used in vaccine safety studies will be used:

- First, an internal comparator design aims to estimate the incidence of GBS, and other immune-mediated demyelinating conditions, during a pre-defined risk window (*e.g.*, 1-42 days post vaccination, recommended by Brighton collaboration[i]) among Medicare beneficiaries who receive RSVpreF versus those who are not vaccinated with RSVpreF at that point in time.
- Secondly, a self-controlled risk interval (SCRI) analysis may also be conducted among RSVpreF vaccinated Medicare beneficiaries to compare the incidence of GBS, and other immune-mediated demyelinating conditions, during the post-vaccination risk window (*e.g.*, 1-42 days following vaccination) to the post-vaccination control window (*e.g.*, 43-84 days following vaccination).

As data source the study will use the Centers for Medicare and Medicaid Services (CMS) Medicare administrative database capturing all paid claims for fee-for-service (FFS) billable healthcare services in inpatient and outpatient settings as well as Part D claims for prescription drugs/vaccines. Medicare data have been used by federal health agencies to successfully monitor and evaluate the risk of GBS following vaccinations for influenza and Shingrix.

Besides primary outcome GBS, other immune-mediated demyelinating conditions will be evaluated as secondary endpoints, including encephalitis/encephalomyelitis, multiple sclerosis, optic neuritis, transverse myelitis, and other acute demyelinating diseases.

Regarding the sample size, assuming a background rate of 4.6 GBS events per 100,000 person years, the applicant calculated that approximately 1.3-1.5 million individuals vaccinated with RSVpreF will be needed to detect a ≥ 3-fold increased risk of GBS during a 42-day risk period with 80% power and a two-sided alpha error rate of 0.05. Although the sample size calculation seems valid, whether the targeted enrollment of 1.3-1.5 million vaccines would be realistic/feasible (or not), is uncertain at this moment, pending the vaccine uptake.

2. **C3671026**, entitled "*Safety of respiratory syncytial virus stabilized prefusion F subunit vaccine (RSVpreF) in pregnant women in a real world setting in Europe*" has been revised to include all eligible pregnant women, including immunocompetent and immunocompromised women, and high-risk pregnancies. This study will complement routine pharmacovigilance activities and will allow timely identification of any emerging trends. Outcomes of interest include stillbirth, preterm birth, small for gestational age, low birth weight, maternal and neonatal death, and other safety events, including Guillain-Barré syndrome if warranted. Upon agency's request more detail has been provided regarding feasibility, data sources (eHR databases in DK; NO; ES; FR; IT; NL; and UK), outcomes of interest, estimates of maternal vaccination coverage, and timelines. These amendments are accepted by the Committee.
3. **Study C3671038** (Category 3 PASS) entitled "*Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in immunocompromised, and renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe"***.**

   In response to the Committee's request for inclusion of persons with renal and hepatic impairment, the applicant proposes a separate planned Observational Study C3671038 and has provided some more detail. Outcomes of interest will include neurological, immunological, cardiac, haematological, and other events (*e.g.*, death). The applicant noted that the proposed list of outcomes may still be amended, as collaborative work is underway in the BeCOME (Beyond COVID Monitoring Excellence) collaboration of vaccine manufacturers, to generate a standardised list of events of interest for monitoring RSV vaccines. The applicant also discussed feasibility, data sources (eHR databases in UK; FR; DE; NL; IT; ES; DK), and prevalence estimates of older adults who are immunocompromised, or renally or hepatically impaired, and

timelines. The applicant agreed that in study C3671038 (Category 3 PASS) Guillain-Barré Syndrome is included in the list of outcomes of interest.

Overall conclusions on the PhV Plan

The CHMP, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan could be sufficient to identify and characterise the risks of the product.

The applicant has agreed to include Guillain-Barré Syndrome in the list of outcomes of interest in study C3671038 (Category 3 PASS).

The applicant's commitments are noted to submit the full protocols for study C3671031 by 30 November 2023, and studies C3671026 and C3671038 by 31 May 2024.

The CHMP also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

Routine Risk Minimisation Measures

Safety Concern	Routine risk minimisation activities
Guillain-Barré syndrome	Routine risk communication: EU SmPC Section *4.8 Undesirable effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Use in immunocompromised pregnant women and high-risk pregnancies	Routine risk communication: EU SmPC Section *4.4 Special warnings and precautions for use* *Routine risk minimisation activities recommending specific clinical measures to address the risk:* *None* *Other routine risk minimisation measures beyond the Product Information:* None
Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old	Routine risk communication: EU SmPC Section *4.4 Special warnings and precautions for use* Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

Summary of additional risk minimisation measures

Routine risk minimisation activities as described in Section V.1 are sufficient to manage the safety concerns of the medicinal product.

Overall conclusions on risk minimisation measures

The CHMP having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.7.4. Conclusion

The CHMP considers that the risk management plan version **0.3** is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic safety update reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

None requested.

2.9.3. Quick response (QR) code

Not applicable.

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Abrysvo (respiratory syncytial virus vaccines) is included in the additional monitoring list as it contains a new active substance, which on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The applicant has developed a vaccine to protect against disease caused by the respiratory syncytial virus (RSV) and sought two indications for use, with revised wording as follows:

- Passive protection against lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age following maternal immunisation during pregnancy. See sections 4.2 and 5.1.
- Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

3.1.1. Disease or condition

RSV is a negative sense, single stranded RNA orthopneumovirus that causes infections of the human respiratory tract. RSV has two subgroups – RSV A and RSV B. The RSV F of A and B subgroups is ~90% identical and it is the primary target of neutralising antibodies that also show some degree of cross-neutralisation. Most of the sequence differences between the mature F glycoproteins of the subgroups are concentrated in the prefusion-specific epitopes that elicit the majority of RSV-neutralising and protective antibody responses.

RSV cases follow a seasonal pattern in many countries that is in line with that of influenza, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall. RSV can affect any age group and almost all children have serological evidence of exposure to the virus by the age of 2 years.

RSV disease in adults

In Europe, RSV infection can also be serious for adults aged 50 years and older as it can cause acute respiratory infection, influenza-like illness or community-acquired pneumonia. Annual RSV attack rates of 4.2% and 7.2% were observed in community-living adults aged ≥60 years in successive seasons. In UK adults aged from 18 years, some authors have estimated of 487,247 outpatient episodes, 17,799 hospitalisations and 8,482 attributable deaths per season. Of these, 36% of GP episodes, 79% of hospitalisations and 93% of deaths were in ≥65-year-olds.

RSV infection has been associated with up to 22% of acute COPD exacerbations in prospective cohort studies and 11% of wintertime hospitalisations for COPD exacerbations. In industrialised countries, the case fatality rate of RSV-ARI was 11.7% for adults with comorbidity but 1.6% for the general population. There are some recognised risk factors for severe RSV disease in older adults, including the

elderly. Immunosenescence can result in a weakened immune response to pathogens and suboptimal response to vaccines. In addition, there may be reduced lung expansion in older adults because of decreased strength of the respiratory muscles and the diaphragm. Older adults may also have decreased protective mucus levels, lung compliance and elastin.

RSV disease in infants

RSV is the leading viral cause of lower respiratory tract infection in children. It may cause bronchiolitis and pneumonia and can lead to fatal respiratory distress. Globally, there are an estimated 33 million episodes of RSV-associated ALRI each year in children aged <5 years resulting in an estimated 3.6 million hospitalisations. Among children <6 months there are an estimated 6.6 million RSV-associated ALRI episodes and 1.4 million hospitalisations.

RSV is a leading cause of paediatric hospitalisation in Europe. In a recent study of the aetiology of severe ARI requiring hospitalisation conducted in 7 countries, RSV was identified as the most common cause of ARI hospitalisations in young children, causing one third of ARI admissions. In a separate European study, rates of RSV hospitalisation varied by country from 8.6 to 22.3 per 1,000 children <1 year of age but patterns across age were remarkably similar. In all countries, RSV-associated hospitalisation rates were significantly higher in children <1 year of age compared to those 1-4 years of age and decreased with increasing age. RSV admissions peaked among infants <1 month.

While virtually all children experience RSV in the first 2 years of life, rates of RSV hospitalisation in infancy are greater among those with medical (e.g. prematurity, low levels of maternal neutralising antibodies) and socioeconomic risk factors.

3.1.2. Available therapies and unmet medical need

Palivizumab is authorised for immunoprophylaxis, given as monthly injections during RSV seasons. In Europe, it is commonly used in infants aged <6 months who were born before 35 weeks of gestation and children aged <2 years of age who have been treated for bronchopulmonary dysplasia within the last 6 months or have a serious heart condition. The effectiveness of palivizumab highlighted the importance of neutralising antibodies in protection against RSV disease. Subsequently, nirsevimab was developed as a single dose, extended half-life prefusion F-specific mAb. It demonstrated efficacy against RSV LRTI in Phase 3 studies and was given EU marketing authorisation in October 2022.
On 06 June 2023, a marketing authorisation in the European Union was granted for Arexvy (recombinant, adjuvanted), for active immunisation to protect adults aged 60 years and older against LRTD caused by RSV.

There are no specific therapeutics indicated for treatment of RSV. Treatment of RSV disease consists primarily of supportive care (e.g. oxygen, hydration and suctioning of secretions). The use of aerosolised ribavirin is usually limited to immunosuppressed persons due to inconvenient administration, questionable benefit, teratogenicity concerns and high cost.

3.1.3. Main clinical studies

The applicant conducted a human challenge study WI257521 in healthy adults aged 18-50 years with a primary readout based on qRT-PCR-confirmed symptomatic RSV infections using several definitions.

C3671013 was the pivotal Phase 3 efficacy study in older adults aged from 60 years. This study was double-blind and placebo-controlled.

Having selected a dose for pregnant women from a Phase 2b dose-finding study C3671003, in which efficacy in infants was exploratory, the applicant conducted a single pivotal Phase 3 study C3671008 to evaluate the efficacy of RSVpreF vaccine in infants born to women vaccinated during pregnancy.

3.2. Favourable effects

Efficacy in adults aged from 60 years

C3671013 was the single pivotal vaccine efficacy study to support use in subjects aged from 60 years. This randomised, double blind, placebo-controlled study was designed to estimate the absolute vaccine efficacy of RSVpreF using a case-driven primary analysis based on RSV-LRTI meeting the primary case definitions that required ≥2 or ≥3 of the listed symptoms to be present.

The study sites covered North and South America, two EU countries, South Africa and Japan. There was stratification at site-based randomisation with an aim to recruit at least 6,000 in each of the sub-groups 60-69 and 70-79 years and at least 800 aged 80+ years. There was also an aim to recruit at least 10% with stable chronic cardiopulmonary conditions but those with unstable conditions or known to be immunosuppressed were excluded. The protocol pre-defined acceptable clinical definitions for RSV-LRTI, severe RSV LRTI (RSV-sLRTI) and acute respiratory infection (RSV-ARI); all required RT-PCR confirmation. Cases were to be reported and counted starting from day 14 after vaccination and primary analyses were to be conducted in the efficacy evaluable population with additional analyses in all-treated (mITT) subjects. Generally, the approach taken was acceptable.

There was a plan for sequential testing of hypotheses such that if the lower bound of the adjusted CI around the point estimate of vaccine efficacy was >20% for RSV-LRTI with ≥2 symptoms, then efficacy was to be estimated for RSV-LRTI with ≥3 symptoms. If the lower bound of the adjusted CI around the point estimate of vaccine efficacy for RSV-LRTI with ≥3 symptoms was >20%, efficacy was to be calculated for severe RSV-LRTI, which was designated as a key secondary endpoint and had the same criterion for concluding on efficacy. Vaccine efficacy against RSV ARI was a planned secondary analysis but this endpoint was not included in the confirmatory testing strategy.

The sample size calculation was based on conducting the primary analysis when at least 59 cases of RSV-LRTI with ≥2 symptoms had accrued in the efficacy evaluable population. However, there was a planned interim analysis when at least 29 evaluable first-episode RSV-LRTI cases with ≥2 symptoms had accrued. Moreover, the interim analysis was to estimate efficacy against RSV-LRTI with ≥3 symptoms if at least 15 cases had accrued and against RSV-sLRTI if 12 cases had accrued. There was no minimum set for including an analysis of RSV-ARI in the interim or final analyses.

By mid-July 2022, more than 34,000 subjects had been randomised and treated and 94% were still being followed in the study. The majority (>22,000; ~60%) was enrolled in N. America, followed by ~8000 (~21%) in Argentina. While the majority was aged 60-69 years (~21,000), ~11,000 were aged 70-79 years and >900 subjects (~6%) were 80+ years. Just over half had at least one of the pre-specified significant underlying conditions. Ultimately, 95% of randomised subjects in each group were eligible for the evaluable efficacy population.

The planned interim efficacy analysis was conducted when 44 first-episode RSV LRTIs with ≥2 symptoms had accrued in the first RSV season and up to a cut-off date of 08 July 2022. At this time, the mean surveillance duration was 206 days in both treatment groups. Vaccine efficacy against RSV-LRTI was 66.7% with a lower bound of the 96.66% CI >28%. The benefit of RSVpreF was apparent

very shortly after commencement of active surveillance and, based on available follow-up data, was maintained at one year.

The majority of cases was due to RSV B and the study was not powered for efficacy analyses by subtype. Nevertheless, using the standard method of calculating vaccine efficacy, the point estimates and 96.66% CI were 88.9 (10.6, 99.8) for RSV A and 56.5 (-0.7, 82.8) for RSV B. These data, along with the clear numerical difference favouring RSVpreF for RSV A and RSV B cases, do not point to any specific concern about efficacy by RSV subtype.

There were 16 first-episode LRTI-RSV cases with ≥3 symptoms using the same cut-off date so the interim analysis of that endpoint was also conducted. With only 2/16 cases in the RSVpreF group, vaccine efficacy was 85.7% and the lower bound of the 96.66% CI was 32%. Of the 16 cases, 11 were due to RSV B, with vaccine efficacy at 90% (96.66% CI 21.8, 99.8). For RSV A, it can only be observed that 3 of the 4 cases occurred in the placebo group. The benefit of vaccination for this endpoint was apparent from ~day 45 post-vaccination onwards and was maintained at one year using all available follow-up data.

Overall, the interim analysis demonstrated that RSVpreF is efficacious in preventing RSV-LRTI in adults aged from 60 years from day 15 post-vaccination onwards. The EOS1 analysis was provided during the procedure and gave results for estimates of VE based on updated numbers of cases that were consistent with those of the interim analysis.

Efficacy in infants born to vaccinated mothers

C3671008 was the single pivotal efficacy study to support use in pregnant women at 24-36 weeks of gestation to prevent RSV-LRTI in their infants during the first 6 months of life. This randomised, double blind, placebo-controlled study was designed to estimate the absolute vaccine efficacy of RSVpreF against RSV LRTI in infants born to vaccinated mothers using a case-driven primary analysis.

Eligible women were to be between 24 and 36 weeks of gestation based on LMP and the earliest ultrasound conducted with an uncomplicated and natural singleton pregnancy. For purposes of providing a population expected to be adherent to study procedures, these women were to be attending antenatal care with planned delivery in a healthcare facility. The protocol defined the infant efficacy endpoints in detail, which were acceptable. It should be noted that these endpoints all involved medically-attended illnesses, defined by any contact with a healthcare professional. However, the proposed indication statement refers only to the disease to be prevented, which is acceptable.

Active surveillance commenced with weekly contacts from 72 h after birth and continued until month 6, after which the frequency of contact was reduced to approximately monthly. Care-givers were also able to initiate contact with study staff in case of intervening onset of illnesses potentially meeting the criteria.

There were parallel primary efficacy endpoints of MA-LRTI and severe MA-LRTI for which there was a Bonferroni multiplicity adjustment procedure. Success of the study required that the lower bound of the CI around the point estimates of vaccine efficacy for either or both endpoints were >20%. Furthermore, for each of these primary endpoints, there was sequential testing for vaccine efficacy based on cases of each that occurred up to day 90, day 120, day 150 and day 180 after birth. Based on several assumptions regarding accrual and 60% vaccine efficacy, 6,900 pregnant women were to be enrolled to provide 124 cases of RSV MA-LRTI in their infants with onset within 90 days of birth.

Interim analyses were planned to assess efficacy and safety after at least 43 cases and/or after at least 62 cases of MA-LRTI due to RSV within 90 days of birth had accrued and results could be used for stopping for futility or stopping for early success. The exact number of cases at each interim analysis was not fixed and could be decided based on operational reasons. The alpha levels used at interim and final analyses depended on the exact fraction of cases available at the interim analysis.

The primary efficacy analysis was conducted in the infant efficacy evaluation population, which was confined to those born at least 14 days after maternal vaccination and excluded any infants who received an anti-RSV monoclonal antibody. The main analysis was also performed based on the mITT efficacy infant population. This plan was acceptable.

Where MA-LRTI and severe MA-LRTI visits had no accompanying valid central or local NAAT test results, positive or negative results were imputed. The plans for imputation included assuming that missing swab results were positive in the same proportion (by vaccine group) as the non-missing swab results in MA-LRTI events (missing-at-random assumption). Alternatively, missing swab results for vaccine group infants were assumed to be positive in higher proportions than the non-missing swab results in MA-LRTI events while missing swab results for placebo group infants were assumed to be positive in the same proportion as the non-missing swab results in MA-LRTI events (missing-not-at-random assumption). In a further sensitivity analysis, any test indicating positivity for RSV was to be accepted and used to define MA-LRTI cases if qualified by clinical symptoms. Where events were adjudicated, the EAC's decision on the event as MA-LRTI or severe MA-LRTI was used. If not adjudicated, the event was assessed according to the protocol criteria for each event.

The results reported in the CSR of December 2022 reflect the second interim efficacy analysis, which was conducted following the predicted end of the fourth RSV season and included 80 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth, of which 39 were severe MA-LRTI. The results led the E-DMC to recommend stopping the study because the success criterion for VE was met for one of the two primary efficacy endpoints. At the time of data cut-off, >75% of the 7392 pregnant women had completed the study and almost 80% of their infants had completed at least to month 6.

Just over half of the adolescent and adult pregnant females (aged from 14-47 years) had been vaccinated between weeks 24 and 32 and ~45% between weeks 32-36. Most infants were born at term (≥93.7% born at ≥37 weeks to <42 weeks) while most of the pre-term infants were near-term at birth (≥4.4% were ≥34 to <37 weeks GA). Less than 2% were excluded from the primary analysis because they were born less than 2 weeks after maternal vaccination.

With 80 cases of RSV MA-LRTI with onset within 90 days of birth, the point estimate of vaccine efficacy was 57.1% with 99.5% CI 14.7, 79.8. Thus, the pre-defined lower bound criterion for success (>20%) was not met even though it was well above zero, which is compatible with a conclusion of superiority for maternal vaccination vs. no vaccination. Although it was understood from the protocol that testing at sequential time points would not occur if the pre-defined criterion for success was not met at the prior time point, the CSR shows sequential analyses. The point estimates of vaccine efficacy remained >50% at days 120, 150 and 180, although there was a small decline to 51.3% at day 180, and the lower bounds of the 97.5% CI were from 28-31%. The graphical display showed separation of the curves from ~2 weeks after birth onwards. Results for the mITT population and planned sensitivity analyses gave similar findings.

Vaccine efficacy against severe RSV MA-LRTI was 81.8% at day 90, falling to 69.4% at day 180 but the lower bounds of the CI were >40% at each time point. Thus, the vaccine was more effective at

preventing severe disease in vaccine breakthrough cases of RSV-LRTI than it was at preventing RSV-LRTI. Graphical display indicated separation of the curves from 2 weeks after birth onwards. Results were similar for the mITT population and for the planned sensitivity analyses.

The overall findings suggest that administration of RSVpreF during pregnancy is superior to no RSVpreF during pregnancy for preventing RSV MA-LRTI in the first 6 months of life.

3.3. Uncertainties and limitations about favourable effects

RSV A and RSV B

At the time that the pivotal efficacy studies were conducted, RSV B predominated over RSV A in causing symptomatic disease in older adults and in infants. It was acceptable that neither C3671013 in older adults nor C3671008 in infants born to vaccinated mothers was powered to determine efficacy against the individual RSV subtypes. Indeed, since the subtype distributions could not be predicted prior to study initiation, it would not have been feasible to power the studies for subtype efficacy.

The available data show at least a numerical benefit for RSVpreF vs. placebo for preventing RSV-LRTI due to RSV A and B in both populations of interest. However, with few RSV A cases, the 95% CI for point estimates of vaccine efficacy for these secondary endpoints were wide, such that lower bounds were not always above zero. It should be noted that the RSV subgroup was not determined for all cases that met the clinical criteria and were laboratory-confirmed. It cannot be ruled out that some bias could have occurred in reporting of subtypes depending on the assay performance (e.g. if subtyping required a minimum amount of virus to be present and viral load was more likely to be higher in older adults given placebo and in infants born to mothers given placebo). While the pivotal studies cannot confirm comparable efficacy against RSV A and B, the immunogenicity data in older adults and in infants indicate broadly comparable NA_{50} titres against the two subtypes. Overall, there is no specific concern raised over the ability of RSVpreF to prevent RSV-LRTI due to RSV A or B.

Efficacy in older adults

The number of cases of severe RSV-LRTI accrued as of the cut-off date was <12 so no analysis was conducted and no claim for prevention of severe cases is made by the applicant. There were insufficient additional cases of severe LRTI at EOS1 to support a robust estimate of VE specific to severe LRTI.

Having reached the success criteria for the analyses of RSV-LRTI, the applicant analysed the secondary endpoint of RSV ARI. With 22 RSVpreF vs. 58 placebo group cases, the point estimate of vaccine efficacy was 62% and the lower bound of the 95% CI was 37%, which supports a conclusion that RSVpreF also has an effect on preventing RSV ARI. However, this was a secondary analysis for which the study was not powered and for which there is no evidence that Type 1 error was controlled.

Efficacy in infants born to vaccinated mothers

The largest proportion of pregnant women was enrolled in the US, where 17 cases of RSV MA-LRTI accrued (2 RSV Pre F and 15 placebo) by day 90, giving a point estimate of vaccine efficacy at 86.8% (95% CI 43.4, 98.5). There were no cases recorded in several participating countries before day 90, possibly influenced by COVID-19 restrictions and parental caution. Whereas similar numbers were enrolled in Argentina and S. Africa, vaccine efficacy by day 90 was shown only in Argentina (65.5%; 15.1, 87.7) and there was no apparent benefit in S. Africa (with 8 cases in the vaccine group and 6

cases in the placebo group). Moreover, the cases accrued up to day 90 indicated that vaccine efficacy was apparent only in the upper income countries.

However, as time passed and cases accumulated, a numerical benefit for infants born to vaccinated mothers began to emerge in several countries with no or very few cases at earlier time points and case rates were lower vs. placebo group infants even in S. Africa. With even fewer cases of severe RSV MA-LRTI recorded, even greater caution is required when viewing the subgroup analyses. However, a similar pattern emerged, with a numerical benefit evident even in S. Africa especially from D120 onwards.

The applicant does not claim a benefit for preventing any RSV disease. However, this was evaluated as an exploratory endpoint (i.e. counting any symptomatic laboratory-proven RSV cases regardless of LRTI) and gave estimates of vaccine efficacy up to day 180 in the range 37-39% with lower bounds of the 95% CIs all above 16 and above 20 from D120 onwards. It is agreed that no claim should be made based on this analysis but it is supportive of the primary analysis.

The subgroup analyses must be viewed with caution due to small or very small denominators in many cases. There appeared to be at least a numerical benefit for RSVpreF for RSV MA-LRTI regardless of maternal vaccination between weeks 24-28, 28-32 or 32-36 weeks of gestation, which supports the recommendations for timing of maternal vaccination made in section 4.2. However, the data point to the possibility that efficacy may be lowest in infants born to mothers immunised in the 24-28 week window of gestation and these data have been described in section 5.1.

Concomitant administrations

In the FIH study, co-administration of 240 µg RSVpreF with seasonal influenza vaccines gave a general trend to lower HAI titres especially in the younger age subgroup, noting that the two age subgroups received different seasonal influenza vaccines. Additional data for HD seasonal influenza vaccine in subjects aged 65-85 years in a separate study suggested no major effect of RSVpreF co-administration on HAI titres in this age range.

To further investigate co-administration with seasonal inactivated influenza vaccine (SIIV), the applicant has conducted a Phase 3 study C3671006 in ~1400 healthy Australian adults aged 65+ years who received RSVpreF + SIIV together or in a staggered fashion. Data from this study indicate that NA GMTs for RSV A and B as well as HAI titres are numerically lower on co-administration although all the lower bounds of the 95% CI around the GMT ratios exceed 0.67. Therefore, co-administration is not precluded but a more extensive description is required in section 4.5.

Co-administration with Tdap was investigated in non-pregnant women aged 18-49 years and indicated no negative effect on anti-RSV A and B NA based on the pre-defined non-inferiority criteria. For anti-T and anti-D, the majority of subjects already had >0.1 IU/mL prior to vaccination, which somewhat limits any conclusion based on results that showed that the pre-defined non-inferiority criteria were met. For proportions with >1.0 IU/mL anti-D, the comparison made between the selected RSVpreF formulation (120 µg) and the placebo group (Tdap alone) suggested a negative effect of co-administration on anti-D (from 24% to 53% in the c-administration group vs. 17.9% to 77% in the Tdap alone group).

Using the combined results from RSVpreF groups, non-inferiority was not shown for anti-PT, anti-FHA and anti-PRN immune responses since the lower bounds of the 2-sided 95% CIs for the GMC ratios of the combined RSVpreF/Tdap groups to the placebo/Tdap group did not exceed 0.67 (range 0.48 to

0.64). When the comparison was made between the 120 µg RSVpreF formulation and Tdap alone, the lower bounds of the CIs were 0.68 for anti-PT, 0.52 for anti-FHA and 0.45 for anti-PRN. In the Phase 3 study C3671008 at least 2 weeks was to elapse between administration of RSVpreF and Tdap.

Current evidence, and the stance taken in the Phase 3 study, should lead to a clear statement in section 4.5 that at least 2 weeks are recommended between administrations of RSVpreF and Tdap.

3.4. Unfavourable effects

The size and extent of exposure of the safety population is sufficient and in line with ICH E1.

The most common adverse reactions reported within the first 30 days included injection site reaction, redness and swelling. Whilst the local reactions experienced by both groups of adults were similar, a higher percentage of pregnant woman experienced local reactions.

The incidence of systemic reactions was also higher in the pregnant population. The most frequently reported systemic event was fatigue which occurred with a similar frequency in both treated and placebo groups. The incidence of fever was low and occurred at a similar frequency in both the placebo group and vaccinated participants. However, a larger percentage of vaccinated subjects took analgesics for muscle pain which could have masked pyrexia.

Muscle pain and headache were more frequently reported in the RSVpreF group compared to placebo in the maternal population and are listed in the SmPC.

Guillain-Barré syndrome and Miller Fisher syndrome occurred in two participants in the older population.

The majority of adverse reactions and events were of mild to moderate intensity. The safety profile was similar in participants who received any dose level or formulation of RSVpreF.

The risk of fetal death (0.2%) was consistent or lower than the estimated background rates. Congenital abnormalities were reported at a similar frequency in the active and placebo treated groups. Developmental delays were reported at a similar frequency across both groups. The risk of preterm delivery was similar in the RSVpreF and placebo groups, except in one group of women where there was a slightly higher number of preterm deliveries. These women were of upper middle-income status and the reason for a slightly higher number of preterm deliveries in this group is not clear. Premature delivery will be further monitored in the planned post authorisation studies.

The condition at birth for live infants was comparable between those born to vaccinated and unvaccinated mothers.

3.5. Uncertainties and limitations about unfavourable effects

The applicant has provided justification for the adverse reactions listed in section 4.8 of the SmPC but has been asked to include some adverse events of special interest (AESI). Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS) occurred in two participants in the older population.

The applicant provided data concerning anti-pyretic use in vaccinated subjects and there was a slightly increased use of analgesics due to myalgia in the maternal population treated with the vaccine. Use of

anti-pyrectic analgesics may mask pyrexia and the applicant has been requested to monitor adverse reactions including pyrexia in the post authorisation setting.

For the AESIs low birth weight as well as premature baby further information on severity (e.g. proportions of diverging weight and age at birth) was requested. In addition, for all cases of congenital anomalies, summary tables based on severity as well as expected background incidence of the respective anomalies were requested.

The applicant provided the requested data and clarified that the higher numbers in the RSV group vs the placebo group mainly come from imbalances observed in upper-middle income countries (7.5% vs 4.1%). As numbers in high and low-income countries were comparable, there was no increase in mortality in preterm births and the overall incidence of preterm births was lower than the background rates in all countries where the study was conducted, no further concerns are raised.

However, the number of preterm deliveries and low birth weight should continue to be monitored in the planned post authorisation studies. Data including potential risk factors for preterm delivery should be collected in the studies.

For all cases of congenital anomalies, a summary table based on severity was provided. There was no difference in rates of SAEs of congenital anomalies between the RSVpreF and the placebo group.

To provide more data about the safety profile of the vaccine, the applicant was requested to provide an update on all available safety data from studies C3671008 and C3671013 and an update documenting resolution of the serious adverse events. The applicant provided the requested data and information on resolution of all serious adverse events and reactions.

The final study reports for both studies C3671008 and C3671013 are due in 2024 and this should be submitted to the agency by the company.

Some populations were excluded from the clinical trials and therefore there is no safety data from individuals with high-risk pregnancies, renal or hepatic impairment or individuals with immunodeficiency. These high-risk populations have been added to the missing information in the safety specifications of the risk management plan.

3.6. Effects Table

Table 57: Effects Table for Abrysvo (based on data cut-offs applied to CSRs in the initial MAA)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects C3671013 in adults aged from 60 years						
VE against RSV-LRTI	≥2 symptoms	cases	RSV PreF 11	Placebo 33	VE 66.7% (96.66% CI 28.8, 85.8)	CSR
VE against RSV-LRTI	≥3 symptoms		2	14	VE 85.7% (96.66% CI 32.0, 98.7)	
VE against RSV-ARI			22	58	VE 62.1% (95% CI 37.1, 77.9)	
Favourable Effects C3671008 in infants born to vaccinated mothers						
VE against MA RSV-LRTI		cases	RSV PreF	Placebo		CSR
	Day 90		24	56	VE 57.1% (14.7, 79.8)	
	Day 120		35	81	VE 56.8 (31.2, 73.5)	
	Day 120		47	99	VE 52.5 (27.8, 68.9)	
	Day 180		57	117	VE 51.3 (29.4, 66.8)	
VE against severe MA RSV-LRTI	Day 90		6	33	VE 81.8 (40.6, 96.3)	
	Day 120		12	46	VE 73.9 (45.6, 88.8)	
	Day 120		16	55	VE 70.9 (44.5, 85.9)	
	Day 180		19	62	VE 69.4 (44.3, 84.1)	
Unfavourable Effects						
Vaccination site pain	Pregnant population		41.5	10.2		CSR
	Population >/=60 years	%	10.5	6.0		
Vaccination site redness	Pregnant population		6.9	0.2		
	Population >/=60 years		2.7	0.7		
Vaccination site swelling	Pregnant population		6.0	0.2		
	Population >/=60 years		2.4	0.5		
Myalgia	Pregnant population		27.5	17.0		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	Population >/=60 years		10.1	8.4		
Headache	Pregnant population		31.0	27.5		
	Population >/=60 years		12.8	11.7		

There was a case of Guillain-Barré syndrome and a case of Fisher Miller syndrome in the older population.

Abbreviations: VE= vaccine efficacy
Notes: The CI were adjusted for multiplicity

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy in adults aged from 60 years

C3671013 was the single pivotal vaccine efficacy study to support use in subjects aged from 60 years. This randomised, double blind, placebo-controlled study was adequately designed to estimate the absolute vaccine efficacy of RSVpreF using a case-driven primary analysis based on RSV-LRTI meeting the primary case definitions that required ≥2 or ≥3 of the listed symptoms to be present.

The planned interim efficacy analysis was conducted when 44 first-episode RSV LRTIs with ≥2 symptoms had accrued in the first RSV season, at which time vaccine efficacy was 66.7% with a lower bound of the 96.66% CI >28%. The benefit of RSVpreF was apparent very shortly after commencement of active surveillance and, based on available follow-up data, was maintained at one year. Based on 16 first-episode LRTI-RSV cases with ≥3 symptoms accrued by the same cut-off date, vaccine efficacy was 85.7% and the lower bound of the 96.66% CI was 32%. The benefit of vaccination for this endpoint was apparent from ~day 45 post-vaccination onwards and was maintained at one year using all available follow-up data. Overall, the interim analysis demonstrated that RSVpreF is efficacious in preventing RSV-LRTI in adults aged from 60 years from day 15 post-vaccination onwards. Therefore, the primary analysis supports a claim for prevention of RSV LRTI in adults aged from 60 years.

Safety in adults aged from 60 years

The majority of adverse reactions and events were of mild to moderate intensity. The most common adverse reactions reported within the first 30 days included injection site reaction, redness and swelling. The most commonly reported systemic side effects included muscle pain and headache. The incidence of fever was low and occurred at a similar frequency in both the placebo group and vaccinated participants.

Guillain-Barré syndrome and Miller Fisher syndrome occurred in two participants in the older population. The applicant has been requested to update section 4.8 of the SmPC with these adverse reactions.

Efficacy in infants born to vaccinated mothers

C3671008 was the single pivotal efficacy study to support use in pregnant women at 24-36 weeks of gestation to prevent RSV-LRTI in their infants during the first 6 months of life. This randomised, double blind, placebo-controlled study was adequately designed to estimate the absolute vaccine efficacy of RSVpreF against RSV LRTI in infants born to vaccinated mothers using a case-driven primary analysis.

The results reported in the CSR of December 2022 reflect the second interim efficacy analysis, which was conducted following the predicted end of the fourth RSV season and included 80 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth, of which 39 were severe MA-LRTI. For prevention of RSV MA-LRTI with onset within 90 days of birth, the point estimate of vaccine efficacy was 57.1% with 99.5% CI 14.7, 79.8. Thus, the pre-defined lower bound criterion for success (>20%) was not met even though it was well above zero, which is compatible with a conclusion of superiority for maternal vaccination vs. no vaccination. The point estimates of vaccine efficacy remained >50% at days 120, 150 and 180 and the lower bounds of the 97.5% CI were from 28-31%. The graphical display showed separation of the curves from ~2 weeks after birth onwards. Vaccine efficacy against severe RSV MA-LRTI was 81.8% at day 90, falling to 69.4% at day 180 but the lower bounds of the CI were >40% at each time point. Graphical display indicated separation of the curves from 2 weeks after birth onwards. Results were similar for the mITT population and planned sensitivity analyses.

The indication statement should refer to passive protection of infants from birth to 6 months of age against RSV LRTI by means of vaccinating their mothers during pregnancy. Since this means rewording of the indication, there is a Major Objection although it can be resolved by simple editing.

Safety in pregnant women and birth status of their infants

The most common adverse reactions reported within the first 30 days included injection site reaction, redness and swelling. A higher percentage of pregnant woman given RSVpreF experienced local reactions compared to those given placebo. The incidence of systemic reactions was also higher in the pregnant population. The most frequently reported systemic event was fatigue, but this occurred with a similar frequency in both treated and placebo groups. Muscle pain and headache were more frequently reported in the RSVpreF group compared to placebo. However, there are no major safety concerns raised by the data. There was a slightly increased number of pregnant women in the upper middle-income group in the active treatment arm that had preterm births. The difference did not reach statistical significance, the absolute increase in number of preterm deliveries was small and did not result in a consequent increase in adverse neonatal outcomes. Maternal and infant outcomes will continue to be monitored in the planned post-authorisation studies. Overall vaccination during pregnancy did not affect rates of fetal loss, congenital abnormalities, developmental delays or preterm delivery and the condition of infants at birth was comparable between those born to vaccinated and unvaccinated mothers.

3.7.2. Balance of benefits and risks

RSVpreF has been shown to prevent RSV-LRTI in adults aged from 60 years and RSV-LRTI in infants born to vaccinated mothers for at least the first 6 months of life. There are no major safety concerns. From a clinical perspective, a positive benefit/risk balance in the proposed indications of prevention of LRTD caused by RSV can therefore be established.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of Abrysvo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Abrysvo is favourable in the following indication(s):

- "Passive protection against lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age following maternal immunisation during pregnancy. See sections 4.2 and 5.1.
- Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

The use of this vaccine should be in accordance with official recommendations."

The CHMP therefore recommends the granting of the marketing authorisation subjects to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that RSV subgroup A glycoprotein F and RSV subgroup B glycoprotein F, stabilised in prefusion conformation and produced in Chinese Hamster Ovary cells by recombinant DNA technology, contained in the medicinal product Abrysvo, is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).