ABRYSVO

(RESPIRATORY SYNCYTIAL VIRUS VACCINE [BIVALENT, RECOMBINANT])

RISK MANAGEMENT PLAN

RMP Version number: 1.1

Data lock point for maternal indication: 09 May 2024

Data lock point for adult indication: 08 May 2024

Date of final sign off: 09 October 2024

Rationale for submitting an updated RMP: Following a request for supplementary information, the MAH is requested to update statements concerning the causal relationship for Guillain-Barré syndrome throughout the RMP since it has been classified as important identified risk (Procedure No. EMEA/H/C/006027/II/0007, dated 19 September 2024).

Summary of significant changes in this RMP:

RMP Part/Module	Major change(s)
PART II Safety Specification Module SVII 1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP	Addition of Post-Authorisation Safety Studies C3671038, C3671026. Amendment of Risk benefit impact of GBS.
Module SVII 3.1 Presentation of Important Identified Risks and Important Potential Risks	Update of the Characterisation of risk, and preventability (Table 38).
PART VI – II.B Summary of Important Risks	Update Table 46 (Important Identified Risk of GBS - Evidence for linking the risk to the medicine)
Annex 8	Updated to reflect the overall changes

Other RMP versions under evaluation: None

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

AA	African American
AE	Adverse Event
AIAN	American Indian and Alaska Native
ADR	Adverse Drug Reaction
ARI	Acute respiratory illness
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention (United States)
COPD	Chronic obstructive pulmonary disease
COVID-19	Severe acute respiratory syndrome coronavirus 2
CHF	(Chronic or Congestive) heart failure
CT	Clinical Trial
ECDC	European Centre for Disease Prevention and Control
EDP	Exposure During Pregnancy
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GBS	Guillain-Barré syndrome
HIV	Human Immunodeficiency Virus
ICD	International Classification of Disease
ICU	Intensive care unit
IFN λ	Interferon alfa
ILI	Influenza-like illness
LRTD	Lower respiratory tract disease
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NZW	New Zealand White
NorEPIS	Norwegian Enhanced Paediatric Immunization Surveillance
OR	Odds ratio
PASS	Post Authorisation Safety Study
PCR	Polymerase chain reaction
PM	Post Marketing
PRAC	Pharmacovigilance Risk Assessment Committee
PSUSA	Periodic Safety Update Report Single Assessment
PT	Preferred Term
RMP	Risk Management Plan
RSV	Respiratory syncytial virus
RSV-A	Respiratory syncytial virus, strain A
RSV-B	Respiratory syncytial virus, strain B
RSVpreF	Respiratory syncytial virus bivalent stabilised prefusion F subunit vaccine
SMQ	Standardised MedDRA Query
Tdap	tetanus, diphtheria and acellular pertussis vaccine
UK	United Kingdom

US	United States
VAERS	Vaccine Adverse Event Reporting System
wGA	Weeks' gestational age
WHO	World Health Organization

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Respiratory syncytial virus vaccine (bivalent, recombinant)
Pharmacotherapeutic group(s) (ATC Code)	J07BX05
Marketing Authorisation Applicant	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Abrysvo
Marketing authorisation procedure	Centralised
Brief description of the product:	*Chemical class* Respiratory syncytial virus vaccine
	Summary of mode of action Abrysvo contains two recombinant stabilised RSV prefusion F antigens representing subgroups RSV-A and RSV-B. Prefusion F is the primary target of neutralising antibodies that block RSV infection. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated lower respiratory tract disease. In infants born to mothers who were vaccinated with Abrysvo between weeks 24 and 36 of gestation, protection against RSV-associated lower respiratory tract disease is due to transplacental transfer of RSV neutralising antibodies. Adults 18 years of age and older are protected by active immunisation.
	Important information about its composition Abrysvo is a solution for injection that consists of equal amounts of two stabilised RSV F antigens, denoted 847A and 847B, representing the two major subgroups A and B, respectively. It 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 vaccine is supplied as lyophilised powder in 2 presentations: - vial of antigens for Abrysvo (powder), pre-filled syringe of solvent and a vial adaptor (with or without a needle). - vial of antigens for Abrysvo (powder) and vial of solvent. After reconstitution, Abrysvo contains trometamol, trometamol hydrochloride, sucrose, mannitol, polysorbate 80, sodium chloride, hydrochloric acid (for pH adjustment) and water for injections.
Hyperlink to the Product Information:	Module 1.3.1.

Indication(s) in the EEA	Current: Abrysvo is indicated for: • 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. • Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.
	Proposed: Abrysvo is indicated for: • 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. • Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.
Dosage in the EEA	Current: *Pregnant individuals* A single dose of 0.5 mL should be administered between weeks 24 and 36 of gestation. *Individuals 60 years of age and older* A single dose of 0.5 mL should be administered.
	Proposed: *Pregnant individuals* A single dose of 0.5 mL should be administered between weeks 24 and 36 of gestation. *Individuals 18 years of age and older* A single dose of 0.5 mL should be administered.
Pharmaceutical form(s) and strengths	Current: After reconstitution, one dose (0.5 mL) contains: • RSV subgroup A stabilised prefusion F antigen[1,2] 60 micrograms • RSV subgroup B stabilised prefusion F antigen[1,2] 60 micrograms (RSV antigens) [1]glycoprotein F stabilised in the prefusion conformation. [2]produced in Chinese Hamster Ovary cells by recombinant DNA technology.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication

Abrysvo (respiratory syncytial virus vaccine, bivalent, recombinant; also referred to as RSVpreF) is indicated for:

- 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.
- Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

SI.1. Indication for maternal immunisation

Passive protection against lower respiratory tract disease caused by RSV in infants from birth through 6 months of age following maternal immunisation during pregnancy.

A literature review was conducted to evaluate the epidemiology of RSV in Europe and the United States. PubMed was searched in October 2022 to identify primary research articles published between January 2022-October 2022 and systematic reviews and meta-analyses published between January 2017 and October 2022. The literature search was conducted using key words such as incidence and prevalence combined with terms representing RSV. Inclusion of articles was limited to those with data on the paediatric population under age 5 years.

Iterative, unstructured searches of PubMed and Google were further conducted to obtain additional information on aspects of RSV epidemiology that were not adequately captured by the initial PubMed searches (e.g., from the Centers for Disease Control and Prevention [CDC], and European Centre for Disease Prevention and Control [ECDC]). Important citations referenced within review articles and meta-analyses were also obtained when relevant.

Since public health measures taken in response to the COVID-19 pandemic temporarily disrupted the transmission and incidence patterns for other infectious diseases[1, 2], epidemiologic data collected between March 2020 and October 2022 were excluded.

Incidence

- *Global*

A recent estimate of the global burden of RSV infections in paediatric subjects under 5 (excluding 5-year-olds) comes from a 2022 systematic review by the RSV Global Epidemiology Network. [3] They included 430 studies published between January 1, 1995 and December 31, 2020 from around the world and 51 unpublished population-based studies, drawing on far more data than they had done in similar, previous estimates.[4,5] The authors

estimated that, globally for the year 2019, there were 33.0 million episodes of acute lower respiratory infections of RSV in paediatric subjects under age 5 years. They also noted that 5 countries collectively account for 43% of the world's paediatric RSV cases under 5: India, China, Nigeria, Pakistan, and Indonesia, [5] and that incidence of RSV-associated acute respiratory infection peaks between the ages of 0 months to 3 months in lower- and middle-income countries, but between the ages of 3 months and 6 months in upper middle-income and high-income countries.[3]

- *US and Europe*

The US Centers for Disease Control and Prevention (CDC) estimates that RSV is responsible for 2.1 million outpatient visits and 58,000 hospitalisations annually among paediatric subjects under 5 years old in the US.[6] In a prospective population-based surveillance study conducted in 2000-04 of 5,067 US paediatric subjects under 5 who went to the hospital or an outpatient visit for an acute respiratory infection, Hall et al. found that 919 (18%) of them were infected specifically with RSV.[7] The proportion was consistent across different care settings, as RSV accounted for 20% of hospitalisations, 18% of emergency room visits, and 15% of outpatient visits. Among RSV cases who were typed, across all 4 years, 80% were RSV-A, 18% RSV-B, and 2% had both strains; RSV-A predominated over RSV-B in 3 of the 4 seasons across 2000-04. During the 2015-16 RSV season, Rha et al. conducted a study similar to the one Hall conducted a decade earlier, this time of 1,043 US paediatric subjects under 5 who were hospitalised with at least one of various acute respiratory infections. Rha et al. found that the proportion of acute respiratory infections that turned out to be RSV specifically was highest in December (52%), January (52%), and February (47%) and lowest in June (4%).[8]

For a study in a US commercially-insured population using the MarketScan database for years 2008-14, Tong et al. analysed 427,289 cases of RSV, 79% of which were under age 5 years, requiring medical attention (hospital or outpatient).[9] For young paediatric subjects, they found the following annual average rates of RSV cases requiring medical attention per 1,000 population per year: 79.0 for age under 1 year, 40.3 for 1-year-olds, and 14.1 for 2-4-year-olds.

In their systematic review of severe RSV in young paediatric subjects and infants in the US, Canada, and Europe, Bont et al. found that RSV accounted for 12–63% of all acute respiratory infections, and 19–81% of acute *viral* respiratory infections, causing hospitalisation in this population.[10] Another study of paediatric patients at a tertiary referral hospital in Spain also reported that RSV accounted for a large proportion of medically attended respiratory infections: 47.3% for ages 0-<6 months, 35.6% for ages 6-12 months, 26.4% for ages 1-2 years, and 13.9% for ages 3-5 years.[11]

Additional data from the systematic review by Bont et al. found that, while vulnerable subgroups such as preterm infants are at elevated risk of severe RSV infections, over 70% of young paediatric subjects hospitalised for RSV had no underlying medical conditions. [10] Overall, the studies reviewed suggested that 75-90% of infants hospitalised with RSV were aged under 12 months, including 44-83% aged under 6 months. In the first year of life, annual hospitalisation rates for RSV infections ranged from 3.2-42.7 RSV hospitalisations

per 1,000 infants per year. For ages 1-4 years, annual hospitalisation rates decreased to 0.6-1.78 RSV hospitalisations per 1,000 infants per year. Similar hospitalisation rates were reported in the Norwegian Enhanced Paediatric Immunization Surveillance (NorEPIS) network. In this study, those aged 0-12 months had an average estimated inpatient admissions rate of 9.9 (95% CI: 9.4-10.4) RSV admissions per 1,000 infants per viral season, while those aged 1-4 years had an average estimated inpatient admissions rate of 1.8 (95% CI: 1.8-1.9) RSV admissions per 1,000 paediatric patients per viral season.[12]

Anderson et al. provided estimates of incidence of severe RSV infection for vulnerable subgroups of preterm winter births. [44] They conducted a pooled analysis of 7 studies with a total of 7,820 infants born at 33-35 weeks' gestational age (wGA, i.e. preterm) during RSV seasons between 2000-14, including 267 infants who were hospitalised for RSV. Of the 7 studies, 4 were European, 1 was US, 1 Canadian, and 1 a mostly European international study. Across the studies, the incidence rates for preterm babies ranged from 3.15-5.92 hospitalisations per 100 patient-seasons. In the pooled analysis, 33–35 wGA infants born and hospitalised within the same RSV season experienced RSV-induced hospitalisation at the rate of 4.52 hospitalisations/100 patient-seasons.

- *Seasonality*

RSV seasonality has been affected by the COVID-19 pandemic, leading to the near disappearance of disease during strict quarantine periods and followed by a strong resurgence outside of traditional seasonal timeframes. The lack of population level exposure to RSV during the pandemic has led to a suspected "immunity debt", leaving infants potentially even more vulnerable to medically significant disease because they did not gain protective, neutralising RSV antibodies through their mothers during pregnancy.[13, 14, 15]

RSV seasonality patterns before COVID-19 pandemic are summarised here. A systematic review stated that the incidence of RSV infection is strongly associated with the winter season, with a general pattern of the RSV seasonal peak preceding the corresponding influenza seasonal peak by 6-8 weeks.[16] For the US during July 2014 through July 2017 (3 RSV seasons), the CDC reported that the median RSV onset occurred at week 41 (mid-October) and lasted 31 weeks until week 18 (early May), with the median national peak of RSV incidence occurring at week 5 (early February).[17] The CDC noted that the onsets of the 2014-17 RSV seasons occurred approximately 2 weeks earlier than the analogous onset estimates for the 2012-14 seasons, and that in 2012-14 RSV detection was done using antigen data while in 2014-17 laboratories used polymerase chain reaction-based detection. This suggests that the kind of RSV detection assay used influences detection of RSV cases and hence RSV surveillance.

There is regional variability in RSV burden and seasonality across the US, with an elevated RSV burden in Florida. For the 2016-17 season, across US Health and Human Services regions except Florida, RSV season onset across the country began between mid-September and mid-November; peaked between late-December and mid-February; and ended between mid-April and mid-May. [6],[17] By comparison to the rest of the country, Florida's RSV season began earlier and lasted longer. [17] Tong et al. conducted a study of the MarketScan database of US commercially-insured individuals that reported annual rates of RSV health care

utilization for over 40 million registrants during the 2008-14 observation period. [9] They found that, regionally, the South consistently had the greatest burden of RSV across all ages (annual range: 43-54%), followed by the North Central region (annual range: 18-23%). Although these regional figures are across all ages, Tong et al. noted that of all RSV cases in the database for the observation period, paediatric subjects under 5 accounted for 79%, including 46% solely by infants under 1 year of age. Since paediatric subjects under 5 are such a large proportion of RSV cases in the database, the overall regional pattern likely applies to paediatric subjects under 5 as well.

For Europe, Broberg et al. used European Centre for Disease Prevention and Control (ECDC) data to estimate peak RSV seasonality for 15 European countries for the seasons spanning 2010-16.[18] Across countries, the length of the RSV season in weeks was similar based on sentinel (median 16, range 9-24) and non-sentinel (median 18, range 8-24) surveillance. The peak weeks for RSV detections were likewise similar by both sentinel (median week 4, range 48-11) and non-sentinel (week 4.5, range 49-17) approaches. RSV detections peaked later, and seasons lasted longer with increasing latitude.

Prevalence

Globally, it has been estimated that about 60-70% of paediatric subjects have been infected with RSV by age 1 years, with 2-3% of them hospitalised for it, and that nearly all paediatric subjects have been infected by age 2 years. [16,19] These could be interpreted as estimates of period prevalence, with a 60-70% period prevalence for the first year of life and a period prevalence approaching 100% for the first 2 years. No estimates of average point prevalence of RSV infection in paediatric subjects aged 5 and under were found. Given the acute nature of the disease, any estimates of point prevalence would be similar to estimates of incidence, which may explain the lack of attention to point prevalence.

In a meta-analysis of 51 studies (28 European, 12 US) of respiratory viruses in paediatric subjects under age 2 years with bronchiolitis diagnosed between October 1999 and December 2017, RSV was the most commonly detected virus at 59.2% (95% CI 54.7%, 63.6%), far more common than the second-most prevalent viral agent (Rhinovirus, 19.3%).[20]

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Demographics

- *Age*

For paediatric subjects under 5 years old, Table 1 presents age distributions from several primary studies. Note that all these studies are for paediatric subjects with severe RSV infections, i.e., infections requiring hospitalisation or an outpatient visit. Thus, these age distributions may not be identical to the distributions for all RSV infections (mild and severe). No published age distribution data for all RSV infections were identified. Consistent with global data from a systematic review and meta-analysis [3] and a global, multi-site prospective cohort study,[21] Table 1, which presents data from individual studies, shows

that paediatric subjects in the US and Europe are at greatest risk of severe RSV infection in the first year of life, especially in the first 6 months. More specifically, across the studies in Table 1, paediatric subjects less than 1 year old account for 58-89% of RSV cases requiring medical attention among paediatric subjects under 5 years old, including paediatric subjects under 6 months accounting for 51-58% of RSV cases requiring medical attention among paediatric subjects under 5.

Table 1. Age of paediatric subjects under age 5 years with severe RSV infection

Study	Years	Country	Case Detection	N	Age Category (months)	Age %
Cai 2020[32]	2009-18	Germany	ICD-10 codes	8,521	*Overall:*	
					0-5	56
					6-23	38
					24-59	6
					ICU-admitted:	
					0-5	75
					6-23	20
					24-59	5
					Ventilated:	
					0-5	77
					6-23	18
					24-59	5
Hall 2009[7]	2000-04	US	Culture or PCR	919	*Hospitalised:*	
					0-5	58
					6-11	17
					12-23	18
					24-59	7
					Outpatient:	
					0-5	25
					6-11	24
					12-23	21
					24-59	30
Kuhdari 2018[47]	2001-14	Italy	ICD-9 codes	57,656[a]	0-11	89
					12-59	8
Rha 2020[8]	2015-16	US	PCR	1,043	0-2	33
					3-5	18
					6-11	17
					12-23	19
					24-59	13
Tong 2020[9]	2008-14	US	ICD-9 codes	Not stated[b]	0-11	58
					12-23	24
					24-59	17

a. Total number of cases included in study across all ages. Corresponding age-category percentages are percentages of total sample size arising from the given age category.
b. Study included 427,289 RSV cases across all ages for the period 2008-14, and paediatric subjects under 5 were 78.5% of the sample, implying 335,422 RSV cases under age 5.

ICD=International Classification of Disease, ICU=intensive care unit, PCR=polymerase chain reaction

- *Gender*

Reviews consistently state that "most"[22] or "nearly all"[23] paediatric subjects are infected with RSV at least once by the age of 2 years. This suggests that the *overall* risk of infection with RSV is similar in males and females. However, males appear to have an elevated risk of *severe* infection, that is, infection requiring medical attention. For paediatric subjects under 5 years old, Table 2 presents gender distributions from several primary studies in terms of the percentage of cases who were male. Most of the studies suggest males having a slightly increased risk of severe infection compared to females, with males being about 55% of severe cases. The pattern persists across different countries and methods of detecting RSV cases. The study by Hall et al. is an exception, with males having a slightly lower risk of severe RSV infection than females. While the difference between the Hall study and the others is not especially large, one contributor to the difference could be the range of RSV seasons, with the Hall study restricted to the early 2000s and the other studies taking place partly or entirely at later periods. Different conditions across different seasons might influence infection patterns.

Table 2. Gender of paediatric subjects under age 5 years with severe RSV infection

Study	Years	Country	Case Detection	N	Male %
Cai 2020[32]	2009-18	Germany	ICD-10 codes	8,521	*Overall:* 57 *ICU-admitted:* 53 *Ventilated:* 54
Hall 2009[7]	2000-04	US	Culture or PCR	919	*Hospitalised:* 43 *Outpatient:* 45
Kuhdari 2018[47]	2001-14	Italy	ICD-9 codes	57,656[a]	55
Rha 2020[8]	2015-16	US	PCR	1,043	56
Jensen 2021[48]	2010-16	Denmark	National register	418,404	56

a Total number of cases included in study across all ages. Corresponding percentage is percentage of total sample that was male for all ages, not restricted to paediatric subjects under 5 years old (97% were under 5).

ICD=International Classification of Disease, ICU=intensive care unit, PCR=polymerase chain reaction

- *Race/Ethnicity*

Available data on race and ethnicity for severe US cases are given in Table 3; no analogous data for Europe were identified. Note that the Hall and Rha studies treated Hispanic status in different ways, making their distributions not directly comparable. Nevertheless, the data suggest that African American paediatric subjects have an elevated risk of severe RSV infection: despite African Americans being less than 15% of the US population,[24] and except for the Hispanic stratum in the Rha study, African American paediatric subjects accounted for about 25-39% of RSV cases requiring medical attention.

Furthermore, numerous studies in the US have demonstrated that American Indian and Alaska Native (AIAN) infants living on Tribal land experience rates of RSV-associated hospitalisation several fold higher than the general US population. [25,26,27,28,29,30,31] A 2000-2001 study comparing RSV-specific infant hospitalisation rates from the US National Hospital Discharge Survey to rates from the Indian Health Services Inpatient Dataset reported 27.4 hospitalisations per 1,000 infants aged <1 year in the general US population, but 34.4 hospitalisations per 1,000 AIAN infants aged <1 year. [29] Differences in hospitalisation rates were most pronounced for AIAN infants from Alaska (70.9 per 1,000) and the Southwest (48.2 per 1,000).[29] A 2009-2011 study comparing RSV-specific infant hospitalisation rates from the US Nationwide Inpatient Sample to rates from the Indian Health Services Inpatient Dataset reported similar patterns in incidence. [30] Overall, there were 16.6 annual RSV-specific hospitalisations per 1,000 infants aged <1 year in the general US population compared to 22.1 annual RSV specific hospitalisations per 1,000 AIAN infants aged <1 year. [30] Once again, the rates were even higher for AIAN infants in Alaska (43.1 per 1,000 infants per year) and the Southwest (25.4 per 1,000 infants per year).[30] Individual studies of the Navajo and White Mountain Apache population and the Alaskan Yukon-Kuskokwim Delta Region population also reported high RSV-specific hospitalisation rates among infants aged <1 year, with a 1997-2000 annual incidence rate of 91 per 1,000 infants in the Navajo and White Mountain Apache population, [27] and 1993-2012 annual incidence rates ranging from 53 per 1,000 infants to 249 per 1,000 infants in the Alaskan Yukon-Kuskokwim Delta Region. [25,28,31]

Table 3. Race and ethnicity of paediatric subjects under age 5 with severe RSV infection

Study	Years	Country	Case Detection	N	Race/Ethnicity	Race/Ethnicity %
Hall 2009[7]	2000-04	US	Culture or PCR	919	*Hospitalised:*	
					White	55
					AA	29
					Hispanic	10
					Other/Unknown	5
					Outpatient:	
					White	36
					AA	39
					Hispanic	16
					Other/Unknown	9
Rha 2020[8]	2015-16	US	PCR	1,043	*Non-Hispanic:*	
					White	59
					AA	25
					Other	15
					Unknown/Refused	0
					Hispanic:	
					White	60
					AA	2
					Other	29
					Unknown/Refused	10

AA=African American, PCR=polymerase chain reaction

Risk Factors

- *Overall Infection*

The literature mentions several risk factors that appear to elevate risk of overall infection with RSV. If, as suggested earlier, "most" or "nearly all" paediatric subjects are infected with RSV at least once by age 2 years, then risk factors for overall incidence of RSV infection may need to be interpreted with caution or considered only weakly predictive. In their retrospective cohort study of German paediatric subjects under 5 hospitalised for RSV, Cai et al. identify as risk factors for RSV infection being less than 1 year old, respiratory disorders, and cardiovascular disorders specific to the perinatal period.[32] While these factors may be especially salient for severe cases of RSV infection, it is plausible that they increased risk of overall RSV infection (mild or severe) because such individuals have weakened immune systems.

- *Severe Infection*

Publications have placed more emphasis on identifying risk factors for severe RSV infections. Although there is no universally accepted definition of severe RSV infection, [10] a common definition in the literature seems to be an infection requiring hospitalisation. While many risk factors for severe disease have been proposed, and some may explain demographic disparities in RSV-specific hospitalisation, [25,31,26] most paediatric subjects hospitalised for RSV infection were healthy prior to infection and had no known risk factors.[33] Table 4 lists risk factors for severe RSV infections mentioned in the literature. As with overall infection, a prominent theme among many risk factors is that they contribute to the individual having a relatively weak immune system.

Table 4. Risk factors for severe RSV infections in paediatric subjects up to 5 years old

Risk Factor	References
Age: <1 year and especially <6 months	Bont 2016,[10] Cai 2020,[32] Hall 2009,[7] Rha 2020,[8] Langley 2022,[21] Havdal 2022[12]
Birth just before or during RSV season	Bont 2016,[10] Andeweg 2021,[35] Mira-Iglesias 2022;[51] Figueras-Aloy 2016[34]
No breastfeeding or short duration of breastfeeding	Figueras-Aloy 2016,[34] Bulkow 2002,[26] Singleton 2007[31]
Congenital heart disease	Fauroux 2017,[33] Mirra 2018,[43] Cai 2020, [32] Havdal 2022[12]
Chronic lung condition, including asthma	Fauroux 2017, [33] Cai 2020, [32] Jensen 2021, [48] Havdal 2022[12]
Neurological or neuromuscular condition	Mirra 2018,[43] Cai 2020, [32] Havdal 2022[12]

Table 4. Risk factors for severe RSV infections in paediatric subjects up to 5 years old

Risk Factor	References
Caesarean delivery	Bont 2016, [10] Jensen 2021[48]
Prematurity	Fauroux 2017,[33] Cai 2020, [32] Hall 2009,[7] Rha 2020,[8] Jensen 2021,[48] Havdal 2022[12]
Presence of siblings	Bont 2016, [10] Andeweg 2021,[35] Jensen 2021, [48] Figueras-Aloy 2016, 34 Sommer 2011[36]
Indoor crowding	Figueras-Aloy 2016, [34] Bruden 2015,[25] Singleton 2007,[31] Bulkow 2002,[26] Sommer 2011[36]
Lower socioeconomic status / parental education	Bont 2016,[10] Figueras-Aloy 2016, [34] Bruden 2015,[25] Sommer 2011, [36] Bulkow 2002[26]
Smoker in household	Bont 2016, [10] Figueras-Aloy 2016, [34] Jensen 2021, [48] Bulkow 2002,[26] Sommer 2011[36]
Male sex	Bont 2016, [10] Jensen 2021, [48] Sommer 2011, [36] Figueras-Aloy 2016 34
Maternal age at delivery	Bont 2016, [10] Jensen 2021[48]
Low birth weight/small for gestational age	Bont 2016, [10] Cai 2020, [32] Figueras-Aloy 2016 34
Immunodeficiency (primary or cancer-related)	Gonzalez-Granado 2022,[37] Havdal 2022[12]
Trisomy 21	Havdal 2022[12]

The main existing treatment options

Currently, treatment consists primarily of supportive care. There is a prophylactic humanized monoclonal antibody, palivizumab (Synagis, AstraZeneca), with demonstrated safety and efficacy against severe RSV disease in high-risk infants.[38,39] Palivizumab neutralises RSV by binding the fusion glycoprotein (F) and its protective effect provides definitive proof of principle that serum neutralising antibody that targets the F glycoprotein can protect against RSV lower respiratory tract disease. Nirsevimab (Beyfortus, Sanofi), a next-generation single dose, extended half-life mAb, demonstrated efficacy against RSV LRTI in Phase 3 studies and received marketing authorisation in the EU in October 2022.[40,41,42]

Natural history of the indicated condition in the untreated population, including mortality and morbidity

- *Morbidity*

RSV infections are thought to be ubiquitous among young paediatric subjects worldwide, with the vast majority being infected at least once by the age of 2 years. [22,23,43] Indeed, bronchiolitis is the most frequent airway infection in the first 2 years of life and RSV is the virus most often responsible. [43] Acquired immunity from infection is temporary and therefore reinfection is common, with perhaps 75% of paediatric subjects experiencing a *second* infection by age 2 years. [22] Information about overall RSV morbidity—that is, morbidity for both cases requiring and not requiring medical attention—is often sparse because national surveillance can be incomplete and infection reporting voluntary. [17] Most information is limited to cases sufficiently severe to require medical attention, whether hospitalisations, outpatient visits, or a combination of the two.

Symptoms of RSV infection include severe lower respiratory tract infection, bronchiolitis, and pneumonia. [23,43] Timing plays a role in the disease, as around 50% cases of RSV hospitalisations among preterm infants occur among those born within the peak RSV season of winter.[44] While the RSV infection itself is acute, it can lead to long-term complications such as impairment in lung function, bronchospasm, recurrent wheezing, asthma, acute otitis media, and allergic sensitisation. [33,43,22,45,46] These long-term complications may be more pronounced for males compared to females. [46]

- *Medical Care*

The literature illuminates various aspects of the care received by RSV patients with infections severe enough to require medical attention. The CDC reports that, annually for the US, RSV infections in paediatric subjects under 5 leads to, on average, 2.1 million outpatient visits and 58,000 hospitalisations. [6] In a US study of commercially-insured RSV cases from 2008-14, outpatient visits accounted for the care setting for about 80% of paediatric subjects under 5 versus hospitalisations accounting for 5-10% for the same age group, with the remainder being emergency room or urgent care visits. [9] Altogether, most RSV cases severe enough to require some levels of medical attention do not require hospitalisation.

For the 2015-16 RSV season at 7 paediatric medical centres across the US, Rha et al. identified 1,043 paediatric subjects under 5 hospitalised for RSV. [8] The median length of hospital stay for subjects who were RSV-positive was 2 days, 69% received supplemental oxygen, 17% were admitted to an ICU, and 3% required mechanical ventilation. Pooled across the 7 centres, the rate of RSV-associated hospitalisations across all sites was 2.9 hospitalisations/1000 population among paediatric subjects under 5, including an even higher rate of 6.3 hospitalisations/1000 population among paediatric subjects under 2. Younger infants had still higher rates of hospitalisation: 14.7 hospitalisations/1000 population in paediatric subjects under 6 months and 18.9 hospitalisations/1000 population among paediatric subjects under 2 months.

Anderson et al. analysed data from 7 European and North American databases totalling 7,820 preterm infants. [44] Out of the 7 datasets, 5 had data on infants hospitalised for RSV infection who received supplemental oxygen. The authors found a wide range across datasets in the proportion receiving oxygen, from 32% (US) to 88% (Ireland). In the pooled analysis, 70% of infants received supplemental oxygen. The median duration that hospitalised infants received supplemental oxygen was consistent across datasets with a median of 4-5 days.

Cai et al. examined hospitalised RSV cases from 84 hospitals in Germany for the period 2009-18; their dataset included 8,521 cases under age 5 years. [32] Of those 8,521 hospitalised cases, 438 (5%) were admitted to the ICU. The authors noted that, of ICU cases that required ventilator support, 81% were paediatric subjects under 5. The paper reported a wealth of additional information on ICU cases, but these were not stratified by age. However, paediatric subjects under 5 represented 89% of all ICU cases in their dataset, making it likely that the rest of the ICU results largely apply to paediatric subjects under 5. For ICU cases across all ages, the mean and median length of ICU stay were 9 and 5 days, respectively. During the ICU stay, 38% required ventilator support. About 91% of ICU-admitted RSV cases were discharged home, 6% transferred to other facilities, and 3% died in the hospital. For ventilated cases, the mean and median ventilation length were 211 and 112 hours, respectively. About 82% of ventilated cases were discharged home, 10% transferred to other facilities, and 8% died in the hospital.

Kuhdari et al. analysed data on 57,656 hospitalised RSV cases across all ages in Italy during 2001-14, of which 89% were under 1 year of age.[47] They found that the under 1-year age category had the highest hospitalisation rate at 674 hospitalisations per 100,000 population. In the period 2001–2014, out of a total of 54,661 hospitalised paediatric subjects 0-2 years old, 93% were less than 1 year old and 24% were under 2 months old. For paediatric subjects 0-14 years old, the average duration of hospitalisation was 5 days.

Using a population-based national register from Denmark, Jensen et al. examined 10,956 paediatric subjects under 5 who were hospitalised for RSV during 2010-16.[48] Of these, 59% were under 6 months and 76% were under 12 months. The incidence of RSV hospitalisation was high in early infancy, peaking during the second month of life at almost 60 cases/1000 child-years, then decreasing to almost no hospitalised cases by age 3 years.

- *Long-Term Consequences of Infection*

Important outcomes of RSV infection are not limited to severe acute symptoms: infection can increase risk of later developing chronic conditions such as impaired lung function, [46] persistent wheezing, [33,45] or asthma. [33,46,45] Estimates of the strength of these relationships vary widely, at least partly due to differences in study design. One systematic review summarised studies of RSV infection before age 3 years as reporting that, subsequently, 4-47% of paediatric subjects develop recurrent wheezing and 8-76% develop asthma after up to 25 years follow-up (average follow-up 6–8 years).[33] A study of 189 Greek paediatric subjects who were hospitalised for RSV infection during infancy found that the following predictors were associated with development of asthma later in childhood: male gender, breastfeeding for less than 3 months, living in a home environment with moisture damage and/or tobacco smoke by at least 2 residents, and sensitization to at least one aeroallergen.[49]

A Norwegian prospective cohort study also reported that male gender was associated with worse impairment in young adult lung function following RSV-related bronchiolitis in infancy. [46]

- *Mortality*

Global mortality was estimated in a 2022 systematic review by the RSV Global Epidemiology Network. [3] The authors estimated that globally, for the year 2019, there were 101,400 total RSV-related deaths in paediatric patients under age 5 years, of which 26,300 were in-hospital deaths. In other words, 0.31% (101,400 out of 33.0 million) of global RSV cases among paediatric patients under age 5 years were estimated to end with RSV-related death. Paediatric subjects under 6 months were at elevated risk of death, with an estimated 13,300 in-hospital deaths due to RSV. Notably, low- and middle-income countries were estimated to account for more than 97% of RSV-attributable deaths in paediatric RSV cases under age 5 years. [3]

Hansen et al. estimated the annual RSV-related mortality burden in the US by examining over 50 million death certificates from the period 1999-2018.[50] Table 5 summarises their key results for paediatric subjects under 5. Similar to the data on severe infections cited in earlier sections, although overall mortality from RSV in paediatric subjects is very low, paediatric subjects under 1 year of age die from RSV at a higher rate than paediatric subjects aged 1-4 years. Table 5 suggests that approximately 250-300 paediatric subjects under the age of 5 years died from RSV annually across the US during the era before COVID-19 public health measures. Notably, while young paediatric subjects are generally at greater risk of being infected with RSV than adults, Hansen et al. estimated much higher RSV mortality rates for older adults than they did for paediatric subjects under 5, with point estimates (in deaths per 100,000 population per year) of 11.8 for 50–64-year-old and 46.8 for those 65 and older. Those aged 5-49 had an estimated RSV mortality rate of essentially zero.

Table 5. Estimated annual RSV-related mortality burden in paediatric subjects under 5 in the US, 1999-2018 (Hansen 2022)[50]

Age Category	Number of RSV-Related Deaths (95% CI)	RSV Mortality Rate, Deaths/100K Population Year (95% CI)
<1 year	106 (82, 131)	2.7 (2.1, 3.3)
1-4 years	168 (157, 179)	1.1 (1.0, 1.1)

Several primary studies of paediatric subjects under age 5 years who were hospitalised with RSV recorded deaths among their observed cases. Two small studies from the US – those by Hall et al. (919 cases) and Rha et al. (1,043 cases) – both reported zero deaths in their datasets. [7,8] In a German study of 8,521 paediatric subjects hospitalised with RSV, the authors reported that 10 (0.1%) died from the infection. [32] These numbers are consistent with

the Hansen modelling estimates suggesting that, while RSV infections are extremely common in young paediatric subjects and often cause significant morbidity, they are rarely fatal.

Important co-morbidities

Among paediatric subjects under 5 hospitalised for RSV infection, up to 67% had neither a known comorbid condition nor were born preterm. [10,7,8] Nevertheless, that leaves a substantial proportion of young paediatric subjects with severe RSV infection who do have a comorbidity. Table 6 lists comorbidities highlighted in the literature.

Table 6. Important comorbidities/co-infections in RSV patients under age 5

Comorbidity	References
Co-infections, especially influenza, rhinovirus, adenovirus, metapneumovirus, bocavirus, coronavirus, and bacteria	Bont 2016,[10] Rha 2020,[8] Kenmoe 2020.[20] Langley 2022,[21] Mira-Iglesias 2022[51]
Chronic lung conditions	Bont 2016,[10] Rha 2020,[8] Mirra 2018,[43] Cai 2020[32]
Congenital heart disease	Bont 2016,[10] Rha 2020,[8] Mirra 2018,[43] Cai 2020[32]
Neurologic and/or neuromuscular conditions	Bont 2016,[10] Rha 2020,[8] Mirra 2018[43]

SI.2. Indication for active immunisation of adults ≥18 years of age and older

Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

The literature search strategy used to evaluate the epidemiology of RSV in the older adult population was identical to that used for the paediatric population. However, the focus was on articles that reported separate data for older adults. Incidence in older adults was commonly reported in age groups of 50-64 years, and 65 years and older. Therefore, while the population of interest was adults aged 60 years and older, data on the blended "50+" and "50-64" age groups were included.

Incidence

- *Global*

While the majority of symptomatic RSV-associated respiratory infections occur in early childhood, a recent systematic review and meta-analysis of RSV-associated acute respiratory illness (ARI) and influenza-like illness (ILI) estimated that RSV infection accounts for 1-7% of ILI-ARI in adults and 1-10% of ILI-ARI in adults ages ≥50 years.[52] In this same meta-analysis, the proportion of ILI-ARI attributable to RSV infection varied by geographic location, with higher estimates in the US and Europe compared to Africa and Asia. [52]

However, it is possible that these observed geographic differences may be driven by differences in surveillance rather than by true differences in the population distribution of RSV infection. [52]

- *North America and Europe*

In the US, many state-based health surveillance systems report the weekly count of PCR detections of RSV, but incidence rates and proportions are not typically reported. [17] This is similar in Europe, where country-based surveillance systems also report RSV case counts, but not incidence rates or proportions. [18,53] Due to these challenges, many of the best estimates of RSV incidence come from independent research studies rather than national or international surveillance systems.

- *Studies of long-term care facilities and medically attended RSV*

Prospective seasonal and annual estimates of RSV incidence among older adults in North America and Europe focus on the incidence of RSV among populations residing in long-term care facilities (Table 7), and among individuals presenting to a medical facility for ARI or ILI (Table 8). In long-term care facilities, seasonal estimates of the incidence of RSV range from 112 to 556 cases per 10,000 persons (Table 7).

Table 7. Incidence of RSV among older adults in long-term care facilities

Author (year)	Country	Study period	Ages included	Annual* incidence of RSV per 10,000 persons
Ellis (2003)[54]	USA	4 years	Ages ≥65 years	124
Johnstone (2014)[55]	Canada	3 respiratory viral seasons	Ages ≥65 years	112
Ursic (2016)[56]	Slovenia	1 respiratory viral season	Median age 84.0 (IQR 79.8-88.8)	556

*Annual incidence represents incidence over the course of one year for studies with yearly study periods, and incidence over the course of one respiratory viral season for studies with seasonal study periods. Annual incidences per 10,000 persons were calculated by multiplying the number of RSV cases per person-year by 10,000.

Seasonal and annual estimates of medically attended RSV ARI incidence are commonly reported in the literature as the number of individuals seeking medical care for ARI or ILI who are RSV-positive per 10,000 persons in the underlying population (e.g., a city, state, hospital catchment area).[57,58,52] When medical care is loosely defined to encompass any medical visit, estimates of medically attended RSV incidence range from 139 per 10,000 persons among adults ≥60 to 199 per 10,000 persons among adults ≥70 (Table 8). These estimates are similar in magnitude to the estimates of seasonal RSV incidence among older adults in long-term care facilities (112 to 556 cases per 10,000 persons as reported in Table 7). When medical care is more strictly defined to encompass only emergency department

visits or inpatient hospitalisations, the estimates of seasonal RSV incidence requiring medical attention drop to between 11 and 20 cases per 10,000 persons ages ≥50 and between <1 (a low outlier) and 34 cases per 10,000 persons ages ≥65 years (Table 8).

Table 8. Incidence of medically attended RSV ILI/ARI in adults aged ≥50 years

Author (year)	Country	Study period	ILI-ARI definition	Medical encounter	Ages included	Annual* incidence of RSV per 10,000 persons (95% CI)
McClure (2014)[59]	USA	4 respiratory viral seasons	acute respiratory symptoms with fever, chills, or cough	any medical visit	≥50 years 50-59 years 60-69 years ≥70 years	154 (132, 180) 124 (99, 156) 147 (110, 196) 199 (153, 258)
Belongia (2018)[60]	USA	12 influenza seasons	fever/feverishness or cough	any medical visit	≥60 years	139 (122, 160)
Fowlkes (2014)[61]	USA	1 year	two or more respiratory symptoms, or fever accompanied by cough or sore throat	outpatient visit	50-64 years ≥65 years	11.0 6.0
Widmer (2014)[62]	USA	1 year	respiratory symptoms or a non-localizing fever	hospitalisation	≥50 years 50-64 years ≥65 years	11.2 (7.1, 17.7) 6.7 (3.3, 13.4) 19.0 (10.4, 34.0)
Widmer (2014)[62]	USA	1 year	respiratory symptoms or a non-localizing fever	emergency department visit	≥50 years 50-64 years ≥65 years	19.5 (9.0, 40.8) 12.8 (4.4, 35.4) 34.0 (11.7, 90.8)
Widmer (2012)[63]	USA	1 year	respiratory symptoms or a non-localizing fever	hospitalisation	≥50 years 50-64 years ≥65 years	15.0 (8.6, 19.8) 8.2 (3.3, 12.3) 25.4 (13.1, 38.0)
Tong (2020)[9]	USA	7 years	ICD codes representing a primary diagnosis of RSV-specific or RSV-attributable respiratory illness	hospitalisation	65-74 years 75-84 years ≥ 85 years	33 55 81
Auvinen (2022)[2]	Finland	4 respiratory viral seasons	severe acute respiratory infection	hospitalisation	≥65 years 65-84 years ≥85 years	1.9-11.8† 1.0-8.9† 11.2-38.7†

Table 8. Incidence of medically attended RSV ILI/ARI in adults aged ≥50 years

Author (year)	Country	Study period	ILI-ARI definition	Medical encounter	Ages included	Annual* incidence of RSV per 10,000 persons (95% CI)
Branche (2022)[64]	USA	3 respiratory viral seasons	fever, cough, sputum production, dyspnoea, sore throat, runny nose, body aches	hospitalisation or emergency department visit	≥65 years 50-64 years 65-74 years 75-84 years ≥85 years	13.7-25.6† 3.4-6.3† 8.3-12.6† 15.5-28.1† 20.7-66.6†
Johnson (2012)[65]	USA	11 years	ICD codes representing RSV, pneumonia due to RSV and bronchiolitis due to RSV	hospitalisation	≥65 years	0.04

ICD=International Classification of Disease
*Annual incidence represents incidence over the course of one year for studies with yearly study periods, and incidence over the course of one respiratory viral season for studies with seasonal study periods.
†Range of point estimates observed over multiple respiratory viral seasons

Several studies reported a positive association between age and incidence of medically attended RSV ARI/ILI. Among studies stratified on age 65 years, the annual incidence of medically attended RSV ARI ranged from 3.4-12.8 cases per 10,000 persons among adults ages 50-64 to 6.0-34.0 cases per 10,000 persons among adults ages 65 years and older.[63,62,61,64]

Two studies included here also considered age-related trends in incidence among those ages 65 years and older. A 2017-2020 study of data from multiple New York hospital systems reported an annual incidence of 8.3-12.6 cases per 10,000 adults ages 65-74 years, an annual incidence of 15.5-28.1 cases per 10,000 adults ages 75-84 years, and an annual incidence of 20.7-66.6 cases per 10,000 adults ages ≥85 years, [64] and a 2008-2014 study of a US commercially-insured population using the MarketScan database found an annual incidence of 33 cases per 10,000 adults ages 65-74 years, 55 cases per 10,000 adults ages 75-84 years, and 81 cases per 10,000 adults ages ≥85 years. [9]

- *Seasonality*

As described in Section SI.1, RSV infection rates vary seasonally with peak incidence occurring in the winter months. [16,17,6,18,66,67] Relevant to the older adult population, data from the US Optum Clinformatics Data Mart and MarketScan suggest that the seasonality of RSV infection is more pronounced among adults over age 65 years compared to adults ages 18-64 years. [66]

Prevalence

The point prevalence of RSV infection among older adults closely tracks disease incidence due to the acute nature of the illness; however, reports on the point prevalence of RSV infection among those seeking medical care for ARI or ILI are important to understanding the medical burden of RSV infection. Results of individual studies that evaluated the proportion of older adults testing positive for RSV while receiving medical attention for ARI are presented below with proportions RSV-positive among adults aged ≥50 ranging from 3.1% to 14.4%, and the proportion RSV-positive among adults aged ≥90 as high as 40.0% (Table 9). A meta-analysis by Shi *et al.* (2020) estimated that the proportion of adults ages ≥65 years and hospitalised with ARI who are RSV-positive is 4.4% (95% CI: 4.0% to 6.5%). [58] Other systematic reviews and meta-analyses reported estimates ranging from 1% to 18% for adults ages ≥50 years, and as high as 40% for adults ages ≥90 years. [57,52]

Table 9. Proportion of patients with medically attended ARI who are RSV-positive, restricted to adults aged ≥50 years

Author (year)	Country	Type of test	Ages included	Proportion RSV-positive
Widmer (2012)[63]	USA	PCR	≥50 years	6.1%
Widmer (2014)[62]	USA	PCR	≥50 years	3.1%
Sumino (2010)[68]	USA	PCR	Mean age 55 years	2.1%
Walker and Ison (2014)[69]	USA	PCR	≥50 years 50-59 years 60-69 years 70-79 years 80-89 years ≥ 90 years	14.4% 7.3% 12.2% 14.3% 38.7% 40.0%
Glezen (2000)[70]	USA	Antibody tests	≥65 years	1.3%
Jain (2015)[71]	USA	PCR	50-64 years 65-79 years 80+ years	3% 4% 4%
Zimmerman (2014)[72]	USA	PCR	≥50 years	8.5%
Sundaram (2014)[73]	USA	PCR	≥50 years	9.2%
Branche (2014)[74]	USA	PCR	Mean age 63 years	6.5%

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Demographics

- *Age*

RSV infection can be severe among older adults, and the incidence of RSV-infection requiring medical attention increases with age. [57,58,52] In a study of a US commercially-insured population using the 2008-2014 MarketScan database, the proportion of RSV cases diagnosed in an inpatient setting increased from 2.8% among those ages 50-64 years to 11.8% among those 85 years and older. [9] Data from a single tertiary hospital also found an age-related increase in the proportion of patients with medically attended ARI who are RSV-positive; the proportion increased from 7.3% among patient 50-59 years to 40.0% among patients aged ≥90 years (Table 9).[69] These findings are consistent with the positive age-related trend in incidence among adults ages 65 years and older. [64,9] They're also consistent with findings from a study conducted in 3 New York City hospitals from 2017-2019 in which 403 hospitalised adults ages 18 years and older had laboratory-confirmed RSV infections.[75] Of these 403 adults, 57% were at least 65 years old and 85% were at least 50 years old.

- *Gender*

Several studies included information on the gender distribution of RSV cases among older adults. In a US community-based, prospective cohort study of adults ages ≥50 years, 53.0% of the cohort was female, while 61.6% of RSV cases were female. [59] The greater proportion of females among medically attended RSV cases compared to the underlying cohort suggests that either RSV infection is more common among females or that females are more likely to seek medical care following RSV infection.

In studies which did not report the gender distribution in the underlying population, the gender distribution of RSV cases must be evaluated with caution. In one such study, a German cohort, which included 122 RSV cases ages ≥65 years and hospitalised during 2009-2018, 50% of RSV cases were female. [32] In the US, a Southern California retrospective cohort examined 664 hospitalised adults ages ≥60 years who tested positive for RSV during 2011-15, and females comprised 61% of cases.[76] Data from these same studies suggest that even if risk of RSV infection is higher among females, disease severity does not differ by gender. For example, Cai *et al.* (2020) reported that, among adults ages 65 years and older, an equal proportion of males and females hospitalised with RSV infection required ventilation, slightly fewer females (28%) compared to males (31%) were admitted to the intensive care unit (ICU) for RSV infection, and slightly fewer males (8%) than females (11%) did not survive their infection with RSV. [32] Gender-based differences in mortality were also not evident in the Southern California cohort where 11% of females and 12% of males ages ≥60 years died within 60 days of hospital admission with RSV. [76]

- *Race and ethnicity*

Two studies that included sizeable populations of older adults reported the distribution of race and ethnicity within their RSV cases. [75,76] However, since the racial and ethnic distributions of the underlying populations were not reported, variations in the incidence of RSV infection by race and ethnicity cannot be inferred from either study.

In Goldman *et al.* (2022), a study of 403 adults hospitalised with RSV, 85% of cases were ≥50 years old. Across all ages, the distribution of cases by race was 26% White, 20% Black or African American, 51% unknown race, and 3% Asian/Native Hawaiian/Other Pacific Islander/American Indian/Alaska Native. [75] The distribution of Hispanic ethnicity was 32% Hispanic, 18% non-Hispanic, and 50% unknown. In Tseng *et al.* (2020), a 2011-2015 study of Kaiser Permanente Southern California patients ages ≥60 years, the distribution of cases by race was 65.5% White, 16.9% Black, 10.4% Asian or Pacific Islander, 3.8% other or multiple, and 3.5% unknown. [76] The distribution of Hispanic ethnicity was 23.2% Hispanic and 76.8% non-Hispanic.

Goldman *et al.* (2022) also quantified RSV severity by race and ethnicity. The occurrence of severe clinical outcome (defined as being admitted to an ICU, receiving mechanical ventilation, or dying during the RSV-associated hospitalisation) was highest among people classified as Black or African American (24%), intermediate among those of unknown race (20%) and lowest among those classified as White (16%). [75] No severe clinical outcomes occurred among the very small population of those classified as Asian/Native Hawaiian/Other Pacific Islander/American Indian/Alaska Native. The occurrence of severe clinical outcome was lower among people classified as Hispanic (15%) compared to those classified as non-Hispanic (22%), or unknown ethnicity (21%).

Risk Factors

- *Risk factors for RSV infection*

Both sociodemographic and health factors are associated with risk of RSV infection (Table 10) Sociodemographic factors that increase risk of contracting RSV during adulthood include older age, living in a long-term care facility, or participating in a senior day care program.[57,60,77,52] Health factors that increase risk of contracting RSV during adulthood include frailty, cardiopulmonary conditions (e.g., asthma, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF]), diabetes, and an acute or chronic immunocompromised state.[78,64,77,57,79,52]

Table 10. Risk factors for RSV infection among older adults

Risk Factor	References
*Older age	Colosia 2017,[57] Belongia 2018,[60] Tin Tin Htar 2020[52]
†Residing in a long-term care facility	Colosia 2017,[57] Childs 2019[77]

Table 10. Risk factors for RSV infection among older adults

Risk Factor	References
End-stage renal disease	Njue 2023[80]
Immunocompromising conditions	Njue 2023[80]
†Participating in a senior day care program	Colosia 2017[57]
†Frailty	Childs 2019[77]
*Chronic cardiopulmonary disease	ECDC 2015,[79] Alimi 2017,[78] Colosia 2017,[57] Belongia 2018,[60] Tin Tin Htar 2020,[52] Branche 2022[64]
*Diabetes	Branche 2022[64]
†Immunosenescence	Childs 2019[77]

*Risk factor reported in at least one study that focused on adults aged ≥60
†Risk factor reported among adults, and risk factor is known to increase in frequency with increasing age

- *Risk factors for RSV-associated morbidity and mortality*

Both sociodemographic and health factors also are associated with risk of poor outcomes following RSV infection (Table 11). Specifically, older age has been correlated with RSV associated morbidity and mortality,[81,60,52] and frailty, immunosenescence, and underlying medical conditions have also been associated with an increased risk of poor RSV outcomes, including hospitalisation, length of hospitalisation, admission to an ICU, use of mechanical ventilation, and mortality (Table 11).[82,57,81,60,83,77,58,52]

Table 11. Risk factors for RSV-associated morbidity and mortality in older adults

Risk Factor	References
*Older age	Pastula 2017,[81] Belongia 2018,[60] Tin Tin Htar 2020[52]
†Frailty	Falsey 2005,[82] Childs 2019,[77] Tin Tin Htar 2020[52]
†Immunosenescence	Childs 2019[77]
End-stage renal disease	Njue 2023[80]
Immunocompromising conditions	Njue 2023[80]
*Chronic cardiopulmonary disease	Falsey 2005,[82] Colosia 2017,[57] Belongia 2018,[60] Ivey 2018,[83] Shi 2020,[58] Tin Tin Htar 2020[52]

*Risk factor reported in at least one study that focused on adults aged ≥60
†Risk factor reported among adults, and risk factor is known to increase in frequency with increasing age

Active immunisation of individuals 18-59 years of age for the prevention of lower respiratory tract disease caused by RSV.

RSV infections can cause a range of symptoms in adults from mild cold-like illnesses to severe disease, hospitalization, and death.[84,85] Severe disease manifestations include pneumonia and non-pneumonia lower respiratory infection, exacerbation of underlying chronic lung[85] and heart disease, and cardiac events, such as arrhythmias and ischemic events.[83]

Incidence

The incidence of RSV disease among adults is frequently underestimated in the published literature for multiple reasons[86,87], including infrequent RSV testing[88], use of case definitions that exclude a portion of RSV disease (eg, community-acquired pneumonia [~20% of RSV-related hospitalizations[89, 90]] or influenza like illness [which requires fever, a symptom less common in RSV infection[91]]), and reduced sensitivity of a single nasopharyngeal swab PCR, which is the sole diagnostic specimen in most settings.[92 93] Further, as mentioned, RSV infection can trigger cardiac hospitalization and chronic lung disease exacerbation, but these events are rarely tested or included in prospective studies.[83] To address these issues in part, prospective studies can be adjusted for reduced single swab sensitivity[94 95] and time-series studies can model the burden of RSV-attributable events by comparing the variability in RSV activity among tested illnesses with the variability in all illness (eg, respiratory hospitalization or cardiopulmonary hospitalizations).[96 97 98]

A substantial burden of RSV disease exists in this population under age 60 years. A recent systematic literature review and meta-analysis described population-based rates of medically attended RSV in the US adult general population by age group and projected visit counts.[95] While annual rates of RSV-associated visits increase with age, the magnitude of this age-related increase in incidence is less pronounced for emergency department visits and outpatient visits than for hospitalizations (Table 12). For example, while the reported hospitalization incidence was 15 times higher among adults over 65 years old than those 18 through 49 years old (281.6 versus 18.8 per 100,000), the increase in outpatient visits was only 1.6-fold (2278.2 versus 1401.3 per 100,000). On this basis, RSV-related medically attended illness remains frequent overall in adults 18 through 49 years of age and those 50 through 64 years of age. Further, absolute numbers of emergency department and outpatient events are higher among those <65 years than those >65 years of age due to the greater size of the <65-year-old population (Table 13). For instance, nearly 2 million RSV-related outpatient visits and over 277,000 emergency department visits occurred in those 18 through 49 years of age each year, which is larger than the 1.4 million outpatient visits and nearly 80,000 emergency department visits that occurred among those older than 65 years.

Similar trends are seen in Europe, where Fleming at al[99] reported that GP visit incidence rates in the UK were more similar among adult age groups compared to hospitalizations and deaths, which increase sharply among those at least 65 years of age (Figure 1). In absolute numbers, more GP visits for RSV disease occurred among persons under age 65 years than those 65 years and older (313,003 versus 174,244, respectively). An observational retrospective database study using a nationally representative hospitalization and mortality

database from Spain for years 2016-2019 reported an incidence rate of RSV-attributable hospitalizations in adults based on standard-of-care diagnostic codes. These incidence rates ranged from 0.4 to 1.2 per 100,000 person-years in adults aged 18-49 years and from 1.7 to 4.8 per 100,000 person-years in adults aged 50-59 years. [96]

Table 12. Pooled Estimates From Random-Effects Model of Rates of RSV-Associated Hospitalizations, Emergency Department Admissions, and Outpatient: Visits per 100,000 US Adults by Study Type by Age Group

Age Group in Years	Hospitalization		Emergency Department visits		Outpatient visits	
	Pooled Reported	Adjusted	Pooled Reported	Adjusted	Pooled Reported	Adjusted
18–49	12.5 (1.9–23.2)	18.8 (2.9–34.8)	131.8 (67.0–253.0)	197.7 (100.5–379.5)	934.2 (380.8–1487.6)	1401.3 (571.2–2231.3)
50–64	66.3 (48.9–83.6)	99.5 (73.4–125.4)	73.6 (59.1–88.1)	110.4 (88.7–132.2)	1148.2 (935.4–1360.9)	1722.2 (1403.2–2041.3)
≥65	187.7 (167.2–208.3)	281.6 (250.8–312.5)	133.3 (0–318.6)	200.0 (0–477.9)	1518.8 (1109.0–1928.7)	2278.2 (1663.4–2893.0)

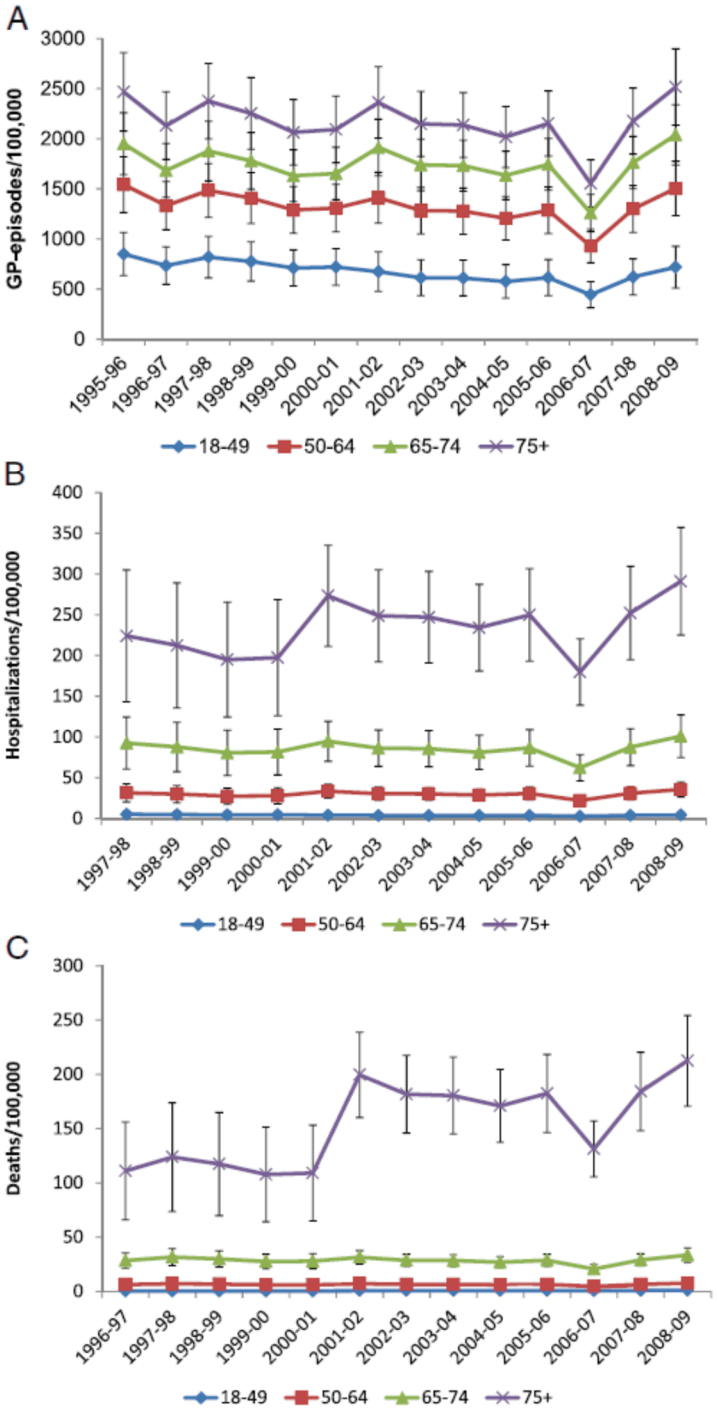
Pooled rates for prospective surveillance studies with and without adjusted for diagnostic testing-related under ascertainment as reported in McLaughlin et al[95]

Table 13. Annual US Hospitalizations and Visit Projections Based on Incidence Rates from Study Meta-analysis

Age Group in Years	US 2022 Population	Hospitalizations		Emergency Department admissions		Outpatient visits	
		Pooled Reported	Adjusted	Pooled Reported	Adjusted	Pooled Reported	Adjusted
18–49	140,480,973	11,800	17,700	185,154	277,731	1,312,338	1,968,507
50–64	62,870,375	28,040	42,060	46,272	69,409	721,857	1,082,785
⩾65	59,710,183	106,165	159,247	79,594	119,391	906,882	1,360,322

Source: Supplemental materials of Mclaughlin, et al[95] (Supplemental Table 6)

Figure 1. Seasonal Incidence of RSV-Associated GP Episodes (A), Hospitalizations (B), and Deaths (C) in the UK



From Fleming et al[99] (Figure 1)
Note: Incidences shown per 100,000

Prevalence

US

Of the 10,311 hospitalized adults who met a standardized acute respiratory illness case definition and were prospectively enrolled across 3 respiratory seasons from hospitals participating across all sites of the US Hospitalized Adult Influenza Vaccine Effectiveness Network (2016–2019) in a multicenter prospective study, 622 (6%) tested positive for RSV.[100] The prevalence of RSV infection was 4.7% among 2300 patients aged 18-49 years and 5.5% in 3423 patients aged 50-64 years.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Demographics

- *Age*

A surveillance study conducted in the US evaluated 2960 healthy subjects, 18–60 years of age (mean age, 30 years) during the 20-year study period from years 1975 to 1995 during the 5–6 months when RSV was active (Hall et al 2001). This study reported that total 211 (7%) subjects were infected with RSV infection. Among those found to be infected with RSV, the highest proportion was of adults aged 18-30 years [112 (53%)] compared to 35%, 10% and 2% of the adults aged 31-40 years, 41-50 years and 51-60 years, respectively.

- *Sex*

A surveillance study conducted in the US evaluated 2960 healthy subjects, 18–60 years of age (mean age, 30 years) during the 20-year study period from years 1975 to 1995 during the 5–6 months when RSV was active (Hall et al 2001). This study reported an acute RSV infection identified in 211 (7%) of these previously healthy persons; Of the 211 RSV infections, 137 (65%) were females.

- *Race/Ethnicity*

No observational studies have reported an incidence of RSV infection among adults aged 18-60 years by race/ethnicity.

Risk factors.

While there is a risk of medically attended RSV illness across the entire population under the age of 60 years, similar to older adults, severe disease risk increases substantially among those with comorbidities and other risk factors.[95 101] The recent MMWR reporting the recommendation for RSV vaccination among older adults mentioned the following risk factors for severe disease: COPD, asthma, CHF, coronary artery disease, cerebrovascular disease, diabetes mellitus, and chronic kidney disease; long-term care facility residence; frailty; and compromised immunity, such as that observed in recipients of hematopoietic stem cell transplantation and patients taking immunosuppressive medications (eg, for solid organ transplantation, cancer treatment, or other conditions).[102] In their recent presentation on risk factors for severe/hospitalized disease among adults under age 60 years, the following additional comorbidities were mentioned: obesity, neurologic conditions, chronic metabolic disease, chronic liver disease, autoimmune disorders and blood disorders. A similar list of risk factors was collated in a recent systematic literature review[101] and, in addition, persons under 60 years of age with lower socioeconomic status were noted to be at twice the risk of RSV-related hospitalization compared to persons of higher socioeconomic status.[97] Of note, the elevated incidence for hospitalization among younger adults with RSV risk factors can be comparable to or higher than incidence among older adults without risk factors.[101] For example, in one recent study, the annual incidences among persons age 20 through 39 years and 40 through 59 years of age with CHF were, respectively, 237 and 403 per 100,000 compared to 167 per 100,000 among all persons 65 years and older.[95 101]

Furthermore, severe RSV disease can lead to death, and the risk of death following hospitalizations is similar for those over and under the age of 65 years. A recent global meta-analysis among high-income countries found RSV-related hospitalization case fatality rates were 5.7% (range: 4.7-7.0) among those 18 through 64 years of age, versus 6.1% (range: 3.3-11.0) among those at least 65 years of age.[103]

The main existing treatment options

Treatment of RSV disease consists primarily of supportive care (e.g. mainly oxygen, hydration and suctioning of secretions).[104] Comprehensive hygiene measures are helpful and cost-effective in limiting the spread of RSV, and should always be advocated as a prophylactic measure, however, they are not sufficiently efficacious to prevent the disease burden. Inpatients diagnosed with RSV infection may be treated with aerosolized ribavirin; however, ribavirin is rarely used to treat RSV, except in the context of severe immunosuppression, because of inconvenient administration, questionable benefit in immunocompetent patients, teratogenicity concerns based on nonhuman animal data, and high cost.[105,106,107] Ribavirin has also not resulted in a meaningful impact upon clinically relevant outcomes, including reductions in mortality, duration of hospitalisation, need for mechanical ventilation, and ICU admission.[108,109,110] Paracetamol and OTC cold medications may be used to relieve milder symptoms.[111]

Currently, there are two vaccines approved for use in adults 60 years of age and older for the prevention of lower respiratory tract disease (LRTD) caused by RSV, in the EU and many

other countries globally[112]: Arexvy received EU marketing authorisation in June 2023, and Abrysvo in August 2023.[2]

Natural history of the indicated condition in the untreated population, including mortality and morbidity

- *Clinical course*

RSV has an incubation period of 3-5 days that is typically followed by upper respiratory symptoms with or without fever.[113,52] In general, RSV symptoms last for <1 week and are similar to symptoms from other viral respiratory infections (e.g., fever, dyspnoea, nasal congestion, wheezing, sputum production) [82,52]; however, RSV disease presentation differs between older adults and young children. [57] For example, RSV viral titres are lower in adults compared to children, and many older adults infected with RSV never experience fever. [57,52]

The severity of RSV symptoms and progression can depend on both viral load and host factors (e.g., expression of ligand IFN- λ 1).[6] Poor outcomes (e.g., hospitalisation, ICU usage, death) are most common among older adults with at least one chronic health condition, e.g., a cardiovascular condition, pulmonary condition, or immunodeficiency. [57,113,83,77,52] US claims data suggest that among adults aged 65 and older who seek medical attention for RSV, 29-39% are diagnosed with pneumonia. [66] Additionally, some adults ages 50 years and older develop severe RSV infection and require hospitalisation. Hospitalisation of older adults with RSV typically lasts 3-6 days with some adults requiring supplemental oxygen or mechanical ventilation and 10-31% of hospitalised adults spending time in an ICU. [57,64] Additional research is needed to understand the long-term impact of severe RSV infection on cardiopulmonary health, frailty, cognitive health and activities of daily living.[114]

- *Mortality*

Before the emergence of COVID-19, the CDC estimated 14,000 RSV-related deaths annually among adults ages 65 years and older within the US. [6] A review from the UK estimated 8,482 RSV-related deaths annually among adults in the UK, with 93% of them occurring in people ages 65 years and older.[115] An US-based study reviewing death certificates issued between 1999-2018 found an annual mortality rate of 2.2 per 100,000 population (95% CI: 2.0 -2.30) among those with RSV infection accompanied by ARI or ILI, [50] and the RSV mortality rate increased with increasing age, i.e., from 0.1 per 100,000 persons (95% CI: 0.1 to 0.1) among those ages 5-49 years to 1.0 per 100,000 persons (95% CI: 0.9 – 1.0) among those ages 50-64 years to 14.7 per 100,000 persons (95% CI: 13.8 – 15.5) among those ages ≥65 years. [50] Additional studies from the US and Germany found similar trends of increasing RSV-mortality with increasing age,[116,117,32] and a review described how mortality rates due to RSV rise from 1 per 100,000 population in ages 18–49 years to 155 per 100,000 in ages 75 years and above. [115] Further, deaths due to RSV increase after age 49 years, representing

[2] Arexvy, Recombinant respiratory syncytial virus pre-fusion F protein, adjuvanted with AS01E. https://www.ema.europa.eu/en/medicines/human/EPAR/arexvy#assessment-history-section. Accessed on: 20 June 2023.

4.2% of all respiratory disease deaths among ages 18–49 years, 5.9% in ages 50–64 years, 5.7% among ages 65–74 years, and 5.9% in ages 75 years and over. [115]

In studies of older adults hospitalised with RSV, the estimated mortality rate ranged from 1.6-10%,[32,57,118,119,58,76,64] with higher mortality rates of up to 20% among lung transplant recipients. [119] Among those hospitalised with RSV, one-year cumulative mortality was also high; a study of 644 US patients hospitalised with RSV between 2011-2015 reported one-year cumulative mortality of 25.8%.[76]

Important co-morbidities

RSV comorbidities for patients ages 50 years and older are presented in Table 14. Comorbid cardiopulmonary conditions (e.g., asthma, COPD, CHF, acute coronary syndrome, arrhythmias, occurrence of myocardial infarction) are the most common [82,57,83,58,120,52,9,121,74] Annually, 4-10% of older adults with chronic cardiopulmonary disease contract RSV (Shi 2021),[120] and at least 50% of RSV patients ages 65 years and older have a comorbid cardiopulmonary condition. [9] Diabetes mellitus and chronic renal disease are the next most common comorbid conditions, affecting at least 10% of RSV patients ages 50 years and older.[9]

Table 14. Important comorbidities/co-infections in RSV patients aged ≥50 years

Comorbidity	References
*Bacterial or fungal co-infection	Falsey 2005,[82] Walker & Ison 2014[69]
*†‡Chronic cardiopulmonary disease	Falsey 1995,[122] Falsey 2005,[82] Widmer 2014,[62] Colosia 2017,[57] Ivey 2018,[83] Zheng 2018,[121] Tin Tin Htar 2020,[52] Tong 2020,[9] Shi 2021,[120] Mesa-Frias 2022,[66] Branche 2022[64]
*Chronic renal disease	Tin Tin Htar 2020,[52] Tong 2020[9]
†‡Diabetes mellitus	Tin Tin Htar 2020,[52] Tong 2020,[9] Shi 2021,[120] Mesa-Frias 2022[66]
*†‡Immunodeficiency	Falsey 2005,[82] Widmer 2012,[63] Widmer 2014,[62] Colosia 2017,[57] Shi 2021,[120] Mesa-Frias 2022[66]
*‡Malignancies	Falsey 2005,[82] Widmer 2012,[63] Tin Tin Htar 2020,[52] Tong 2020[9]
‡Neurological/musculoskeletal	Tong 2020[9]

*Risk factor reported among adults described as "elderly" or aged ≥50 years
†Risk factor reported among adults aged ≥60 years
‡Risk factor reported among adults aged ≥65 years

Module SII. Non-Clinical Part of the Safety Specification

The key studies in the nonclinical toxicity assessment for RSVpreF consisted of a GLP-compliant repeat-dose toxicity study in Wistar Han rats and a GLP-compliant combined fertility and developmental toxicity study in NZW rabbits. In both studies, RSVpreF was administered intramuscularly at 2x the clinical dose (120 µg each of 847A and 847B; total 240 µg antigen per dose), with or without $Al(OH)_3$.

In the repeat-dose toxicity study, a total of 3 doses of RSVpreF administered on Days 1, 22, and 36 was tolerated without evidence of systemic toxicity, produced an anticipated inflammatory response, and elicited a functional antibody response. Non-adverse immune responses and/or inflammatory changes were evident at the injection sites and draining lymph nodes. Clinical pathology changes, when present, were consistent with immune stimulation or inflammation at the injection sites.

No indications of maternal systemic toxicity or effects on mating performance, female fertility, or embryo-foetal or postnatal survival, growth, or development in the F1 offspring were observed in the combined fertility and developmental toxicity study in NZW rabbits following the administration of RSVpreF, with or without $Al(OH)_3$, for a total of 4 doses (twice premating and on Gestation Days 10 and 24).

In summary, the nonclinical safety findings related to RSVpreF administration represent an expected immune reaction to vaccine administration and are clinically manageable or acceptable risks in the intended populations. No identified or potential important risks were noted (Table 15).

Table 15. Key safety findings and relevance to human usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity **Repeat-Dose Toxicity in Rats** RSVpreF (2x clinical dose) was tolerated without evidence of systemic toxicity. 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.	Non-adverse local reactions are an anticipated vaccine effect that are clinically manageable and acceptable. Therefore, they are not considered an important risk to humans.
Reproductive/developmental toxicity No vaccine-related effects on mating performance or female fertility, or the survival, growth, or development of foetuses or offspring were observed in a fertility and developmental toxicity study of RSVpreF in rabbits at 2x the clinical dose.	No effects are anticipated in pregnant women or their offspring.
Genotoxicity [a] N/A	
Carcinogenicity [a] N/A	
Safety pharmacology [a] N/A	

Table 15. Key safety findings and relevance to human usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage

a. No genotoxicity, carcinogenicity, safety pharmacology, or studies evaluating pharmacodynamic drug interactions were conducted. These studies are generally not considered necessary to support the development and licensure of vaccine products for infectious diseases.[123,124].

Module SIII. Clinical Trial Exposure

Clinical study exposure data are provided for the following studies, at the cut-off date of 10 November 2023 for global phase 3 pivotal study (C3671008) for the maternal indication and 01 February 2024 for the older adult indication (C3671013).

Studies		Age Range
Phase 1 studies:		
	C3671001 A Phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding, first-in-human study to describe the safety, tolerability, and immunogenicity of a respiratory syncytial virus vaccine (RSV vaccine) in healthy adults	18-85 years
Phase 2 studies		
	C3671002 A Phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding first-in-human study to describe the safety, tolerability, and immunogenicity of an adjuvanted respiratory syncytial virus (RSV) vaccine in healthy older adults	65-85 years
	C3671003 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	≥18 and ≤49 years
	C3671004 A Phase 2b, placebo controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a respiratory syncytial virus (RSV) vaccine when administered concomitantly with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy nonpregnant women 18 through 49 years of age	≥18 and ≤49 years
Phase 3 studies		
	C3671006 A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of Respiratory Syncytial Virus prefusion F subunit vaccine when co-administered with seasonal inactivated influenza vaccine in adults ≥65 years of age	≥65 years
	C3671008 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	≤49 years
	C3671013 A Phase 3 study to evaluate the efficacy, immunogenicity, and safety of respiratory syncytial virus (RSV) prefusion f subunit vaccine in adults	≥60 years
	C3671014 A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of 3 lots of respiratory syncytial virus (RSV) prefusion F subunit vaccine in healthy adults	≥18 and ≤49 years
	C3671023 A Phase 3 protocol to evaluate the safety, tolerability, and immunogenicity of Respiratory Syncytial Virus (RSV) prefusion F subunit vaccine in adults at high risk of severe RSV disease - Substudy A	≥18 to <60 years

SIII.1. Clinical Trial Exposure for Maternal Indication

Table 16. Exposure Pregnant Women ≤49 Years

Pregnant women	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
1 dose	4160	3813	4160
Total Exposure	4160	3813	4160

Note: Includes C3671003 and C3671008 studies.
[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP May24/ adsl_s001_ex_m Date of Generation: 09MAY2024 (03:02)

Table 17. Exposure Pregnant Women by Age Group and Gestational Age at Administration

Age Group	No. of Participants Pooled RSVpreF (including with and without adjuvant)	No. of Participants RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
≤49	4160	3813	4160
Total	**4160**	**3813**	**4160**
Gestational Age at Administration			
<24 weeks			
≥24 weeks to <28 weeks	1079	975	1079
≥28 weeks to <32 weeks	1236	1120	1236
≥32 weeks to ≤36 weeks	1841	1714	1841
>36 weeks	4	4	4
Total	**4160**	**3813**	**4160**

Note: Includes C3671003 and C3671008 studies.
[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP May 24/ adsl_s005_ex_age_m Date of Generation: 09MAY2024 (03:02)

Table 18. Exposure Pregnant Women by Racial and Ethnic Origin

Racial Origin	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
White	2742	2482	2742
Black or African American	820	745	820
Asian	462	457	462
American Indian or Alaska Native	39	38	39
Native Hawaiian or other Pacific Islander	10	9	10
Multiracial	30	30	30
Not reported	50	45	50
Unknown	7	7	7

Table 18. Exposure Pregnant Women by Racial and Ethnic Origin

Racial Origin	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
Ethnic Origin			
Hispanic/Latino	1190	1095	1190
Non-Hispanic/non-Latino	2939	2688	2939
Not reported	29	28	29
Unknown	2	2	2
Total	**4160**	**3813**	**4160**

Note: Includes C3671003 and C3671008 studies.
[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP May 24/ adsl_s005_ex_re_m Date of Generation: 09MAY2024 (03:02)

Table 19. Exposure Newborn Infant Participants

Newborn Infant Participants	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
1 dose	4115	3773	4115
Total Exposure	**4115**	**3773**	**4115**

Note: Infants are presented according to their mother's vaccine group.
Note: Includes C3671003 and C3671008 studies.
[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP May 24/ adsl_s001_ex_i Date of Generation: 09MAY2024 (03:02)

Table 20. Number (%) of Newborn Infant Participants

Study ID	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant) (N=4115)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant) (N=3773)	Total Vaccine RSVpreF Doses (N=4115)
C3671003	456 (11.1)	114 (3.0)	456 (11.1)
C3671008	3659 (88.9)	3659 (97.0)	3569 (88.9)

Note: Infants are presented according to their mother's vaccine group.
Note: Includes C3671003 and C3671008 studies.
[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP May 24/ adsl_s001_n_i Date of Generation: 09MAY2024 (03:02)

Table 21. Exposure of Newborn Infant Participants by Racial and Ethnic Origin

Racial Origin	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
White	2671	2419	2671
Black or African American	805	731	805
Asian	448	446	448
American Indian or Alaska Native	43	43	43
Native Hawaiian or other Pacific Islander	15	13	15
Multiracial	75	71	75
Not reported	48	40	48
Unknown	10	10	10
Ethnic Origin			
Hispanic/Latino	1209	1112	1209
Non-Hispanic/non-Latino	2852	2610	2852
Not reported	52	49	52
Unknown	2	2	2
Total	**4115**	**3773**	**4115**

Note: Infants are presented according to their mother's vaccine group.
Note: Includes C3671003 and C3671008 studies.
[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP May 24/adsl_s005_ex_re_i Date of Generation: 09MAY2024 (03:02)

Table 22. Exposure All Female Participants ≤49 years

Female participants ≤49 years	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
1 dose	5547	4596	5547
Only pregnant women[1]	4144	3797	4144
Only female non-pregnant women[2]	1403	799	1403
Total Exposure	**5547**	**4596**	**5547**

1. C3671003 and C3671008 studies
2. C3671001, C3671004 and C3671014 studies
Note: Revaccination data of C3671001 is not included and only the data after the first vaccination of C3671001 is included.
[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s001_ex_f Date of Generation: 22NOV2022 (03:54)

Table 23. Number (%) of - All Female Participants ≤49 years by Racial and Ethnic Origin

	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant) (N=5547)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant) (N=4596)	Total Vaccine RSVpreF Doses (N=5547)
Race			
Black or African American	3731 (67.3)	3038 (66.1)	3731 (67.3)
Asian	1098 (19.8)	898 (19.5)	1098 (19.8)
American Indian or Alaska Native	529 (9.5)	501 (10.9)	529 (9.5)
Native Hawaiian or other Pacific Islander	52 (0.9)	47 (1.0)	52 (0.9)
Multiracial	20 (0.4)	14 (0.3)	20 (0.4)
Not reported	49 (0.9)	38 (0.8)	49 (0.9)
Unknown	59 (1.1)	51 (1.1)	59 (1.1)
Black or African American	9 (0.2)	9 (0.2)	9 (0.2)
Ethnicity			
Hispanic/Latino	1428 (25.7)	1253 (27.3)	1428 (25.7)
Non-Hispanic/non-Latino	4077 (73.5)	3305 (71.9)	4077 (73.5)
Not reported	40 (0.7)	36 (0.8)	40 (0.7)
Unknown	2 (<0.1)	2 (<0.1)	2 (<0.1)
Age at vaccination (years)			
N	5547	4596	5547
Mean (SD)	30.4 (7.10)	30.0 (6.72)	30.4 (7.10)
Median (Range)	30.0 (16, 49)	30.0 (16, 49)	30.0 (16, 49)

For pregnant women participants cross-reference with Table 16

[redacted] Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s005_sum_f Date of Generation: 22NOV2022 (03:54)

SIII.2. Clinical Trial Exposure for Adult Indication

Table 24. Exposure Adults ≥18 Years

Adults ≥18 Years	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
1 dose	22753	21274	22753
Total Exposure	**22753**	**21274**	**22753**

Note: Pooled Studies - C3671001, C3671002, C3671004, C3671006, C3671013 Main Efficacy Study, C3671014, C3671023 - Substudy A.. For study C3671013 multi-enrollers were not included.

[redacted] Source Data: adsl Table Generation: 08MAY2024 (01:24) Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_oa 2024

Table 25. Exposure by Age Group and Gender (Adults ≥18 Years)

	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)		No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)		Total Vaccine RSVpreF Doses	
Age Group	**M**	**F**	**M**	**F**	**M**	**F**
≤49 years	575	1542	423	938	575	1542
50-59 years	104	140	94	124	104	140
60-69 years	6161	6256	6018	6104	6161	6256
70-79 years	3497	3325	3341	3142	3497	3325
≥80 years	584	569	551	539	584	569
Total	**10921**	**11832**	**10427**	**10847**	**10921**	**11832**

Note: Pooled Studies - C3671001, C3671002, C3671004, C3671006, C3671013 Main Efficacy Study, C3671014, C3671023 - Substudy A.. For study C3671013 multi-enrollers were not included.
[redacted] Source Data: adsl Table Generation: 08MAY2024 (01:41)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_oa 2024

Table 26. Exposure by Racial and Ethnic Origin (Adults ≥18 Years)

Racial Origin	**No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)**	**No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)**	**Total Vaccine RSVpreF Doses**
White	18257	17074	18257
Black or African American	2669	2464	2669
Asian	1522	1474	1522
American Indian or Alaska Native	61	54	61
Native Hawaiian or other Pacific Islander	32	25	32
Other	1	0	1
Multiracial	87	69	87
Not reported	86	76	86
Unknown	38	38	38
Ethnic Origin			
Hispanic/Latino	7884	7759	7884
Non-Hispanic/non-Latino	14664	13318	14664
Not reported	205	197	205
Total	**22753**	**21274**	**22753**

Note: Pooled Studies - C3671001, C3671002, C3671004, C3671006, C3671013 Main Efficacy Study, C3671014, C3671023 - Substudy A. For study C3671013 multi-enrollers were not included.
[redacted] Source Data: adsl Table Generation: 08MAY2024 (02:08)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_oa 2024

SIII.3. Overall Clinical Trial Exposure

Table 27. Exposure (All Studies)

All Studies	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)	Total Vaccine RSVpreF Doses
1 dose	31028	28860	31028
Total Exposure	**31028**	**28860**	**31028**

Note: Pooled Studies - C3671001, C3671002, C3671003, C3671004, C3671006, C3671008, C3671013 Main Efficacy Study, C3671014, C3671023 - Substudy A. For study C3671013 multi-enrollers were not included.
[redacted] Source Data: adsl Table Generation: 08MAY2024 (01:42)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_all 2024

Table 28. Exposure by Age Group and Gender

	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)		No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)		Total Vaccine RSVpreF Doses	
Age Group	**M**	**F**	**M**	**F**	**M**	**F**
≤49 years	2663	7729	2340	6607	2663	7729
50-59 years	104	140	94	124	104	140
60-69 years	6161	6256	6018	6104	6161	6256
70-79 years	3497	3325	3341	3142	3497	3325
≥80 years	584	569	551	539	584	569
Total	**13009**	**18019**	**12344**	**16516**	**13009**	**18019**

Note: Pooled Studies - C3671001, C3671002, C3671003, C3671004, C3671006, C3671008), C3671013, Main Efficacy Study, C3671014, C3671023 - Substudy A.. For study C3671013 multi-enrollers were not included.
[redacted] Source Data: adsl Table Generation: 08MAY2024 (01:57)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_all 2024

Table 29. Exposure by Racial and Ethnic Origin

All Studies			
Racial Origin	**No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)**	**No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)**	**Total Vaccine RSVpreF Doses**
White	23670	21975	23670
Black or African American	4294	3940	4294
Asian	2432	2377	2432
American Indian or Alaska Native	143	135	143
Native Hawaiian or other Pacific Islander	57	47	57
Other	1	0	1
Multiracial	192	170	192
Not reported	184	161	184
Unknown	55	55	55
Ethnic Origin			
Hispanic/Latino	10283	9966	10283

Table 29. Exposure by Racial and Ethnic Origin

All Studies			
Racial Origin	**No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant)**	**No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant)**	**Total Vaccine RSVpreF Doses**
Non-Hispanic/non-Latino	20455	18616	20455
Not reported	286	274	286
Unknown	4	4	4
Total	**31028**	**28860**	**31028**

Note: Pooled Studies - C3671001, C3671002, C3671003, C3671004, C3671006, C3671008 , C3671013, Main Efficacy Study, C3671014, C3671023 - Substudy A. For study C3671013 multi-enrollers were not included.
[redacted] Source Data: adsl Table Generation: 08MAY2024 (02:23)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_all 2024

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Study for Maternal Indication within the Development Programme

Table 30. Exclusion Criteria in Pivotal Clinical Study for Maternal Indication

Criterion Reason for exclusion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information
Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection.	To ensure the safety of the study population.	No/ Information concerning this criterion is provided in the SmPC Section 4.4 *Special warnings and precautions for use*.
History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g. anaphylaxis) to any component of the study intervention(s) or any related vaccine.	To ensure safety of the study population.	No/ Information concerning this criterion is provided in the SmPC Sections 4.4 *Special warnings and precautions for use.*
High risk pregnancy: (e.g. current pregnancy resulting from in vitro fertilization, preeclampsia, placental abnormality, uncontrolled endocrine disorder, pre-pregnancy body mass index (BMI) of >40 kg/m2 etc.)	To ensure the safety of the study population.	Yes/ Not applicable.
History of prior pregnancy complications (prior preterm delivery, stillbirth or neonatal death, or previous infant with known genetic disorder or congenital anomaly)	To ensure the safety of the study population.	No/ No impact on the safety of the target population.

Table 30. Exclusion Criteria in Pivotal Clinical Study for Maternal Indication

Criterion Reason for exclusion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information
Major illness of the maternal participant or conditions of the foetus that will substantially increase the risk associated with the maternal or infant participant's participation in, and completion of, the study or could preclude the evaluation of the maternal participant's response.	To ensure the safety of the study population.	No/ No impact on the safety of the target population.
Congenital or acquired immunodeficiency disorder, immunocompromised pregnant women, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, within the year prior to enrolment	To avoid confounding the assessment of immune response in the study population.	Yes/ Ongoing clinical study C3671032 (NCT06325657); enrolling maternal participants living with HIV and their infants will describe immune responses in this population).
Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.	To ensure the safety of the study population.	No/ No impact on the safety of the target population.
Participation in other studies involving an investigational product within 28 days prior to consent and/or during study participation.	To avoid confounding the assessment of immune response in the study population.	No/ No impact on the safety of the target population.
Receipt of monoclonal antibodies within the year prior to enrolment or the use of systemic corticosteroids for >14 days within 28 days prior to study enrolment.	To avoid confounding the assessment of immune response in the study population.	No/ No impact on the safety of the target population.
Current alcohol abuse or illicit drug use. Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales.	To ensure the safety of the study population.	No/ No impact on the safety of the target population.

Table 30. Exclusion Criteria in Pivotal Clinical Study for Maternal Indication

Criterion Reason for exclusion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information
Receipt of blood or plasma products or immunoglobulin (Ig), from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (eg, RhoGAM), which can be given at any time.	To avoid confounding the assessment of immune response in the study population.	No/ No impact on the safety of the target population.
Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation.	To avoid confounding the assessment of immune response in the study population.	No/ No impact on the safety of the target population.
Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.	To ensure informed consent to participate is appropriately obtained and ensure ethical conduct of the study.	No/ No impact on the safety of the target population.
Participants who are breastfeeding at the time of enrolment.	To ensure the safety of the study population.	No/ No impact on the safety of the target population.

SIV.2. Exclusion Criteria in Pivotal Clinical Study for Adult Indication within the Development Programme

Table 31. Exclusion Criteria in Pivotal Clinical Study in Adults ≥18 Years

Criterion Reason for exclusion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information
Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection.	To ensure the safety of the study population.	No/ Information concerning this criterion is provided in the SmPC Section 4.4 *Special warnings and precautions for use*.
History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s) or any related vaccine.	To ensure safety of the study population.	No/ Information concerning this criterion is provided in the SmPC Sections 4.4 *Special warnings and precautions for use.*

Table 31. Exclusion Criteria in Pivotal Clinical Study in Adults ≥18 Years

Criterion Reason for exclusion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information
Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.*	To avoid confounding the assessment of immune response in the study population.	No/ Minimal potential impact on target population.
Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination*	To avoid confounding the assessment of immune response in the study population.	Yes/ Not applicable
Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.	To ensure the safety of the study population.	No/ No impact on the safety of the target population.
Participation in other studies involving an investigational product within 28 days prior to consent and/or through and including the 6-month follow-up visit (Visit 3).	To avoid confounding the assessment of immune response in the study population.	No/ No impact on the safety of the target population.
Immunocompromised, individuals who receive chronic systemic treatment with immunosuppressive therapy, including cytotoxic agents, monoclonal antibodies, systemic corticosteroids, or radiotherapy. *	To avoid confounding the assessment of immune response in the study population.	Yes/ Not applicable
Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration.	To avoid confounding the assessment of immune response in the study population.	No/ No impact on the safety of the target population.
Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation.	To avoid confounding the assessment of immune response in the study population.	No/ No impact on the safety of the target population.

* A clinical study in high-risk and immunocompromised participants 18 years of age and older (C3671023) started in May 2023 and is ongoing. It is a phase 3 study assessing safety, tolerability, and immunogenicity of a single dose of Abrysvo in adults 18 to <60 years of age considered to be at high risk of RSV disease due to certain chronic medical conditions (Substudy A, completed) and immunocompromised adults ≥18 years of age who will receive 2 doses of Abrysvo (Substudy B, ongoing).

SIV.3. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical studies in the development plan are limited in size and, therefore, unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

SIV.4. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 32. Exposure of special populations included or not in clinical trial development programme for Maternal Indication

Type of Special Population	Exposure
Pregnant women	Pregnant women were included in the studies supporting the maternal indication (please refer to Table 16).
Breastfeeding women	Breastfeeding women were not included in the Abrysvo clinical development programme.
Patients with relevant comorbidities:	
- Patients with hepatic impairment	Not included in the clinical development programme.
- Patients with renal impairment	
- Immunocompromised patients*	A clinical study in maternal participants living with HIV and their infants (C3671032, NCT06325657) is ongoing.
- Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Please refer to Table 18.
Subpopulations carrying relevant genetic polymorphisms	No data are available.
Pregnant paediatric population	Pregnant participants ≤49 years (including pregnant participants <18 years) are included in the pivotal C3671008 study.
Other	Not applicable

*A clinical study in maternal participants living with HIV and their infants (C3671032) started in March 2024 and is ongoing. It is a phase 3 study assessing safety, tolerability, and immunogenicity of a single dose of Abrysvo in pregnant participants living with HIV and their infants.

Table 33. Exposure of special populations included or not in clinical trial development programme for Adult Indication

Type of Special Population	Exposure
Patients with relevant comorbidities:	
- Patients with hepatic impairment	Participants with hepatic or renal impairment are included in C3671023 Substudy A (completed). Immunocompromised participants (including participants with end-stage renal disease on hemodialysis) are included in C3671023 Substudy B (ongoing).
- Patients with renal impairment	
- Immunocompromised patients	
- Patients with a disease severity different from inclusion criteria in clinical trials	Not included in clinical development programme.
- Patients with stable cardiovascular disease	Are included in the pivotal C3671013 study and C3671023 Substudy A.
- Patients with respiratory diseases (including participants with COPD or asthma under corticosteroid therapy if chronic corticosteroids do not exceed a prespecified dose equivalent of prednisone)	
Population with relevant different ethnic origin	Please refer to Table 26.
Subpopulations carrying relevant genetic polymorphisms	No data are available.
Other	Not applicable.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Due to country-specific logistics, it is not possible to determine with certainty the number of individuals who received Abrysvo in the post-authorisation period. Estimated worldwide doses distributed should only serve as a proxy for patient exposure.

With these caveats in mind, the estimated cumulative and interval worldwide unit distribution for Abrysvo from launch (in the United States) through 30 April 2024 is approximately 7,862,765 doses.

Cumulative and reporting period estimated exposures by gender and age group based on data provided by IQVIA[3] are summarized in Table 34. Distribution by region is based on doses distributed by market and summarized in Table 35.

[3] Of note, IQVIA data should not be regarded as complete sales information. Some countries where Abrysvo is sold may not be covered by IQVIA. In addition, IQVIA requires a minimum threshold of sales after which it will start tracking a product; thus, data from countries where the product does not have sizeable sales

Table 34. Cumulative (to 30 April 2024) Estimated Exposure for Abrysvo - US

Total doses	Sex			Age (years)			
	M	F	UNK	0-15	16-65	> 65	UNK
[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-

M= male F= female UNK= age unspecified US= United States

Table 35. Cumulative (to 30 April 2024) Estimated Exposure for Abrysvo - Rest of World

Total doses	Sex			Age (years)			
	M	F	UNK	0-15	16-65	> 65	UNK
1,419,763	9.4%	90.6%		0.0%	100.0%	0.0%	
	133,458	1,286,305	-	-	1,419,763	-	-

M= male F= female UNK= age unspecified

Table 36. Cumulative (to 30 April 2024) Estimated Exposure for Abrysvo by Region

Region/Country/Other	% of Doses	Total
[redacted]	[redacted]	[redacted]
Western EU	7.5%	552,226
Latin America	6.0%	446,660
Africa/Middle East	0.0%	-
Asia (excl. Japan)	0.0%	-
Central and Eastern Europe	0.2%	14,622
[redacted]	[redacted]	[redacted]
Australia/New Zealand	0.0%	0
Total	100%	7,395,368

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

No potential for drug abuse or dependence with Abrysvo is expected.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Table 37 lists the safety concerns at the initial RMP submission for Abrysvo.

would not be captured by IQVIA. Furthermore, IQVIA does not capture retail sales data and hospital data in all countries. Therefore, the sales volumes obtained through the use of IQVIA are likely to result in a large underestimate of the actual distributed product.

Table 37. Safety concerns at the initial submission

Important identified risk	None
Important potential risk	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

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

None.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Guillain-Barré syndrome

Risk-benefit impact:

In view of available data on GBS from clinical trials and spontaneous reports from post-marketing experience, a causal relationship between RSVpreF and the serious AE of GBS is at least a reasonable possibility. The available information on clinical trial and post-marketing reports of GBS is limited and in most cases potential confounding factors and alternative aetiologies are present.

Although GBS is a serious adverse event, given the rarity of the event, the overall benefit-risk profile of Abrysvo remains favourable. For addressing this important identified risk, the following PASS will be conducted:

- *A Post-Marketing Safety Study of Respiratory Syncytial Virus Vaccine among Older Adults in the United States* (C3671031).
- *A post-authorisation safety study of ABRYSVO in immunocompromised, or renally or hepatically impaired adults aged 60 years and older in a real world setting in Europe and UK* (C3671038).
- *A post-authorisation safety study (PASS) of ABRYSVO (respiratory syncytial virus stabilised prefusion subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK* (C3671026).

Important Potential Risk: None

Missing information

Risk-benefit impact: The safety profile of the vaccine is not known in:

- immunocompromised pregnant women and high-risk pregnancies due to their exclusion from pivotal clinical studies. A clinical trial (C3671032) in HIV-positive pregnant women and a PASS (*Safety of respiratory syncytial virus stabilized prefusion F subunit vaccine (RSVpreF) in pregnant women and their offspring in a real world setting in Europe* (C3671026) will address this missing information.
- immunocompromised older adults or renally or hepatically impaired older adults aged 60 years and older due to their exclusion from pivotal clinical studies. In order to address this information, a clinical trial (C3671023 – A Phase 3 Protocol To Evaluate The Safety, Tolerability, And Immunogenicity Of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine In Adults At High Risk Of Severe RSV Disease - Substudy B) and a non-interventional study are conducted: *Safety of respiratory syncytial virus stabilized 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).

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

There were no new safety concerns identified for Abrysvo.

Following the request made in PRAC Rapporteur's preliminary assessment report dated 15 April 2024 (EMEA/H/C/PSUSA/00000102/202311), the MAH has reclassified Guillain-Barré syndrome to important identified risk.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Guillain-Barré syndrome has been reported in one clinical trial in adults ≥60 years of age (C3671013). Although GBS has not been reported in clinical trials in pregnant women nor in non-pregnant participants <60 years, given the biological plausibility, GBS has been added as an important identified risk for all populations intended to be vaccinated with Abrysvo.

Table 38. Guillain-Barré syndrome

Potential mechanisms	Guillain-Barré syndrome is a peripheral neuropathy with acute onset and is characterized by acute flaccid paralysis, symmetrical weakness of the limbs, and hyporeflexia or areflexia, which reaches a maximum severity within 4 weeks. GBS typically occurs after an infectious disease in which the immune response generates antibodies that cross-react with gangliosides at nerve membranes. This autoimmune response results in nerve damage or functional blockade of nerve conduction. GBS is a life-threatening disease and the mortality rates in EU and North America vary between 3% and 7%. [125, 126] An increase of GBS of about 1 case per million above the background incidence has been associated with the 1976 New Jersey Swine Influenza vaccination programme and of about 1 case per thousand associated with rabies vaccination. [127, 128]
Evidence source and strength of evidence	Cases of GBS have been reported in study C3671013 (2 cases with a plausible temporal relationship with vaccination) and in post-marketing experience.

Table 38. Guillain-Barré syndrome

Characterisation of the risk

Most studies that estimate incidence rates of GBS were done in Europe and North America and showed a similar range of 0.8-1.9 cases per 100000 people per year. The annual incidence rate of GBS increases with age (0.6 per 100000 per year in children and 2.7 per 100000 per year in elderly people aged 80 years and over). Seasonal fluctuations, presumably related to variations in infectious antecedents, have been reported, but these observations are rarely statistically significant.
Currently, intravenous immunoglobulin (IVIg) and plasma exchange are proven effective treatments for GBS.

Clinical trials data from CT Dataset

Guillain-Barré syndrome events (4)	
	Total events n (%)
Serious events	4 (100.0)
Hospitalizations	4 (100.0)
Outcome: Resolved/resolving	3 (75.0)
Outcome: Not resolved	1 (25.0)

Note: Pooled Studies - C3671001, C3671002, C3671003, C3671004, C3671006, C3671008, C3671013 - Main Efficacy Study, C3671014, C3671023 - Substudy A. For study C3671013 multi-enrollers were not included.
Note: All the cases for Guillain-Barrè syndrome were reported in C3671013 - Main Efficacy Study.
Note: The total number of Guillain-Barrè syndrome cases is the denominator for the percentage calculations.
[redacted] Source Data: adae Table Generation: 10MAY2024 (01:10)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adae_s001_gbs_all_2024

Post-marketing data from PM Safety Database

In the post-marketing experience, through 30 April 2024, 27 cases (28 relevant PTs) were received by the MAH corresponding to 4.3% of the total PM cases received cumulatively. Distribution of events by seriousness and clinical outcome is provided below:

				Distribution of Events by Outcome N (%)				
PT	**# of Events (% of Total PTs)**	**# Serious Events (% of PT)**	**# Events with Criterion of Hospitalization (% of PT)**	**Fatal**	**Resolved / Resolving**	**Resolved with Sequelae**	**Not Resolved**	**Unk/ No Data**
All PTs	28 (100)	28 (100)	22 (78.6)	(0)	3 (10.7)	(0)	16 (57.1)	9 (32.1)
Guillain-Barre syndrome	27 (96.4)	27 (100)	21 (77.8)	(0)	2 (7.4)	(0)	16 (59.3)	9 (33.3)
Ascending flaccid paralysis	1 (3.6)	1 (100)	1 (100)	(0)	1 (100)	(0)	(0)	(0)

Overall, 27 post-marketing cases with GBS were reported, 24 of them originated from VAERS. Most of them (23 out of 27) were assessed by the MAH as Brighton

Table 38. Guillain-Barré syndrome

	collaboration (BC) level 4,[4] 3 of them as BC5 (thus not as GBS cases) and 1 of them as BC3. Eight of the 27 cases reported co-vaccination (Shingrix, Imovax, Fluad, Comirnaty, Tdap) and at least 3 of the co-administered vaccines have GBS/polyneuropathy as a labeled adverse reaction. Three cases reported GBS onset on the same vaccination day and one case reported time to onset of 2 days after vaccination; this latency does not suggest a temporal relationship with vaccination. One case reported a pre-existing peripheral neuropathy. Three cases reported an infection preceding or concomitant to vaccination, which suggests an alternative etiology triggering the event. In two cases, GBS was self (patient) diagnosed or a patient inquiry. In several of the 27 cases there was underlying medical history that represented strong confounding factors including peripheral neuropathy, multiple sclerosis or cancer. Although it is acknowledged that the spontaneously reported GBS cases are not well-documented (mostly missing diagnostic examination, medical history and concomitant medication) a causal relationship between RSVpreF and Guillain-Barré syndrome remains at least a reasonable possibility.
Risk factors and risk groups	The overall incidence rate of GBS is estimated to range from 1.65-3.11 [129], [130]per 100,000 person-years, and increases with age, with an estimated incidence ranging from 4.6-7.8 [131], [132]in adults 60 years and older. Many different preceding infections have been identified in patients with the disorder, but only for a few microorganisms has an association been shown in case-control studies *C jejuni* is the predominant infection, found in 25–50% of the adult patients, with a higher frequency in Asian countries. Other infections associated with Guillain-Barré syndrome are cytomegalovirus (CMV), Epstein-Barr virus, influenza A virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*. An association of Guillain-Barré syndrome with hepatitis E has been identified in patients from both the Netherlands and Bangladesh.[133, 134] An emerging relation between Guillain-Barré syndrome and acute arbovirus infection including Zika and chikungunya is being closely monitored and is the subject of major interest as the global epidemic spreads.
Preventability	There are no known precautions to prevent GBS.
Impact on the risk-benefit balance of the product	GBS could have a significant impact on a patient's quality of life, and mortality rates in EU and North America vary between 3% and 7%.
Public health impact	Although GBS is a serious life-threatening disease, given the rarity of the event, it is not expected to have a significant impact on public health.

Important potential risk: There are no important potential risks for Abrysvo.

SVII.3.2. Presentation of the Missing Information

Safety concerns and other concerns due to missing or partially missing information from the clinical trial programme are provided below.

[4] Sejvar JJ et al Vaccine 29 (2011) 599–612

Table 39. Use in immunocompromised pregnant women and high-risk pregnancies

Evidence source: The safety profile of Abrysvo has not been investigated in immunocompromised pregnant women and high-risk pregnancies. Population in need of further characterisation: A non-interventional post-authorisation safety study (C3671026) is planned to assess the safety of Abrysvo in all pregnant women and their offspring, including immunocompromised pregnant women and high-risk pregnancies. A clinical study (C3671032) in HIV-positive pregnant women in South Africa is ongoing to address this missing information.

Table 40. Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old

Evidence source: The safety profile of Abrysvo has not been investigated in immunocompromised, or renally or hepatically impaired older adults ≥60 years old. *Population in need of further characterisation: A non-interventional post-authorisation safety study (C3671038) is planned to assess the safety of Abrysvo in immunocompromised, or renally or hepatically impaired older adults ≥60 years old. A clinical study (C3671023*) in immunocompromised participants is ongoing to address this missing information.

* C3671023 Substudy B enrolled immunocompromised adults 18 and older who qualified for enrollment with one of the four following medical conditions: 1. Solid organ transplantation (heart/lung/liver/kidney transplant with minimum 3 months post transplantation) 2. End-stage renal disease on maintenance hemodialysis (these patients have renal impairment) 3. On active immunomodulator therapy for an autoimmune inflammatory disorder (at a stable dose) 4. Non-small cell lung cancer (NSCLC) on per-protocol therapy.

Module SVIII. Summary of the Safety Concerns

Table 41. Summary of Safety Concerns

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

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance for the lifecycle of a product is a critical component to the detection, assessment, understanding and mitigation of AEs. Objectives of routine pharmacovigilance includes having processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports and aggregate data globally, following global safety Standard Operating Procedures and regulatory guidance.

Pfizer monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

There are no specific adverse event follow-up questionnaires addressing any of the safety concerns for this RMP.

- **Other forms of routine pharmacovigilance activities for safety concerns:**

As part of the signal detection activities will include analysis of (not limited to):

- Spontaneous cases
- Clinical trial data
- Literature

If the review of the data leads to an impact on the benefit risk of the product, a benefit-risk discussion and any warranted product information updates will be submitted via appropriate variation procedure. Data will be summarised in a dedicated section in the PSUR.

Furthermore, routine PV activities for the maternal recipients of Abrysvo will include the use of the exposure during pregnancy (EDP) questionnaire to obtain general information on the pregnancy and the pregnancy outcome in pregnant women receiving RSV vaccine reporting adverse event(s). For prospective EDP cases (where the pregnancy is ongoing), the EDP questionnaire will be sent to collect preliminary information such as source of information, maternal information (e.g., demographics and pregnancy), exposure to products (including use of recreational drugs), any medical history (including any obstetrical history) as well as any paternal information, as applicable. Following the expected date of delivery, a second EDP follow-up questionnaire will be sent to gather additional information on the outcome of the pregnancy and collect delivery and neonatal information. If clinically indicated, follow-

up may be required for a period of time following the birth of the child to identify any progression or change in the development of the baby.

III.2. Additional Pharmacovigilance Activities

As immunocompromised pregnant women and women with high-risk pregnancies, and immunocompromised or renally or hepatically impaired older adults ≥60 years old were not included in the clinical studies to date, and to address the safety concern of Guillain-Barré syndrome, the MAH plans to conduct the 3 PASS summarised below.

Study short name and title:

A post-authorization safety study of Guillain Barré syndrome (GBS) following Abrysvo among older adults in the United States (C3671031).

Rationale and study objectives:

As the phase 3 study RENOIR (C3671013) was not powered to evaluate the risk of rare adverse events, a PASS is planned to further evaluate the risk of GBS, other immune-mediated demyelinating conditions and polyneuropathies following Abrysvo administration among older adults.

Study design:

This will be 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) among Medicare beneficiaries who receive Abrysvo versus those who are not vaccinated with Abrysvo at that point in time. Secondly, a self-controlled risk interval (SCRI) analysis may also be conducted among Abrysvo vaccinated Medicare beneficiaries to compare the incidence of GBS, other immune-mediated demyelinating conditions and polyneuropathies during the post-vaccination risk window (e.g., 1-42 days post vaccination) to the post-vaccination control window (e.g., 43-84 days post vaccination).

Study population:

Eligible Medicare beneficiaries who receive Abrysvo and a comparator cohort of Medicare beneficiaries who do not receive Abrysvo.

Milestones:

Protocol submission to the EMA: 30 November 2023

Planned final report submission to the EMA: 31 May 2030

Study short name and title:

A post-authorisation safety study (PASS) of Abrysvo (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK (C3671026).

Rationale and study objectives:

As immunocompromised pregnant women and high-risk pregnancies were not included in the clinical studies to date, the MAH plans to address this missing information by conducting a PASS with the following objectives:

1) To evaluate the safety of Abrysvo in all pregnant women and their offspring who receive Abrysvo, compared to a relevant matched comparator group of pregnant women and their offspring who do not receive Abrysvo;

2) To evaluate the safety of Abrysvo in immunocompromised pregnant women and high-risk pregnancies and their offspring who receive Abrysvo, compared to a relevant matched comparator group of pregnant women and their offspring who do not receive Abrysvo.

Study design:

This is a multi-database cohort study utilizing electronic health care data sources from among members of the Vaccine Monitoring Collaboration for Europe (VAC4EU).

Study population:

The study population will include:

All eligible pregnant women and their offspring who receive Abrysvo and a relevant matched comparison group of pregnant women and their offspring who do not receive Abrysvo.

Milestones:

Protocol submission to the EMA: 31 Mar 2024

Planned final study report submission to the EMA: 28 Sep 2029

Study short name and title:

A post-authorisation safety study of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK (C3671038).

Rationale and study objectives:

As immunocompromised, or renally or hepatically impaired older adults aged 60 years and older were not included in the clinical studies to date, the MAH plans to address this missing information by conducting the PASS summarised below.

To estimate the incidence and rate ratios of safety events of interest in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older who receive Abrysvo compared to a relevant matched comparator group of persons who do not receive Abrysvo.

Study design:

This is a multi-database cohort study utilizing electronic health care data sources from among members of the Vaccine Monitoring Collaboration for Europe (VAC4EU).

Study population:

The study population will be comprised of all eligible immunocompromised, or renally or hepatically impaired older adults aged 60 years and older who receive Abrysvo and a relevant matched comparator group of persons who do not receive Abrysvo.

Milestones:

Protocol submission to the EMA: 31 Mar 2024

Planned final study report submission to the EMA: 28 Sep 2029

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 42. 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)				
A post-authorization safety study (PASS) of Guillain -Barré syndrome (GBS) following Abrysvo among older adults in the United States (C3671031) (Planned)	To evaluate the risk of GBS, other immune-mediated demyelinating conditions and polyneuropathies following Abrysvo administration among older adults	Guillain-Barré syndrome	Submission of final study protocol Submission of final study report	30 November 2023 31 May 2030
A post-authorisation safety study (PASS) of Abrysvo (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK (C3671026) (Planned)	To evaluate the safety of Abrysvo 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 28 Sep 2029
A post-authorisation safety study (PASS) of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK (C3671038) (Planned)	To evaluate the safety of Abrysvo 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 28 Sep 2029

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

The risks associated with the use of Abrysvo are minimized through provision of relevant information in the SmPC and the package leaflet (PL) to support safe use of the product.

Table 43. Description of routine risk minimisation measures by safety concern

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

V.2. 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.

V.3. Summary of Risk Minimisation Measures

Routine risk minimisation actions include the use of SmPC and package leaflet (PL) to support safe use of the vaccine. No additional risk minimisation measures are proposed.

Table 44. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Guillain-Barré syndrome	Routine risk minimisation measures: EU SmPC Section *4.8 Undesirable effects* Medicine's legal status: Medicinal product subject to medical prescription. Additional RMMs: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Abrysvo post-authorisation safety studies in the EU include GBS as a safety outcome among immunocompromised, or renally or hepatically impaired older adults (C3671038) and among pregnant women and their offspring in a real world setting in Europe and UK (C3671026). Post-authorization safety study of GBS following Abrysvo among older adults in United States (C3671031).
Important Potential Risk		
None		
Missing Information		
Use in immunocompromised pregnant women and high-risk pregnancies	Routine risk minimisation measures: EU SmPC Section 4.4 *Special warnings and precautions for use* Medicine's legal status: Medicinal product subject to medical prescription. Additional RMMs: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A post-authorisation safety study (PASS) of Abrysvo (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK (C3671026).

Table 44. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old	Routine risk minimisation measures: EU SmPC Section 4.4 *Special warnings and precautions for use* Medicine's legal status: Medicinal product subject to medical prescription. Additional RMMs: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A post-authorization safety study of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK (C3671038).

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ABRYSVO (respiratory syncytial virus stabilised prefusion F subunit vaccine [bivalent, recombinant])

This is a summary of the risk management plan (RMP) for Abrysvo. The RMP details important risks of Abrysvo, how these risks can be minimised, and how more information will be obtained about Abrysvo's risks and uncertainties (missing information).

Abrysvo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and vaccine recipients on how Abrysvo should be used.

This summary of the RMP for Abrysvo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Abrysvo's RMP.

I. The Medicine and What It Is Used For

Abrysvo is indicated for 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, and for active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV. It contains RSV subgroup A stabilised prefusion F protein (60 micrograms) and RSV subgroup B stabilised prefusion F protein (60 micrograms) as the active substances and it is given intramuscularly.

Further information about the evaluation of Abrysvo's benefits can be found in Abrysvo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Abrysvo, together with measures to minimise such risks and the proposed studies for learning more about Abrysvo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to vaccine recipients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the vaccine recipient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Abrysvo is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Abrysvo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Abrysvo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 45. List of important risks and missing information

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

II.B Summary of Important Risks

Guillain-Barré syndrome has been reported in one clinical trial in adults ≥60 years of age (C3671013). Although GBS has not been reported in clinical trials in pregnant women, nor in non-pregnant participants <60 years, given the biological plausibility, GBS has been added as an important identified risk for all populations intended to be vaccinated with Abrysvo.

There are no important potential risks for Abrysvo.

Table 46. Important identified risk - Guillain-Barré syndrome

Evidence for linking the risk to the medicine	A total of 27 post-marketing cases with GBS were reported, 24 of them originated from VAERS. Most of them (23 out of 27) were assessed by the MAH as Brighton collaboration (BC) level 4, 3 of them as BC5 (thus not as GBS cases) and 1 of them as BC3. [5] Eight of the 27 cases reported co-vaccination (Shingrix, Imovax, Fluad, Comirnaty, Tdap) and at least 3 of the co-administered vaccines have GBS/polyneuropathy as a labelled adverse reaction. Three cases reported GBS onset on the same vaccination day and one case reported time to onset of 2 days after vaccination; this latency does not suggest a temporal relationship with vaccination. One case reported a pre-existing peripheral neuropathy. Three cases reported an infection preceding or concomitant to vaccination, which suggests an alternative aetiology triggering the event. In two cases, GBS was self (patient) diagnosed or a patient inquiry. In several of the 27 cases there was underlying medical history that represented strong confounding factors including peripheral neuropathy, multiple sclerosis or cancer. Although it is acknowledged that the spontaneously reported GBS cases are not well-documented (mostly missing diagnostic examination, medical history and concomitant medication) a causal relationship between RSVpreF and Guillain-Barré syndrome remains at least a reasonable possibility.
Risk factors and risk groups	The overall incidence rate of GBS is estimated to range from 1.65-3.11 [129, 130]per 100,000 person-years, and increases with age, with an estimated incidence ranging from 4.6-7.8[131 132] in adults 60 years and older. Many different preceding infections have been identified in patients with the disorder, but only for a few microorganisms has an association been shown in case-control studies C *jejuni* is the predominant infection, found in 25–50% of the adult patients, with a higher frequency in Asian countries. Other infections associated with Guillain-Barré syndrome are cytomegalovirus (CMV), Epstein-Barr virus, influenza A virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*. An association of Guillain-Barré syndrome with hepatitis E has been identified in patients from both the Netherlands and Bangladesh. [133,134] An emerging relation between Guillain-Barré syndrome and acute arbovirus infection including Zika and chikungunya is being closely monitored and is the subject of major interest as the global epidemic spreads.
Risk minimisation measures	Routine risk minimisation measures EU SmPC Section *4.8 Undesirable effects* Additional risk minimisation measures None

[5] Sejvar JJ et al Vaccine 29 (2011) 599–612.

Table 46. Important identified risk - Guillain-Barré syndrome

Additional pharmacovigilance activities	Additional pharmacovigilance activities Post-authorisation safety studies planned to be conducted in the EU include GBS as a safety outcome among immunocompromised, or renally or hepatically impaired older adults (C3671038) and among pregnant women and their offspring (C3671026). In addition, a post-marketing safety study focusing on GBS, other immune-mediated demyelinating conditions and polyneuropathies among older adults is planned to be conducted in US (C3671031). See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 47. Missing information - Use in immunocompromised pregnant women and high-risk pregnancies

Risk minimisation measures	Routine risk communication EU SmPC Section *4.4 Special warnings and precautions for use* Additional risk minimisation measures No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities A post-authorisation safety study (PASS) of Abrysvo (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK(C3671026). See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 48. Missing information - Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old

Risk minimisation measures	Routine risk communication EU SmPC Section *4.4 Special warnings and precautions for use* Additional risk minimisation measures No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities A post-authorisation safety study (PASS) of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK (C3671038). See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for Abrysvo.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study title: A post-authorisation safety study (PASS) of Abrysvo (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK (C3671026)

Purpose of the study: As immunocompromised pregnant women and high-risk pregnancies were not included in the clinical studies to date, the MAH plans to address this missing information by conducting a PASS study with the following objectives:

To estimate the prevalence and rate ratios of adverse pregnancy and maternal outcomes at or after birth in all eligible pregnant, including immunocompromised pregnant women and women with high-risk pregnancies and their offspring a who receive Abrysvo, compared to a relevant matched comparator group of pregnant women and their offspring who do not receive Abrysvo.

Study title: A post-authorisation safety study of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK (C3671038)

Purpose of the study: As immunocompromised, or renally or hepatically impaired older adults aged 60 years and older were not included in the clinical studies to date, the MAH plans to address this missing information by conducting a PASS study with the following objectives:

To estimate the incidence and rate ratios of safety events of interest in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older who receive Abrysvo compared to a relevant matched comparator group of persons who do not receive Abrysvo.

Study title: A post-authorization safety study of Guillain-Barré Syndrome (GBS) following Abrysvo among older adults in the United States (C3671031)

Purpose of the study: As the phase 3 study, RENOIR (C3671013), was not powered to evaluate the risk of rare adverse events, the MAH plans to further evaluate the risk of GBS, other immune-mediated demyelinating conditions, and polyneuropathies following Abrysvo administration in older adults in the US.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 - Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 - Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Exposure During Pregnancy

1. According to the information provided, exposure to a product may have occurred during pregnancy or around the time of conception. Please confirm and complete all questions to the best of your ability and knowledge.

☐ Yes ☐ No ☐ Unknown

Maternal Obstetrical History

1. Occupation

_____

2. Was the mother previously pregnant?

☐ Yes ☐ No ☐ Unknown

If Yes, how many times:_____

3. Number of other children

_____

4. Outcome of previous pregnancies (e.g., live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy)

_____

5. Did the mother experience previous pregnancy complications?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

6. Did the mother experience previous fetal/neonatal abnormalities?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

7. Does the mother have a history of sub-fertility?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

8. Was the mother treated for infertility?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

9. Mother's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

10. Does the mother have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Results of serology tests (e.g., rubella, toxoplasmosis, etc.)

Maternal Information

1. Ante-natal check-up (e.g., fetal ultrasound, serum markers, etc.). Please specify dates in dd-Mmm-YYYY format and check-up results for this pregnancy.

_____

2. First day of last menstrual period (dd-Mmm-yyyy)

_____

3. Number of fetuses for this pregnancy

_____

4. Estimated delivery date for this pregnancy (dd-Mmm-yyyy)

_____

5. Gestational period at time of initial suspect drug exposure

_____ ☐ Trimester ☐ Month

6. Did the mother smoke during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the mother drink alcohol during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Did the mother use illicit drugs during this pregnancy?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

9. Did the mother experience any problems before delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

10. Did the mother experience any problems during delivery (including delivery complications, fetal distress, amniotic fluid abnormal, abnormal placenta)?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Did the mother experience any problems after delivery?

☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

12. Mode of delivery

☐ Vaginal ☐ Cesarean ☐ Unknown

13. Outcome of this pregnancy

- ☐ Full term live birth
- ☐ Premature live birth
- ☐ Post-mature live birth
- ☐ Stillbirth
- ☐ Late foetal death
- ☐ Ectopic pregnancy
- ☐ Molar pregnancy
- ☐ Spontaneous abortion/miscarriage
- ☐ Induced/elective abortion
- ☐ Unknown

14. Date of outcome of this pregnancy (dd-Mmm-yyyy)

_____

Neonatal Information

1. Sex (at birth)

☐ Male ☐ Female

2. Weight at birth (number and unit)

_____ ☐ kg ☐ lbs & oz

3. Length at birth (number and unit)

_____

4. Head circumference at birth (number and unit)

_____

5. Apgar score at 1 min

_____

6. Apgar score at 5 min

_____

7. Gestational age at birth in weeks

_____

8. Outcome of Fetus/Infant

☐ Healthy newborn
☐ Congenital malformation/anomaly (specify below)
☐ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify below)
☐ Intrauterine death
☐ Neonatal death
☐ Outcome pending (not born yet)
☐ Perinatal complications (specify below)
☐ Post-perinatal complications (specify below)
☐ Unknown

Please specify:

Paternal Information

1. Father's Age

_____ ☐ Years ☐ Months ☐ Days

Age Group:

☐ Adolescent (12-17 Years) ☐ Adult (18-64 Years) ☐ Elderly (65 or older)

2. Occupation

_____

3. Father's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

4. Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

5. Did the father smoke during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

6. Did the father drink alcohol during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the father use illicit drugs during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Does the father have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable