ABRYSVO (RESPIRATORY SYNCYTIAL VIRUS VACCINE [BIVALENT, RECOMBINANT])

RISK MANAGEMENT PLAN

RMP Version number: 0.3

Data lock point for maternal indication: 02 September 2022

Data lock point for older adult indication: 13 October 2022

Date of final sign off: 27 June 2023

Rationale for submitting an updated RMP: The applicant is responding to CHMP day 120 list of outstanding issues for Abrysvo (procedure no. EMEA/H/C/006027/0000):

- Update of studies C3671038 and C3671026 (category 3 PASS) with the inclusion of the Guillain-Barrè syndrome as an outcome of interest. Update of Part VI "Summary of activities in the risk management plan by medicinal product" in line with the updates made in other parts of the RMP.

Summary of significant changes in this RMP:

RMP Part/Module	Major change(s)
PART I Product overview	Indications aligned with the SmPC proposed with applicant's responses to D120 list of outstanding issues
PART II Safety Specification Module SIII CT Exposure	Older adult and overall CT exposure tables updated to include participants from studies C3671013 (end of Season 1) and C3671006
Module SIV Populations not studied in CT	Addition of information about study C3761023 and updates to Table 29
Module SVII Identified and Potential Risks	Table 32 and 33 updated to reflect GBS as a potential risk for both populations Editorial changes to PASS studies C3671026, C3671038 and C3671031
PART III – III.1 Additional Pharmacovigilance Activities	EDP (exposure during pregnancy) questionnaire added

PART III – III.3 Summary table of Pharmacovigilance Activities	Table 37 *Ongoing and planned additional pharmacovigilance activities* updated
PART V V.1 Routine Risk Minimisation Measures	Addition of GBS in 4.8 section of the SmPC
PART V V.3 Summary of Risk Minimisation Measures	Addition of GBS in 4.8 section of the SmPC (Table 39)
PART VI – II.A List of Important Risks and Missing Information	List of safety concerns amended to reflect GBS as a potential risk for both populations (Table 40)
PART VI – II.B Summary of Important Risks	Updated information on the Important potential risk of GBS
PART VI – II.C.2 Other Studies in Post-Authorisation Development Plan	Update to the PASS study C3671031
Annex 2	Update to PASS study C3671031
Annex 3	Update to PASS study C3671031
Annex 4	Addition of EDP questionnaire
Annex 8	Updated to reflect the overall changes

Other RMP versions under evaluation: 0.2

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
AIAN	American Indian and Alaska Native
ADR	Adverse Drug Reaction
AER	Adverse Event Report
ARI	Acute respiratory illness
CDC	Centers for Disease Control and Prevention (United States)
CDS	Core Data Sheet
COPD	Chronic obstructive pulmonary disease
COVID-19	Severe acute respiratory syndrome coronavirus 2
CSP	Core Safety Profile
CHF	Congestive heart failure
DLP	Data-Lock Point
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	(US) Food and Drug Administration
HA	Health Authority
HLT	High Level Term
IBD	International Birth Date
ICD	International Classification of Disease
ICU	Intensive care unit
IFN λ	Interferon alfa
ILI	Influenza-like illness
LLT	Lowest Level Term
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
PT	Preferred Term
RNA	Ribonucleic acid
RSI	Reference Safety Information
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
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query

SOC	System Organ Class
UK	United Kingdom
US	United States
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 60 years of age and older are protected by active immunisation.
	Important information about its composition RSVpreF 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. The RSVpreF vaccine presentation 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 drug product is supplied in a 2 mL clear glass vial. Prior to use, the lyophilised drug product is reconstituted with sterile water solvent in a single-use prefilled syringe using a vial adapter and the entire content is withdrawn to enable a dose of 0.5 mL for intramuscular administration. After reconstitution, RSVpreF 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: Not Applicable

	Proposed (if applicable): Abrysvo is indicated for: • Maternal immunisation during pregnancy to provide protection in infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV). • Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.
Dosage in the EEA	Current: Not applicable
	Proposed: Abrysvo is administered as a single dose (0.5 mL).
Pharmaceutical form(s) and strengths	Current: Not applicable
	Proposed: Powder and solvent for solution for injection After reconstitution, one dose (0.5 mL) contains: RSV subgroup A stabilised prefusion F antigen 60 micrograms RSV subgroup B stabilised prefusion F antigen 60 micrograms
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

Respiratory syncytial virus bivalent stabilised prefusion F subunit vaccine (RSVpreF) is indicated for:

- Maternal immunisation during pregnancy to provide protection in infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV).
- Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

SI.1. Indication for maternal immunisation

Maternal immunisation during pregnancy to provide protection in infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV).

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, 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 ≥60 years

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 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 among 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 among 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. Among studies stratified on age 65 years, the annual incidence of medically attended RSV 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]
†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,[80,60,52] 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).[81,57,80,60,82,77,58,52]

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

Risk Factor	References
*Older age	Pastula 2017,[80] Belongia 2018,[60] Tin Tin Htar 2020[52]
†Frailty	Falsey 2005,[81] Childs 2019,[77] Tin Tin Htar 2020[52]
†Immunosenescence	Childs 2019[77]
*Chronic cardiopulmonary disease	Falsey 2005,[81] Colosia 2017,[57] Belongia 2018,[60] Ivey 2018,[82] 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

The main existing treatment options:

Treatment of RSV disease consists primarily of supportive care (e.g. mainly oxygen, hydration and suctioning of secretions).[83] 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.[84, 85, 86] 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.[87, 88, 89] Paracetamol and OTC cold medications may be used to relieve milder symptoms.[90]

Arexvy, a vaccine indicated for active immunisation for the prevention of lower respiratory tract disease caused by RSV in adults 60 years of age and older, received marketing authorisation in the EU in June 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.[91,52] 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) [81,52]; 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. [57,91,82,77,52] 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

[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.

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.[92]

- *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.[93] 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 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,[94, 95,32] 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. [93] Further, deaths due to RSV increase after age 49 years, representing 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. [93]

In studies of older adults hospitalised with RSV, the estimated mortality rate ranged from 1.6-10%,[32,57, 96, 97,58,76,64] with higher mortality rates of up to 20% among lung transplant recipients. [97] 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 12. Comorbid cardiopulmonary conditions (e.g., asthma, COPD, CHF, acute coronary syndrome, arrhythmias, occurrence of myocardial infarction) are the most common [81,57,82,58, 98,52,9, 99,74] Annually, 4-10% of older adults with chronic cardiopulmonary disease contract RSV (Shi 2021),[98] 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 12. Important comorbidities/co-infections in RSV patients aged ≥50 years

Comorbidity	References
*Bacterial or fungal co-infection	Falsey 2005,[81] Walker & Ison 2014[69]
*†‡Chronic cardiopulmonary disease	Falsey 1995,[100] Falsey 2005,[81] Widmer 2014,[62] Colosia 2017,[57] Ivey 2018,[82] Zheng 2018,[99] Tin Tin Htar 2020,[52] Tong 2020,[9] Shi 2021,[98] Mesa-Frias 2022,[66] Branche 2022[64]

Table 12. Important comorbidities/co-infections in RSV patients aged ≥50 years

Comorbidity	References
*Chronic renal disease	Tin Tin Htar 2020,[52] Tong 2020[9]
†‡Diabetes mellitus	Tin Tin Htar 2020,[52] Tong 2020,[9] Shi 2021,[98] Mesa-Frias 2022[66]
*†‡Immunodeficiency	Falsey 2005,[81] Widmer 2012,[63] Widmer 2014,[62] Colosia 2017,[57] Shi 2021,[98] Mesa-Frias 2022[66]
*‡Malignancies	Falsey 2005,[81] 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 13).

Table 13. 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	

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.[101, 102].

Module SIII. Clinical Trial Exposure

Clinical study exposure data are provided for the following studies, at the cut-off date of 02 September 2022 for the safety dataset and 30 September 2022 for the efficacy dataset in the global phase 3 pivotal study (C3671008) for the maternal indication and 13 October 2022 for the older adult indication (C3671013).

Studies		Maternal/Older Adult
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	Maternal/Older Adult
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	Older Adult
	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	Maternal
	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	Maternal

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	Older Adult
	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	Maternal
	C3671013 A Phase 3 study to evaluate the efficacy, immunogenicity, and safety of respiratory syncytial virus (RSV) prefusion f subunit vaccine in adults	Older Adult
	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	Maternal/Older Adult

SIII.1. Clinical Trial Exposure for Maternal Indication

Table 14. 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	4144	3797	4144
Total Exposure	4144	3797	4144

PFIZER CONFIDENTIAL Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s001_ex_m Date of Generation: 22NOV2022 (03:54)

Table 15. 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	4144	3797	4144
Total	**4144**	**3797**	**4144**
Gestational Age at Administration			
<24 weeks			
≥24 weeks to <28 weeks	1078	974	1078
≥28 weeks to <32 weeks	1237	1121	1237
≥32 weeks to ≤36 weeks	1825	1698	1825
>36 weeks	4	4	4
Total	**4144**	**3797**	**4144**

PFIZER CONFIDENTIAL Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s005_ex_age_m Date of Generation: 22NOV2022 (03:54)

Table 16. 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	2728	2468	2728
Black or African American	820	745	820
Asian	460	455	460
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
Ethnic Origin			
Hispanic/Latino	1176	1081	1176
Non-Hispanic/non-Latino	2937	2686	2937
Not reported	29	28	29
Unknown	2	2	2
Total	**4144**	**3797**	**4144**

PFIZER CONFIDENTIAL Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s005_ex_re_m Date of Generation: 22NOV2022 (03:54)

Table 17. 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	4024	3682	4024
Total Exposure	**4024**	**3682**	**4024**

Note: Infants are presented according to their mother's vaccine group.
PFIZER CONFIDENTIAL Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s001_ex_i Date of Generation: 22NOV2022 (03:54)

Table 18. Number (%) of Newborn Infant Participants

Study ID	No. of Participants Exposed Pooled RSVpreF (including with and without adjuvant) (N=4024)	No. of Participants Exposed RSVpreF 120 µg (with NO adjuvant) (N=3682)	Total Vaccine RSVpreF Doses (N=4024)
C3671003	456 (11.3)	114 (3.1)	456 (11.3)
C3671008	3568 (88.7)	3568 (96.9)	3568 (88.7)

Note: Infants are presented according to their mother's vaccine group.
PFIZER CONFIDENTIAL Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s001_n_i Date of Generation: 22NOV2022 (03:54)

Table 19. 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	2625	2373	2625
Black or African American	786	712	786
Asian	422	420	422
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	1163	1066	1163
Non-Hispanic/non-Latino	2807	2565	2807
Not reported	52	49	52
Unknown	2	2	2
Total	**4024**	**3682**	**4024**

Note: Infants are presented according to their mother's vaccine group.
PFIZER CONFIDENTIAL Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s005_ex_re_i Date of Generation: 22NOV2022 (03:54)

Table 20. 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.
PFIZER CONFIDENTIAL Source Data: adsl Output File: ./mat_1008_bl_eff/RSV_Maternal_RMP/adsl_s001_ex_f Date of Generation: 22NOV2022 (03:54)

Table 21. 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 14
PFIZER CONFIDENTIAL 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 Older Adult Indication

Table 22. 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	22302	20823	22302
Total Exposure	**22302**	**20823**	**22302**

Note: Pooled Studies - C3671001, C3671002, C3671004, C3671006, C3671013(Cut-off Date: 13OCT2022), C3671014.
For study C3671013 multi-enrollers were not included.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 14JUN2023 (10:03)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_oa v2

Table 23. 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	474	1403	322	799	474	1403
50-59 years	12	19	2	3	12	19
60-69 years	6163	6256	6020	6104	6163	6256
70-79 years	3497	3325	3341	3142	3497	3325
≥80 years	584	569	551	539	584	569
Total	**10730**	**11572**	**10236**	**10587**	**10730**	**11572**

Note: Pooled Studies - C3671001, C3671002, C3671004, C3671006, C3671013(Cut-off Date: 13OCT2022), C3671014.
For study C3671013 multi-enrollers were not included.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 14JUN2023 (10:03)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_oa v2

Table 24. 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	17947	16764	17947
Black or African American	2564	2359	2564
Asian	1496	1448	1496
American Indian or Alaska Native	62	55	62
Native Hawaiian or other Pacific Islander	30	23	30
Other	1	0	1
Multiracial	83	65	83
Not reported	81	71	81
Unknown	38	38	38
Ethnic Origin			
Hispanic/Latino	7779	7654	7779
Non-Hispanic/non-Latino	14321	12975	14321
Not reported	202	194	202
Total	**22302**	**20823**	**22302**

Note: Pooled Studies - C3671001, C3671002, C3671004, C3671006, C3671013(Cut-off Date: 13OCT2022), C3671014.
For study C3671013 multi-enrollers were not included.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 14JUN2023 (10:03)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_oa v2

SIII.3. Overall Clinical Trial Exposure

Table 25. 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	30470	28302	30470
Total Exposure	**30470**	**28302**	**30470**

Note: Pooled Studies - C3671001, C3671002, C3671003, C3671004, C3671006, C3671008 (Cut-off Date: 02SEP2022), C3671013 (Cut-off Date: 13OCT2022), C3671014. For study C3671013 multi-enrollers were not included.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 14JUN2023 (10:04)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_all v2

Table 26. 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	2513	7532	2190	6410	2513	7532
50-59 years	12	19	2	3	12	19
60-69 years	6163	6256	6020	6104	**6163**	**6256**
70-79 years	3497	3325	3341	3142	**3497**	**3325**
≥80 years	584	569	551	539	**584**	**569**
Total	**12769**	**17701**	**12104**	**16198**	**12769**	**17701**

Note: Pooled Studies - C3671001, C3671002, C3671003, C3671004, C3671006, C3671008 (Cut-off Date: 02SEP2022), C3671013 (Cut-off Date: 13OCT2022), C3671014. For study C3671013 multi-enrollers were not included.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 14JUN2023 (10:04)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_all v2

Table 27. 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	23300	21605	23300
Black or African American	4170	3816	4170
Asian	2378	2323	2378
American Indian or Alaska Native	144	136	144
Native Hawaiian or other Pacific Islander	55	45	55
Other	1	0	1
Multiracial	188	166	188
Not reported	179	156	179
Unknown	55	55	55
Ethnic Origin			
Hispanic/Latino	10118	9801	10118

Table 27. 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	20065	18226	20065
Not reported	283	271	283
Unknown	4	4	4
Total	**30470**	**28302**	**30470**

Note: Pooled Studies - C3671001, C3671002, C3671003, C3671004, C3671006, C3671008 (Cut-off Date: 02SEP2022), C3671013 (Cut-off Date: 13OCT2022), C3671014. For study C3671013 multi-enrollers were not included.
PFIZER CONFIDENTIAL Source Data: adsl Table Generation: 14JUN2023 (10:04)
Output File: ./nda_oa_unbl/OA_ISS_UNBL/adsl_s001_ex_all v2

Module SIV. Populations Not Studied in Clinical Trials

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

Table 28. 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 (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.*
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 28. 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/ 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 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 28. 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 Older Adult Indication within the Development Programme

Table 29. Exclusion Criteria in Pivotal Clinical Study in Adults ≥60 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 29. Exclusion Criteria in Pivotal Clinical Study in Adults ≥60 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.

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 30. 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 14).
Breastfeeding women	Breastfeeding women were not included in the RSVpreF clinical development programme.
Patients with relevant comorbidities:	
- Patients with hepatic impairment	Not included in the clinical development programme.
- Patients with renal impairment	
- Immunocompromised patients	
- Patients with a disease severity different from inclusion criteria in clinical trials	
Population with relevant different ethnic origin	Please refer to Table 16.
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

Table 31. Exposure of special populations included or not in clinical trial development programme for Older Adult Indication

Type of Special Population	Exposure
Patients with relevant comorbidities:	
- Patients with hepatic impairment	Not included in any of the completed clinical studies to date.
- Patients with renal impairment*	

Table 31. Exposure of special populations included or not in clinical trial development programme for Older Adult Indication

Type of Special Population	Exposure
- Immunocompromised patients*	
- Patients with a disease severity different from inclusion criteria in clinical trials	
- Patients with stable cardiovascular disease	Are included in the pivotal C3671013 study.
- Patients with respiratory diseases (including participants with COPD or asthma under corticosteroid therapy if chronic corticosteroids do not exceed a dose equivalent to 10 mg/day of prednisone)	
Population with relevant different ethnic origin	Please refer to Table 24.
Subpopulations carrying relevant genetic polymorphisms	No data are available.
Other	Not applicable

*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 RSVpreF 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) and immunocompromised adults ≥18 years of age who will receive 2 doses of RSVpreF (substudy B).

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Not applicable as RSVpreF is not currently marketed in the EU.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

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

Module SVII. Identified and Potential Risks

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

Table 32 lists the safety concerns at the initial RMP submission for RSVpreF.

Table 32. Safety concerns at the initial submission

Important identified risk	None
Important potential risk	Guillain-Barrè 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: None

Important Potential Risk: Guillain-Barrè syndrome

Risk-benefit impact:

GBS is a life-threatening condition, nevertheless no causal relationship has been yet established with RSVpreF and given the rarity of the event, the overall benefit-risk profile remain unchanged and favourable. For addressing this important potential risk, the following PASS study is proposed: *A Post-Marketing Safety Study of Respiratory Syncytial Virus Vaccine among Older Adults in the United States* (C3671031).

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.
- 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, two non-interventional studies are proposed: *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) and *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

Not applicable; this is an initial RMP submission for RSVpreF.

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

SVII.3.1.1. Important Identified Risk: None

SVII.3.1.2. Important Potential Risk: Guillain-Barrè syndrome has been reported in the clinical trial in adults ≥60 years of age (C3671013). Although GBS has not been reported in clinical trials in pregnant women, given the biological plausibility, GBS has been added as an important potential risk for both populations intended to be vaccinated with RSVpreF.

Table 33. Guillain-Barrè syndrome

Potential mechanisms	Guillain-Barrè 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%. [103, 104] 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. [105, 106]
Evidence source and strength of evidence	Two cases of GBS and one case of Miller Fisher syndrome were reported in the older adult phase 3 study (C3671013) in participants vaccinated with RSVpreF. Two cases were assessed as possibly related to the administered vaccine by the investigator (both had either confounding factors or an alternative aetiology), and one case, assessed as not related by the investigator, was reported eight months after RSVpreF vaccination (unplausible temporal relationship). One additional case of GBS was reported in the placebo group. No cases of GBS were reported in the phase 3 study in maternal participants (C3671008).
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.
Risk factors and risk groups	The annual incidence rate of GBS increase 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. 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. [107, 108] 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.

Table 33. Guillain-Barrè syndrome

Preventability	As current data does not support a causal relationship between RSVpreF vaccine and increased risk GBS, there are no known precautions.
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	Among all clinical studies capturing RSVpreF among adults 60+ years of age, there are 2 cases of GBS (1 case of GBS and one case of Miller Fisher syndrome in the RSVpreF group; event outcome reported as resolved with sequalae and resolved respectively) reported out of 2,386 person-years of exposure as of 13 Oct 2022 within a 42-day risk window (among 20,752 participants 60+ years of age exposed to any RSVpreF dose and assuming no loss to follow-up within 42 days [20752*42]/365.25). These two cases were assessed as possibly related to RSVpreF vaccination by the investigator. Two additional cases (one GBS in the RSVpreF group and one GBS in the placebo group) occurred at 8- and 14-months follow-up, respectively, and were outside the plausible risk window for a temporal relationship and not deemed related to RSVpreF vaccination by the investigator (outcome reported as recovered for both cases). 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.

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.

Table 34. Use in immunocompromised pregnant women and high-risk pregnancies

Evidence source: The safety profile of RSVpreF 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 RSVpreF in all pregnant women and their offspring, including immunocompromised pregnant women and high-risk pregnancies.

Table 35. Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old

Evidence source: The safety profile of RSVpreF 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 RSVpreF in immunocompromised, or renally or hepatically impaired older adults ≥60 years old.

Module SVIII. Summary of the Safety Concerns

Table 36. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Guillain-Barrè 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

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 RSVpreF will include the use of the Exposure During Pregnancy (EDP) questionnaire to obtain general information on the pregnancy and the pregnancy outcome. 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-Barrè syndrome, Pfizer plans to conduct the PASS studies summarised below.

Study short name and title:

A post-marketing safety study of respiratory syncytial virus vaccine 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 post-marketing safety study is planned to further evaluate the risk of GBS, other immune-mediated demyelinating conditions and polyneuropathies following RSVpreF 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 RSVpreF versus those who are not vaccinated with RSVpreF at that point in time. Secondly, a self-controlled risk interval (SCRI) analysis may also be conducted among RSVpreF vaccinated Medicare beneficiaries to compare the incidence of GBS, 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 RSVpreF and a comparator cohort of Medicare beneficiaries who do not receive RSVpreF.

Milestones:

Planned final protocol submission to the FDA: 30 November 2023

Planned final report submission to the FDA: 31 May 2030

Study short name and title:

Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in pregnant women and their offspring in a real world setting in Europe (C3671026).

Rationale and study objectives:

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

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

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

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 RSVpreF and a relevant matched comparison group of pregnant women and their offspring who do not receive RSVpreF vaccination.

Milestones:

Planned final protocol submission: 31 Mar 2024

Planned Final Study Report: 30 Sep 2029

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

Study short name and title:

Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe (C3671038).

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, Pfizer 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 RSVpreF compared to a relevant matched comparator group of persons who do not receive RSVpreF.

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 RSVpreF and a relevant matched comparator group of persons who do not receive RSVpreF.

Milestones:

Planned final protocol submission: 31 Mar 2024

Planned Final Study Report: 30 Sep 2029

III.3. Summary Table of Additional Pharmacovigilance Activities

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

Table 37. On-going and planned additional pharmacovigilance activities

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

Table 38. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Guillain-Barrè 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 39. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risk		
Guillain-Barrè 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: Post-authorisation safety studies in the EU of RSVpreF include GBS as a safety outcome among immunocompromised, or renally or hepatically impaired older adults (C3671038) and among pregnant women and their offspring (C3671026). Post-marketing safety study in respiratory syncytial virus vaccine among older adults in United States (C3671031).
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: Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in pregnant women and their offspring in a real world setting in Europe (C3671026).
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: Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in

		immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe (C3671038).

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ABRYSVO (respiratory syncytial virus 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 the maternal immunisation during pregnancy to provide protection in infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV), and for active immunisation of individuals 60 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 https://www.ema.europa.eu/en/medicines/human/EPAR/abrysvo.

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 40. List of important risks and missing information

Important identified risks	None
Important potential risks	Guillain-Barrè 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

II.B Summary of Important Risks

There are no important identified risks for RSVpreF. Guillain-Barrè syndrome has been reported in adults ≥60 years of age. Although GBS has not been reported in clinical trials in pregnant women, given the biological plausibility, GBS has been added as an important potential risk for both populations intended to be vaccinated with RSVpreF.

Table 41. Important potential risk - Guillain-Barrè syndrome

Evidence for linking the risk to the medicine	Two cases of GBS and one case of Miller Fisher syndrome were reported in the older adult phase 3 study (C3671013) in participants vaccinated with RSV. Two cases were assessed as possibly related to the administered vaccine by the investigator (both had either confounding factors or an alternative aetiology), and one case, assessed as not related by the investigator, was reported eight months after RSV vaccination (unplausible temporal relationship). One additional case of GBS was reported in the placebo group. No cases of GBS were reported in the phase 3 study in maternal participants (C3671008).

Table 41. Important potential risk - Guillain-Barrè syndrome

Risk factors and risk groups	The annual incidence rate of GBS increase 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. 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. [107,108] 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
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 42. 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 Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in pregnant women and their offspring in a real world setting in Europe (C3671026). See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 43. 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 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). 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: Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in pregnant women and their offspring in a real world setting in Europe (C3671026)

Purpose of the study: As immunocompromised pregnant women and high-risk pregnancies were not included in the clinical studies to date, Pfizer 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 RSVpreF, compared to a relevant matched comparator group of pregnant women and their offspring who do not receive RSVpreF.

Study title: Safety of respiratory syncytial virus stabilised prefusion F subunit vaccine (RSVpreF) in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe (C3671038)

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, Pfizer 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 RSVpreF compared to a relevant matched comparator group of persons who do not receive RSVpreF.

Study title: A post-marketing safety study of respiratory syncytial virus vaccine among older adults in the United States; version 4.0, 14 June 2023 (C3671031)

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

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

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

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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Exposure During Pregnancy (EDP) Follow-up Questionnaire

Manufacturer Reference Number (case number)

Complete all questions and boxes to the best of your ability and knowledge. If more space is needed, please attach additional pages. Forward additional relevant information as it becomes available.

Information previously provided does not need to be repeated on this form.

****Privacy notice to be provided to reporters in applicable countries (e.g., China, United Kingdom, European Economic Area countries): Adverse event information,, your contact details and the personal information that you provided shall be processed by Pfizer in accordance with Pfizer Pharmacovigilance Privacy Policy, which is available on https://privacycenter.pfizer.com/safety***

☐ **Check if you grant permission for us to contact your healthcare professional (HCP) for additional information. If agreed, please provide contact information.**

General Information

Source of Information: ○ HCP ○ Patient ○ Other, please specify

Name, address, and contact details of the source/ reporter:

Name and contact information of gynaecologist/obstetrician:

Mother's Information - Demographics

Date of Birth (dd-Mmm-yyyy) **OR Age (years) or age group (e.g., adult):**	**Height:** ○ **cm** ○ **ft & in.**	**Weight:** ○ kgs ○ lbs

Occupation:

Mother's Information - Pregnancy

First day of last menstrual period Date (dd-Mmm-yyyy):	**Number of foetuses:**	**Estimated delivery date** (dd-Mmm-yyyy):

Gestational period at time of initial exposure: _____ **Months** _____ **Trimester**

Manufacturer Reference Number (case number)

Mother Information – Exposure to Products – Pfizer Drug Details

Please complete the drug details below.

Product	Indication	Start date (dd-Mmm-yyyy)	Stop date (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

Were any other drugs taken during pregnancy (e.g., prescription, over-the-counter)? ○ No ○ Yes, please complete the drug details below.

Product	Indication	Start date (dd-Mmm-yyyy)	Stop date (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

Manufacturer Reference Number (case number)

Mother's Information - Recreational Drug Use During Pregnancy

Did the mother smoke during this pregnancy?	○ No ○ Yes: Number per day?	_____
Did the mother drink alcohol during this pregnancy?	○ No ○ Yes: Frequency?	_____
Did the mother use illicit drugs during this pregnancy	○ No ○ Yes: Frequency?	_____

Mother's Information - Obstetrical History

(Check the box if not applicable) ☐ Not Applicable: No previous pregnancy

Number of previous pregnancies:	**Number of other children:**

Outcome of previous pregnancies (*live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy*). Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility:

Mother's Information – Relevant History

Maternal medical history – risk factors for adverse pregnancy outcomes including environmental or occupational exposures, medical disorder (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS, and other predisposing factors for neurodevelopmental disorders). Family history of congenital abnormality/ genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Treatment for infertility (*specify*):

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

Ante-natal check-up (specify dates and results) (e.g., fetal ultrasound, serum markers, etc):

Manufacturer Reference Number (case number)

Mother's Information - Delivery

Any problems before delivery? ○ No ○ Yes: please specify:

Any problems during delivery? (*including delivery complications, foetal distress, amniotic fluid abnormal, abnormal placenta*): ○ No ○ Yes: please specify:

Any problems after delivery? ○ No ○ Yes: please specify:

Mode of delivery e.g., natural birth (i.e., vaginal delivery without medication or anesthesia), cesarean section:

Outcome of Pregnancy

○ Full term live birth ○ Premature live birth ○ Stillbirth ○ Late foetal death ○ Ectopic pregnancy ○ Molar pregnancy ○ Spontaneous abortion/miscarriage

○ Induced/elective abortion ○ Unknown

Date of Outcome of Pregnancy (dd-Mmm-yyyy):

Gestational age at birth in weeks, (if known): _____ Weeks

Neonatal Information - Outcome of Infant

○ Normal New born

Apgar Score: 1 min _____ 5 min_____

○ Congenital malformation/Anomaly (specify) :

○ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify)*:

○ Unknown

Manufacturer Reference Number (case number)

Neonatal Information – Infant Details

Gender (sex):	Weight at birth:	Length at birth:	Head circumference at birth:
○ Male ○ Female	○ Grams ○ lbs ozs	○ cm ○ in	○ cm ○ in

Follow-up of Infant

(Check the box if not applicable) ☐ Not Applicable

Malformation/anomalies diagnosed:
Developmental assessment:
Infant illnesses, hospitalizations, drug therapies, breastfeeding:

Fetal Information

(Check the box if not applicable) ☐ Not Applicable
(In the event of an elective termination, spontaneous abortion, late fetal death – provide details if available)

Reason for termination:
Gestational age at termination:
Results of physical examination (gender, external anomalies) and pathology:

Manufacturer Reference Number (case number)

Paternal Information (Check the box if not applicable) ☐ Not applicable

Age (years):	**Date of Birth** (dd-Mmm-yyyy):	**Occupation:**

Relevant History:
Risk factors including environmental or occupational exposures, e.g., AIDS, toxins. Family history of congenital abnormality/ genetic diseases, consanguinity (or any family relation or lineage) between parents (*specify degree*):

Paternal Information - Exposure to Products

Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during the mother's pregnancy? ○ No ○ Yes: please specify

Product	Indication	**Start date** (dd-Mmm-yyyy)	**Stop date** (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

Paternal Information – Exposure to Products – Recreational Drug Use

Did the father smoke during the mother's pregnancy? ○ No ○ Yes: Number per day? _____

Did the father drink alcohol during the mother's pregnancy? ○ No ○ Yes, Frequency? _____

Did the father use illicit drugs during the mother's pregnancy ○ No ○ Yes, Frequency? _____

For Internal Pfizer Use – Completion by the DSU			
AER Number	**Telephone Number**		
Person Contacted		**Pfizer Receipt Date**	**Safety Receipt Date (Date of Contact)***
Privacy notice provided ** ○ **Yes** ○ **No** ○ **Not applicable**			
Transcription Certification *I hereby certify that the data transcribed into this form accurately and completely reflect the information provided. Where required by local regulations, the reporter has been made aware that their personal information will be shared with Pfizer's related parties.*			
Signature		**Date**	
Preparer of the Report			

* Date of filling in the form = Safety Receipt Date (Date of Contact).

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

Not applicable.

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