Module 1.8.2

European Union Risk Management Plan (EU-RMP) for the respiratory syncytial virus PreFusion protein 3 Older Adult (RSVPreF3 OA) vaccine/AREXVY

RMP version to be assessed as part of this application		
RMP Version number	2.0	
Data lock point for this RMP	03 November 2023	
Date of final sign off	11 July 2024	
Rationale for submitting an updated RMP		
Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in the present EU-RMP**
Part I	-	Updated to reflect the new indication Addition of pharmacotherapeutic code
Part II	Module SI	Updated to reflect the new indication and new literature information
Part II	Module SII	Addition of DART study
Part II	Module SIII	Addition of RSV OA=ADJ-018 exposure data
Part II	Module SIV	Updated to reflect the new product information and RSV OA=ADJ-018 exposure data and to align with the proposed SmPC
Part II	Module SV	Updated with post-authorisation exposure data
Part II	Module SVI	Updated to reflect the new product information
Other RMP versions under evaluation Not applicable		

RMP Version number	Submitted on	Procedure number
Not applicable	Not applicable	Not applicable
Details of the currently approved RMP Not applicable		
Version number	**Approved with procedure**	**Date of approval (opinion date)**
1.0	EMEA/H/C/006054	26 April 2023

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

ARI	Acute respiratory infection
AS	Adjuvant System
AS01	Adjuvant System 01, liposome-based adjuvant system containing two immuno-enhancers – 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and the saponin QS-21
$AS01_B$	Adjuvant System 01, liposome-based adjuvant system containing 50 µg of MPL and 50 µg of QS-21 in 500 µL
$AS01_E$	Adjuvant System 01, liposome-based adjuvant system containing 25 µg of MPL and 25 µg of QS-21 in 500 µL
BW	Bodyweight
CEP	Clinical and epidemiological plan
CHO	Chinese hamster ovary
COPD	Chronic obstructive pulmonary disease
DOPC	Dioleoyl phosphatidylcholine
EMA	European Medicines Agency
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline Biologicals SA
ICH	International Council for Harmonization
ICU	Intensive care unit
ILI	Influenza-like illness
LRTD	Lower respiratory tract disease
LTCF	Long-term care facility
MHLW	Ministry of Health, Labour and Welfare
MPL	3-O-desacyl-4'-monophosphoryl lipid A
OR	Odds ratio
pIMD	Potential immune-mediated disorder
QS-21	*Quillaja saponaria* Molina, fraction 21
RMP	Risk management plan
RSV	Respiratory syncytial virus
RSVPreF3	Respiratory syncytial virus PreFusion protein 3
RSVPreF3 OA	Respiratory syncytial virus PreFusion protein 3 Older Adult
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics
US	United States
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
AREXVY	*Not applicable*

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Respiratory Syncytial Virus recombinant glycoprotein F stabilized in the pre-fusion conformation (RSVPreF3)
Pharmacotherapeutic group(s) (ATC Code)	J07BX05
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Biologicals SA
Medicinal products to which this RMP refers	RSV vaccine (recombinant, adjuvanted)
Invented name(s) in the European Economic Area (EEA)	*AREXVY*
Marketing authorization procedure	Centralized procedure for submission of an application for a Community Marketing Authorization under Article 3(1) of the Regulation (EC) No 726/2004
Brief description of the product	**Chemical class** The RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) vaccine is composed of recombinant RSV glycoprotein fusion (F) antigen stabilized in the pre-fusion conformation (RSVPreF3) adjuvanted with $AS01_E$ adjuvant system. The RSVPreF3 antigen (120 micrograms [µg] per dose) is supplied as a lyophilized fraction in a 3 mL clear glass vial, and the $AS01_E$ adjuvant system (0.5 mL per dose) is supplied as a liquid fraction in a 3 mL clear glass vial. The liquid $AS01_E$ Adjuvant System is used to reconstitute the lyophilized antigen, prior to administration. The RSVPreF3 antigen is a purified recombinant protein produced in Chinese hamster ovary (CHO) cells. $AS01_E$ contains 25 µg of each of the immuno-enhancers *Quillaja saponaria* Molina, fraction 21 (QS-21) and 3-O-desacyl-4'-

	monophosphoryl lipid A (MPL) combined with liposomes. MPL is a purified, non-toxic endotoxin derivative prepared from the lipopolysaccharide (LPS) of *Salmonella minnesota* R595 strain. QS-21 is a natural saponin molecule purified from the bark of the South American tree, *Quillaja saponaria* Molina. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in a phosphate buffered saline solution containing sodium phosphate dibasic (Na_2HPO_4), potassium phosphate monobasic (KH_2PO_4), sodium chloride (NaCl) and water for injection.
	Summary of mode of action The RSVPreF3 antigen is an engineered version of the naturally occurring F protein stabilized in its pre-fusion conformation by introduction of cysteine residues leading to the formation of a disulfide bond and filling of hydrophobic cavities. The F protein is a major surface antigen of the RSV virus that is well conserved among RSV A and RSV B subtypes and that was shown to elicit most of the RSV neutralizing activity present in serum from previously RSV-infected individuals. The RSVPreF3 antigen elicited higher levels of neutralizing antibodies in animal models than those observed with an RSV F protein in the post-fusion conformation of the naturally occurring protein. $AS01_E$ contains two immuno-stimulatory components, QS-21 and MPL, as well as liposomes. $AS01_E$ induces a transient innate-immune response that leads to the activation of antigen presenting cells that further activate T cells. The liposomes are acting as vehicles for the MPL and QS-21 immuno-enhancers. MPL has been shown in various pre-clinical and clinical studies to induce enhanced immune responses both at humoral and cellular levels. QS-21 is known to be a strong immunostimulant, in particular of the Th1 type

	cell-mediated immunity and cytotoxic T-lymphocytes activity.
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD).
Indication(s) in the EEA	**Current (if applicable):** Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in: • adults 60 years of age and older; • adults 50 through 59 years of age who are at increased risk for RSV disease. The use of this vaccine should be in accordance with official recommendations **Proposed (if applicable):**
Dosage in the EEA	**Current (if applicable):** The vaccination schedule consists of a single 0.5 mL dose administered intramuscularly. The need for revaccination with a subsequent dose has not been established. **Proposed (if applicable):** Not applicable
Pharmaceutical form(s) and strengths	**Current (if applicable):** RSVPreF3 antigen: lyophilized fraction for suspension for injection $AS01_E$: liquid fraction for injection, containing QS-21, MPL and liposomes After reconstitution, one dose (0.5 mL) contains 120 µg of RSVPreF3 antigen, 25 µg QS-21, 25 µg MPL and liposomes.

	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Lower respiratory tract disease (LRTD) caused by respiratory syncytial virus

INCIDENCE

In adults, advanced age, and chronic conditions are leading to a high RSV disease burden with an increased risk of serious disease. Due to these factors, evidence suggests that RSV burden is substantial in the adult population aged 60 years and above, as well as aged 50-59 years who has a chronic condition leading to an increased risk for RSV disease.Most studies investigating the incidence of RSV in older adults report seasonal attack rates. Several prospective cohort studies in the US have been done since 2000, most commonly using an acute respiratory infection (ARI) case definition. Across various studies during winter seasons from 2000 to 2016 in the US, RSV-ARI attack rates ranged from 0.06% to 7.0%, with the majority of estimates between 1% and 2% [Falsey, 2005; McClure, 2014; Falloon, 2017; Belongia, 2018; Jackson, 2021; Jackson, 2021]. These estimates were obtained from the general population of older adults living in the community. Attack rates tended to increase with age, ranging from an RSV-ARI attack rate 14.7/1,000 individuals for those aged 60-69 to 19.9/1,000 individuals for those aged ≥70 years in one study [McClure, 2014] to a medically-attended RSV attack rate of 3.3 per 1,000 person-years for people aged 65-74, 5.5 per 1,000 person-years for people aged 75-84 and 8.1 per 1,000 person-years for people aged 85 and over in another study [Tong, 2020]. Juhn et al [2023] provided both seasonal attack rates and annual incidence rates, finding that in the 2019-2020 season, the overall attack rate among adults aged ≥50 years was 2.50% (95% CI: 1.90-3.21) with an incidence rate of 48.62 per 1,000 person-years (95% CI: 36.92-62.86).

Evidence from other countries is scarcer. An international prospective cohort study among three European countries followed participants aged ≥60 years for the 2017-2018 and 2018-2019 RSV seasons [Korsten, 2021]. RSV was confirmed by polymerase chain reaction (PCR) in 2.1% of participants in the first season (95%CI: 1.0-3.7%) and 4.9% of participants in the second season (95%CI: 3.2-7.1%). A group of community-dwelling older adults aged ≥50 years old from five European countries were followed over the 2019-2020 season. The overall incidence rate was 37.25/1,000 person-years, with an attack rate of 1.73% (95% CI: 0.96-2.36) [Narejos Pérez, 2023].

Several systematic reviews and meta-analyses have also been published. A systematic analysis to assess the global, regional and national burden of lower respiratory infections in 195 countries, found the incidence of RSV-LRTD in older adults ≥70 years to be 6.3 cases/1,000 persons [GBD, 2018]. Similarly, a recent worldwide systematic review and meta-analysis to assess the global burden of RSV-ARI in adults ≥65 years found an estimated RSV-ARI attack rate of 6.7 cases/1,000 person-years in industrialized countries [Shi, 2020]. In another systematic literature review and meta-analysis considering adults

≥60 years of age in high-income countries, RSV was estimated to have caused 5.2 million cases of RSV ARI (3 million in Europe and 1.2 million in the US), 470 000 hospitalizations (270 000 in Europe and 110 000 in the US) and 33 000 in hospital deaths (20 000 in Europe and 8 000 in the US) in 2019 [Savic, 2023].

Among adults 50-59 years of age, underlying medical conditions, including diabetes, coronary artery disease, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease, chronic liver disease and heart failure, can increase the risk of severe RSV disease [Pleasants, 2022; Sullivan, 2018; Tsao, 2022; Tsao, 2023; Wang, 2021; CDC, 2021; CDC, 2018].

Incidence rates of RSV disease are frequently derived from population-based Influenza surveillance systems in adults ≥65 years of age, explaining the limited epidemiological data available for the younger population. However, several studies underline the high burden of severe RSV-related disease in adults 50-59 years of age.

RSV-LRTD incidence rates in 50-59 and ≥60 years of age individuals reporting ARI are similar, as shown by the data from 2 recent prospective active surveillance cohort studies conducted during the prepandemic RSV season 2019-2020 in healthy and medically stable community dwelling adults in the US and Europe, respectively. In the study conducted in the US, the incidence rate for RSV-LRTD was 52.6 (95% CI: 29.4, 86.7)/1000 person-year in adults 50 59 years of age and 34.2 (95% CI: 24.6, 46.5) in the overall population ≥50 years of age. Age group-specific incidence rates ranged from 19.4 (95% CI: 8.4, 38.2) in the 60-69 years of age group to 34.8 (95% CI: 12.8, 75.8)/1000 person-year in the ≥80 years of age group [Juhn, 2023]. In the European study, the incidence rate for RSV LRTD was 31.6 (95% CI: 14.1, 70.8)/1000 person-year in adults 50-59 years of age and 29.1 (95% CI: 16.8, 50.4) in the overall population ≥50 years of age. Age-group specific incidence rates ranged from 19.2 (95% CI: 4.0, 56.0) in the 70-79 years of age group to 41.9 (95% CI: 16.5, 106.2)/1000 person-year in the 65-69 years of age group (unpublished data).

PREVALENCE

Various case definitions are used when assessing the prevalence of RSV, notable ARI, influenza-like illness (ILI) and LRTD.

When assessing moderate-to-severe ILI episodes for adults ≥65 years in 14 different countries across North America, Europe and East Asia, RSV was detected in 7.4% of cases, with values ranging between 0% and 17.1% across countries, making it the third most frequently reported respiratory virus present in moderate-to-severe ILI episodes [Falsey, 2014].

Bruyndonckx et al. reported on a prospective cohort study conducted from October 2007 to April 2010 in 12 countries in Europe [Bruyndonckx, 2020]. They found a 5.9% prevalence of RSV among LRTD outpatients aged ≥ 60 years. Patients aged ≥75 years were significantly more likely to test positive for RSV when compared to those aged 18-59 years [OR: 2.27 (95%CI: 1.12– 4.64)].

Prevalence of RSV among community-dwelling adults aged ≥65 years old in Italy and Portugal ranged from 4.7% to 14.2% depending on location and season [Sáez-López, 2019; Pellegrinelli, 2020]. In hospital-based studies in Italy and Spain, prevalence of RSV in older adults varied from 1.7% to 9.6% [Gimferrer, 2019; Leli, 2021]. In France, the ILI sentinel virological surveillance network reported a prevalence of RSV in adults ≥65 years at 4.2% during two consecutive seasons 2015-16 and 2016-17 [Souty, 2019], while a hospital-based study in the same country and same age group found a prevalence of RSV of 4.7%.

Overall, based on the literature, the median prevalence of RSV-ARI among adults aged ≥60 years and older in high-income countries, including Europe, is around 6.5% (4.1%-7.8%).

For adults with chronic conditions, evidence suggests that the prevalence of RSV is particularly high among those with respiratory comorbidities. In two studies in Canada, the prevalence of RSV among hospitalized COPD patients aged ≥50 years old with ARI was between 3.69% and 7.41% [Mulpuru, 2022; De Serres, 2009]. In the US, the RSV proportion was 7.9% among emergency department outpatients 50 years or older with an exacerbation of COPD [Camargo, 2008]. Likewise, immunocompromised population may have a higher prevalence of RSV, with one study finding a prevalence of RSV of 5.10% among adult hematopoietic cell transplant patients aged 50-73 [D'angelo, 2015].

SI.1.1 Demographics of the population in the authorised indication and risk factors for the disease

Risk factors

Age

As a consequence of immunosenescence, age plays an important role in RSV infections. RSV infection has been associated with excess mortality and hospitalization in those aged 50 and older. Walker et al. reported that the proportion of RSV-positive patients in an American hospital increased with each 10-year age group, from 7.3% (50–59 years), to 12.2% (60–69 years), 14.3% (70–79) years, and 38.7% (80–89 years) [Walker, 2014]. In a US retrospective study between 2004 and 2010 RSV was identified in 8.2% of medically attended ARI in individuals aged 50-64 years, it was 10.2% in those aged 65-79 years and 10.5% in those aged ≥80 years [Sundaram, 2014]. A prospective population-based surveillance study estimated the incidence of RSV hospitalization in adults ≥18 years of age during 3 seasons (2017 to 2020) [Branche, 2022]. The incidence of RSV hospitalisation was approximately 33.5 to 63.0/100,000 in the 50-64 years of age group and 136.9 to 255.6/100,000 in the ≥65 years of age group.

Chronic conditions, immunocompromised condition and frailty

Several chronic conditions have been shown in the literature to be risk factors for RSV, notably chronic obstructive pulmonary disease (such as COPD, asthma), cardiovascular conditions, diabetes mellitus, renal conditions, immunosuppression and frailty.

In a study among hospitalized patients in the US, among those aged ≥65 years the incidence rate for RSV was between 3.5 and 13.4 times higher in those with COPD compared to those without COPD [Branche, 2021]. Among those with diabetes, the ratio was between 2.3 and 6.4 and among those with coronary artery disease between 3.7 and 6.5. Chronic heart failure was presented in different age groups: those aged 60-79 had an incidence ratio between 5.9 and 7.6, while those aged ≥ 80 had an incidence ratio between 4.9 and 5.4. There was no significant difference in the incidence of RSV between those with and without obesity in any age group. One cluster of hospitals showed a significantly higher incidence rate for those aged ≥65 with asthma than those without, a ratio of 2.27 (95%CI=1.67-3.09), whereas for the other cluster of hospitals, the ratio was not significant (2.52, 95%CI=0.81-7.86).

In a study among hospitalized patients in Italy, Portugal and Cyprus, chronic kidney disease, solid neoplasms, and obstructive sleep apnea or obesity hypoventilation syndrome were associated with greater odds of serious complications including pneumonia, non-invasive ventilation and hospital death [Boattini, 2021]. However, diabetes, COPD or asthma and chronic heart failure were not associated with greater odds of complications or death. In a study among nursing home residents in the Czech Republic during the 2004-2005 winter season, however, chronic heart failure (class II) was associated with a higher risk of RSV-positive ARI (OR: 2.31; Beran, 2021). This study also found that diabetes requiring insulin treatment (OR: 9.82) was a risk factors for RSV-positive ARI.

Underlying conditions such as COPD, asthma, coronary artery disease, chronic heart failure and diabetes were also associated with a statistically significant higher hospitalisation rate in patients 50-64 years of age, except for asthma in 1 of the 3 locations [Branche, 2022].

A study by Tong et al. found that among patients with RSV in the US, the proportion of high-risk comorbidities increased with age: in the 65-74 age group, around 50% of people had chronic pulmonary disease, whereas this was almost 70% in the age group ≥85. For chronic cardiac disease in the same age groups the numbers were around 50% and more than 80% respectively [Tong, 2020].

In Belgium, 7.1% of immunocompromised patients (defined as presence of a disease and/or treatment known to impair the immune system such as solid organ transplant under immunosuppressive therapy, solid or hematological malignancy under chemotherapy or other underlying disease needing long-term high-dose corticosteroid therapy or immunosuppressive therapy) with upper or lower tract infection were RSV-positive [Steensels, 2019].

Severe clinical manifestations of RSV in the aged may also be due to frailty of the host, global immunosenescence, or an age-related decline in RSV-specific immune functions. Immune dysregulation has been described in older persons, with age-related changes most clearly demonstrated in cellular immunity [Falsey, 1999]. Complication rates of RSV among frail older persons have been variable with rates of pneumonia ranging from 5-67% and death from 0-20% [Falsey, 1998].

Long-term care facilities/nursing homes

People living in LTCFs, the collective name for skilled nursing facilities and assisted living facilities, may be at greater risk of RSV infection.

A prospective study in a nursing home in Slovenia found an ARI incidence rate of 3.8/1,000 resident-days (95%CI: 2.90–4.89), with 14.7% of infections due to RSV, and an attack rate among exposed residents of 11.6% [Uršič, 2016]. A prospective study during the 2004-2005 winter season in nursing homes in the Czech Republic found higher incidence rates, at 45.82 per 1,000 person-years for RSV ARI and 30.40 per 1,000 person-years for RSV LRTD [Beran, 2021]. A prospective cohort study in Europe and the US found an RSV acute ARI incidence rate of 47.85/1,000 person-years (95% CI: 22.58–101.4), with an attack rate of 2.26% in adults aged 65 years and above living in LTCFs in 2019-2020 [Narejos Pérez, 2023]. A systematic literature review of the burden of respiratory infections among older adults in LTCFs presented a range of attack rates from 1.1% to 10.8% (in non-outbreak conditions), and higher rates in outbreaks of 12.9-13.5% [Childs, 2019].

SI.1.2 The main existing treatment options

For years, only two FDA-approved drugs have been available for prevention or treatment of RSV infection, but they are indicated only for the pediatric population in specific high-risk individuals: humanized monoclonal antibody palivizumab for prophylaxis in children at high risk of RSV disease, including preterm infants, and aerosolized antiviral drug ribavirin for treatment of severe RSV infections in hospitalized infants and children [**Error! Reference source not found.**, 2012]. Even with the recent approval of Nirsevimab, the available treatments are still limited to the paediatric population. As of 2023, two vaccines for the prevention of RSV-associated LRTD in adults aged 60 years and older have been licensed in the USA and EU [Venkatesan, 2023]. To date, there is no licensed vaccine for the prevention of LRTD caused by RSV in adults 50-59 years of age who are at increased risk for RSV disease.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

RSV is a member of the enveloped Pneumovirus family and is composed of 10 genes that encoded 11 proteins [Pandya, 2019]. There are two major genetic RSV subtypes, A and B. These subtypes co-circulate, and the predominance of one over the other varies by year and geographic location [Waris, 1991; Staadegaard, 2021]. RSV epidemics occur yearly during late fall, winter, and early spring (last about 5 months) in temperate climates; in tropical climates the patterns are less predictable and can be related to the rainy season or RSV may persist at low levels throughout the year [Obando-Pacheco, 2018]. The ongoing SARS-CoV-2 pandemic has significantly impacted the timing and burden of RSV epidemics in countries across the world, due to non-pharmaceutical interventions.

The virus is a highly contagious seasonal pathogen that is transmitted from person-to-person via direct or close contact with contaminated secretions, including respiratory droplets or fomites [Hall, 2015; Hall, 1981]. The incubation period of RSV ranges from

2-8 days, and duration of viral shedding is usually 3-10 days [Waris, 1992; Hall, 1977; Hall, 1976; Hall, 1975; Okiro, 2010]; shedding can continue for up to 4 weeks in the presence of primary infection, younger age, increase severity of disease, or underlying medical conditions [Lehners, 2016; Tabatabai, 2018; Cheng; 2008].

RSV infection does not confer long-term immunity; therefore, re-infection with RSV occurs throughout life and is common in all age groups [Simoes, 1999; Krilov, 2011]. RSV is a major contributor to respiratory morbidity and mortality in infants, young children, and older adults worldwide.

Most studies on the case fatality ratio of RSV concern in-hospital deaths. In-hospital deaths attributable to RSV among adults are largely in people aged ≥65 years [Schmidt, 2019; Saravanos, 2019]. However, this does not capture all deaths due to RSV, as various studies show increased mortality after discharge [Auvinen, 2022; Descamps, 2021].

Adults hospitalized with RSV disease, including patients with underlying chronic conditions, frequently require mechanical ventilation and intensive care admission leading to prolonged hospitalization. When comparing adults aged 45-59 years with those aged ≥60 years or adults aged 50-64 years with those aged ≥65 years, similar proportions of mechanical ventilation (18.6% vs. 16.6%), ICU admission (11-23% vs. 15 18%), hospital length of stay (6-6.2% vs 5-8%) and case fatality (3-6.2% vs 5-6.9%) are reported [Pastula, 2017; Havers, 2022; Choi, 2022].

In Europe, in-hospital mortality varies considerably. In one study in Finland from July 2007 to April 2009, none of the RSV-positive older adult (aged ≥65 years) patients hospitalized due to ARI complications died during their hospitalization [Aronen, 2019]. Another study in Finland also did not find any in-hospital mortality among adult RSV patients with a median age of 73 years but did find that there was 6% mortality 3 months after admission [Auvinen, 2021]. In various studies in France, Italy, Portugal, Cyprus and Belgium, in-hospital RSV case fatality among older adults was between 3% and 12.1% [Loubet, 2020; Subissi, 2020; Boattini, 2021; Descamps, 2021]. One French study during the 2017/2018 and 2018/2019 winter seasons found a 3% in-hospital mortality rate among adults with a mean age of 73 hospitalized with RSV, comparable with mortality due to influenza in the same population [Descamps, 2021]. The cumulative mortality after 30 days was three times higher than in-hospital mortality and in 90 days, four times higher.

A recent American modelling study based on death certificate data estimated up to 12,600 RSV-attributable respiratory and circulatory deaths among those aged ≥65 years per year [Hansen, 2022].

SI.1.4 Important comorbidities

In adults, the highest RSV disease burden is observed in older individuals and those with conditions such as lung or heart disease and diabetes [CDC, 2023a]. In these patient populations, RSV can exacerbate conditions like COPD, asthma, or chronic heart failure, and lead to severe outcomes such as pneumonia, hospitalization and death [Prasad, 2021; Branche, 2022].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

In accordance with the Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004), the World Health Organization (WHO) Guidelines on nonclinical evaluation of vaccines [WHO, 2005], the WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines [WHO, 2013], the FDA Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications [FDA, 2006], WHO Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccine [WHO, 2019], European Medicines Agency (EMA) Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of RSV disease [EMA/CHMP/257022/2017] (into effect in 2019), and the Ministry of Health, Labour and Welfare (MHLW) Guideline for Nonclinical studies of preventive vaccines for infectious diseases [PFSB/ELD Notification No. 0527-1, 27th May 2010], nonclinical studies were performed with *Arexvy*.

The vaccine formulations tested in the Good Laboratory Practice (GLP) toxicology studies were comparable to the formulations used during the early clinical development of *Arexvy*: the nonclinical toxicity studies were performed with RSVPreF3 formulated with $AS01_B$, the highest dose of AS01 tested in the early clinical phases which is composed of 50 µg MPL and 50 µg QS-21 immuno-enhancers.

$AS01_E$, which contains half dose of MPL and QS-21 versus $AS01_B$, was selected after the Phase 1/2 clinical studies. The nonclinical package of AS01 as well as the immuno-enhancers MPL and QS-21 alone, including pharmacology (mode of action), biodistribution and toxicology studies has been already included and assessed in the context of a marketed product, *Shingrix*.

An overview of the GLP toxicology studies performed with *Arexvy* and RSVPreF3/$AS01_B$, is provided in Table 2 and their results are briefly summarized below.

Table 2 Key safety findings from non-clinical studies and relevance to human usage

Key safety findings from nonclinical studies	Relevance to human usage
RSVPreF3 OAnonclinical toxicity program consists of 2 repeat-dose toxicity studies with 3 intramuscular injections of RSVPreF3/$AS01_B$ ($AS01_B$ containing 50 µg MPL and QS-21, double the amount compared to $AS01_E$) at 2-week interval, necropsies on Day 32 (terminal group) and on Day 57 (recovery group). **Key safety findings:** No signs of adverse systemic toxicity were reported in two 3-dose studies, but local toxicity was observed as follows: minimal to slight myofiber degeneration/necrosis and minimal to moderate mixed	All vaccine-related effects noted were considered to reflect a normal immunologic response to the vaccine. There were no findings observed that would raise a specific safety concern for the use of RSVPreF3 with $AS01_B$ adjuvant in humans.

inflammatory cells infiltrates. After a 4-week recovery period, these effects were resolved or reduced in incidence or severity.	
RSVPreF3/AS01$_E$ (Arexvy) developmental and reproductive toxicity program consists in one female fertility, embryo-fetal, pre- and post-natal development study with intramuscular administration of *Arexvy* to New Zealand White rabbit females 20 and 14 days before pairing, on gestation day 3, 9, 16 and 24, and on lactation day 7. **Key safety findings:** The intramuscular administration of *Arexvy* was well tolerated in the rabbit and demonstrated no effects on female fertility, embryo-fetal, pre- and post-natal development. There were no noteworthy findings in this study. The transfer of antibodies to fetuses and pups was demonstrated.	There were no findings observed that would raise a specific safety concern for the use of *Arexvy* in humans.

RSVPreF3 OA nonclinical toxicity program

Administration of RSVPreF3/AS01$_B$ was well tolerated for 3 administrations when given every 2 weeks as an intramuscular injection of 120 µg or 240 µg RSVPreF3 per dose (studies COV 8363131, COV 8384096). Changes were limited in severity, did not impact animal health and well-being, and demonstrated complete or partial recovery. The doses used in the repeated dose toxicity studies were up to 33-fold higher per administration when compared to the intended clinical dose. This was calculated by comparing the highest dose on a standard bodyweight (BW) basis given to rabbits (240 µg RSVPreF3/3 kg BW) with that given to an adult human (120 µg RSVPreF3/50 kg BW).

In conclusion, no adverse findings were identified as all described findings did not impact the animals' health, were limited in severity, and/or can be considered secondary to the expected vaccine response.

RSVPreF3/AS01$_E$ (*Arexvy*) developmental and reproductive toxicity program

The intramuscular administration of *Arexvy* was well tolerated in the rabbit and demonstrated no effects on female fertility, embryo-fetal, pre- and post-natal development when administered to New Zealand White rabbit females 28 and 14 days before pairing, on gestation day 3, 9, 16 and 24, and on lactation day 7. The multiple injections were timed to allow the development of an immune response prior to the gestation phase, and exposure to the antigen and other components of the vaccine formulation during gestation and lactation. There were no noteworthy findings in this study. Effective vaccine uptake was confirmed in 100% of female rabbits treated with RSVPreF3/AS01$_E$ that developed the expected immune response, and the transfer of antibodies to fetuses and pups was demonstrated.

Conclusions from nonclinical studies and relevance to human usage:

In conclusion, GSK has performed GLP nonclinical toxicology studies with *Arexvy*, RSVPreF3/AS01$_B$, the AS01$_B$ Adjuvant System and its individual immuno-enhancers QS-21 and MPL. These GLP studies were performed in accordance with available regulatory guidance and did not highlight any safety concerns. The early response to AS01 has been investigated in a variety of nonclinical pharmacology studies in adult mice in order to better understand the mechanism underlying antigen-specific adaptive responses promoted by AS01-containing vaccines. The effects of AS01 (i.e., cytokine induction, cell recruitment and cell activation) are transient, returning to baseline after 7 days, showing that the response to immuno-enhancers included in AS01 is limited in time.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Up to 02 November 2023, *Arexvy* has been used in 20,540 healthy volunteers in clinical trials within the clinical and epidemiological plan (CEP) for the prevention of LRTD caused by respiratory syncytial virus. Of these, 5,068 received 2 doses, among which at least 40 received 3 doses.

An overview of the cumulative number of individuals exposed to *Arexvy* by age, gender, racial group and ethnicity for completed GSK-sponsored interventional studies is presented in Table 3 and Table 4. Cumulative exposure details for the ongoing pivotal study RSV OA=ADJ-006 are presented in Table 5, as of 05 May 2023.

Table 3 Cumulative exposure from ongoing and completed clinical trials within CEP (exposed set)

Study	*AREXVY*	RSV out of specification
	n	n
Ongoing	16,699	0
Completed	3,841	860[b]
Total	20,540	860

AREXVY: participants receiving *Arexvy* formulation
RSV out of specification: participants receiving another formulation of the vaccine than *Arexvy*
n = number of participants
Data as of 02 November 2023

Table 4 Demographic characteristics of participants from completed clinical trials within CEP by age group, gender, racial group and ethnicity (exposed set)

Parameter	*AREXVY* (N=3,841)	RSV out of specification (N=860)
	n	n
Age at vaccination		
18-59 years	0	36
≥60 years	3,841	824
Gender[a]		
Male	1,912	370
Female	1,929	490
Racial group[a]		
American Indian or Alaska Native	14	1
Asian	44	23
Black of African American	291	65
Native Hawaiian or Other Pacific Islander	5	0
White	2,849	767
Other	636	4
Unknown	2	0

Ethnicity[a]		
Hispanic or Latino	676	32
Not Hispanic or Latino	3,164	828
Unknown	1	0

AREXVY: participants receiving *Arexvy* formulation
RSV out of specification: participants receiving another formulation of the vaccine than *Arexvy*
Data as of 02 November 2023

Table 5 Demographic characteristics of participants from the ongoing pivotal study RSV OA=ADJ-006 by age group, gender, racial group and ethnicity (exposed set)

Parameter	***AREXVY*** **(N=12,470)**
	n
Age at vaccination	
18-59 years	0
≥60 years	12,470
Gender	
Male	5,981
Female	6,489
Racial group	
American Indian or Alaska Native	44
Asian	953
Black of African American	1,064
Native Hawaiian or Other Pacific Islander	11
White	9,890
Other	508
Ethnicity	
Hispanic or Latino	682
Not Hispanic or Latino	11,783
Unknown	5

AREXVY: participants receiving *Arexvy* formulation
Data as of 05 May 2023

Among the 12,470 individuals exposed to the first dose of *Arexvy* in the pivotal efficacy study RSV OA=ADJ-006, 40.0% had at least one underlying comorbidity, including cardiorespiratory conditions (COPD, asthma, any chronic respiratory/pulmonary disease, or chronic heart failure) for 20.4% of participants and endocrine metabolic conditions (diabetes, advanced liver or renal disease) for 25.9% of participants; 189 were frail, 4,795 were pre-frail and 7,465 were fit.

Study RSV OA=ADJ-018, which enrolled participants aged 50 years and above, was ongoing at the data lock point of this RMP. In that study, 769 participants 50-59 years of

age, including 386 participants with stable pre-defined chronic conditions leading to an increased risk for RSV disease, and 381 participants ≥60 years of age received one dose of *Arexvy*.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Missing information relevant for the approved indication is included in module SVII

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5 Exclusion criteria

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine	*Arexvy* should not be administered to subjects with known hypersensitivity to any component of the vaccine in order to limit the risk of such reaction upon vaccination.	No	Statement included in Summary of Product Characteristics (SmPC) Section 4.3, Contraindications and Section 4.4, Special warnings and precautions for use
Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe	The intramuscular administration of a vaccine could cause adverse effects in people with thrombocytopenia or any coagulation disorder since bleeding may occur.	No	Statement included in SmPC Section 4.4, Special warnings and precautions for use
Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine during the period beginning 30 days before the first dose	These products could influence the individual's immune response to the vaccine and could affect the accurate assessment	No	Statement included in SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction

of study vaccine, or planned use during the study period	of *Arexvy*-related adverse events.		Co-administration of *Arexvy* with other vaccines commonly used in the target population is being studied
Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before each dose and ending 30 days after each dose of study vaccine administration, with the exception of inactivated, split virion and subunit influenza vaccines which can be administered up to 14 days before or from 14 days after each study vaccination		No	
Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or invasive medical device)		No	
Previous vaccination with any RSV vaccine	An history of vaccination with an RSV vaccine could limit the ability to accurately assess the efficacy, safety and immune response of *Arexvy*.	No	Statement in SmPC Section 4.2, Posology and method of administration The need for revaccination with *Arexvy* has not been established. Clinical trials evaluating the immunogenicity, safety and efficacy of multiple doses of the RSVPreF3 OA candidate vaccine are ongoing.
Administration of long-acting immune-modifying drugs or planned administration at any time during the study period	The administration of such drugs would limit the ability to accurately assess the efficacy,	No	Individuals being administered long-acting immune-modifying drugs, immunoglobulins, blood or plasma derivatives may

	safety and immune response of *Arexvy*.		benefit from vaccination to get protected against LRTD caused by RSV. There is no reason to believe that administration of immunoglobulins would influence vaccine efficacy or safety.
Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the study vaccine administration or planned administration during the study period.	To avoid confounding the assessment of the humoral or cellular immune response in the study population	No	
Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy	Immunocompromised participants may have impaired immune responses to vaccines and would therefore limit the ability to demonstrate efficacy, which is the primary pivotal endpoint.	No	Statement included in SmPC Section 4.4, Special w*arnings and precautions for use* Safety and immunogenicity data on *Arexvy* are not available for immunocompromised individuals. Patients receiving immunosuppressive treatment or patients with immunodeficiency may have a reduced immune response to *Arexvy*.
Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the first vaccine dose or planned administration during the study period			

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table 6 Limitations to detect adverse reactions in clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Up to 02 November 2023, over 20,000 individuals have received at least one dose of *Arexvy* in the clinical development program.	Within the clinical development program, adverse events associated with exposure to *Arexvy* in over 20,000 subjects comprising the integrated safety population have been evaluated. Adverse drug reactions occurring at a frequency of less than 0.005% (i.e., 1/20,000 subjects) may only be observed when a larger population is exposed.
Due to prolonged exposure	Not applicable	The vaccine is intended for single dose administration. The ongoing studies RSV OA=ADJ-004 and RSV OA=ADJ-006 are evaluating the impact of additional doses of *Arexvy*.
Due to cumulative effects	Not applicable	No cumulative effects or specific organ toxicity has been observed with *Arexvy*.
Which have a long latency	Potential immune-mediated diseases (pIMDs) may have a long latency from vaccine exposure to disease onset. Because adjuvants act directly as immuno-stimulants there is a theoretical possibility that adjuvanted vaccines may induce an abnormal immune response that could trigger the onset of immune-mediated	One may assume that the development of autoimmunity (if a causal association between the event and vaccination exists) is similar to the classical time frame of several weeks suggested for the onset of post-infectious autoimmune phenomena. The risk becomes very low several months following the last vaccine dose received [Tavares Da Silva, 2013]. Incidence rates (number of newly diagnosed cases per year) vary depending on the autoimmune diseases, with estimates ranging from less than one newly diagnosed case to more than 20 cases of adult-onset per

	diseases in susceptible individuals [Di Pasquale, 2015]. Therefore, pIMDs in *Arexvy* clinical trials are collected during 6 months after vaccine administration, which is considered a reasonable theoretical risk interval for these diseases. pIMDs considered related to study vaccination are collected up to study end.	100,000 person-years [El-Gabalawy, 2010; Pohl, 2016].

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Table 7 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	There are no data on the effects of *Arexvy* on human fertility, on the use of *Arexvy* in pregnant women, or on the excretion of *Arexvy* in human or animal milk. *Arexvy* is not recommended during pregnancy or in breast-feeding/lactating women. After administration of an investigational unadjuvanted RSVPreF3 vaccine to 3,557 pregnant women in a single clinical trial, an increase in preterm births was observed compared to placebo. Results from animal studies with *Arexvy* do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients	Individuals with a chronic condition judged serious or unstable by the investigators were excluded from clinical studies. This exclusion criterion allowed enrolment of a proportion of participants with common comorbidities for this older population such as cardiovascular diseases, hypertension, diabetes, osteoarthritis, neurological diseases, renal impairment and chronic pulmonary diseases (including asthma and COPD).

• Patients with a disease severity different from inclusion criteria in clinical trials	Adverse events related to *Arexvy* were not found to be impacted by the presence of comorbidities in clinical trials. Individuals with confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., current malignancy, human immunodeficiency virus) or immunosuppressive/cytotoxic therapy (e.g., medication used during cancer chemotherapy, organ transplantation, or to treat autoimmune disorders) were not included in the study population.
Population with relevant different ethnic origin	Although *Arexvy* clinical program was not designed to specifically assess the vaccine efficacy, immunogenicity and safety among such populations, individuals with different geographic ancestry or ethnic origins have been included in *Arexvy* clinical trials. Please refer to Table 4 for exposure information by ethnic origin/race from the studies. It is of note that the safety of a vaccine in different ethnic groups is difficult to compare if not assessed within the same country and health system as specifics of the healthcare system/access to the medical care impact reporting of certain events. Also, different environmental factors and different comorbidities across regions can affect the safety data consistency.
Subpopulations carrying relevant genetic polymorphisms	To date, there is no information suggesting the existence of polymorphism relevant to the efficacy or safety of *Arexvy* in the currently authorised indication.
Other	Not applicable

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The patient exposure can be approximated by the number of doses distributed, which is the only worldwide data available with regard to subject exposure for a vaccine in a post-approval setting. It is important to note the distribution database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g., vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the database. Distribution data are available per complete month, but not for a specific date within a month and constitute proprietary information from GSK and is not intended for public disclosure.

SV.1.2 Exposure

Since first approval on May 3, 2023, until October 31, 2023 (approximately 6 months), it is estimated that 6,246,500 *Arexvy* doses have been distributed globally.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

No potential for illegal use of the vaccine has been identified.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

The following risks are listed in the *Arexvy*'s SmPC and do not qualify to be listed as safety concerns in the RMP as per GVP Module V.

Section of the SmPC	Risk
4.3 Contraindications	Hypersensitivity reactions
4.4 Special warnings and precautions for use	Bleeding due to intramuscular administration in individuals with thrombocytopenia or any coagulation disorder Injury from fainting due the vaccination process itself
4.8 Undesirable effects	Abdominal pain Arthralgia Chills Fatigue Fever Headache Hypersensitivity reactions (such as rash) Injection site pain, erythema, swelling and pruritus Lymphadenopathy Malaise Myalgia Nausea Pain Vomiting

REASON FOR NOT INCLUDING AN IDENTIFIED OR POTENTIAL RISK IN THE LIST OF SAFETY CONCERNS IN THE RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Abdominal pain
- Arthralgia
- Chills
- Fatigue
- Fever
- Headache
- Injection site pain, erythema, swelling and pruritus
- Myalgia

- Nausea
- Vomiting

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Lymphadenopathy
- Malaise
- Pain

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):

- Bleeding due to intramuscular administration in individuals with thrombocytopenia or any coagulation disorder
- Hypersensitivity reactions
- Injury from fainting due the vaccination process itself

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risk: None

Important potential risk: None

Missing information: None

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

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

There are no important identified/potential risks associated with *Arexvy*.

SVII.3.2 Presentation of the missing information

There is no missing information associated with *Arexvy*.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 8 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required.

III.2 Additional pharmacovigilance activities

Not required

III.3 Summary Table of additional Pharmacovigilance activities

Table 9 Ongoing 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 authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There is no post-authorisation efficacy study required for this product.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

Not applicable

V.3 Summary of risk minimisation measures

Not applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for the RSVPreF3 OA candidate vaccine

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

The *Arexvy*'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Arexvy* should be used.

This summary of the RMP for *Arexvy* 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 *Arexvy*'s RMP.

I. The medicine and what it is used for

Arexvy is authorised for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults aged 60 years and above, and in adults 50 through-59 years of age who are at increased risk for RSV disease (see SmPC for the full indication). It contains the RSVPreF3 antigen as the active substance and it is given by intramuscular injection.

Further information about the evaluation of *Arexvy*'s benefits can be found in *Arexvy*'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/arexvy

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of *Arexvy*, together with measures to minimise such risks and the proposed studies for learning more about *Arexvy*'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 patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 patient (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 reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of *Arexvy* 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 *Arexvy*. 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).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorisation or specific obligation of *Arexvy*.

II.C.2 Other studies in post-authorization development plan

There are no studies required for *Arexvy*.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

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

Not applicable