EU RMP	
Drug Substance	Nirsevimab
Version Number	1
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European Union Risk Management Plan (EU RMP) for Beyfortus® (Nirsevimab)

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

Beyfortus® is a trademark of the Sanofi Group of companies.

Administrative Information

Rationale for submitting an updated RMP

Not applicable for initial marketing authorisation submission.

Summary of significant changes in this RMP

Not applicable – Version 1

Other RMP versions under evaluation	**Version number:** Not applicable for Version 1 **Submitted:** Not applicable for Version 1 **Procedure Number:** Not applicable for Version 1
Details of currently approved RMP	**Version number:** Not applicable for Version 1 **Approved with procedure:** Not applicable for Version 1 **Date of approval:** Not applicable for Version 1

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
AESI	Adverse Event of Special Interest
ADA	anti-drug antibody
ADE	antibody-dependent enhancement of disease
AOM	acute otitis media
CHD	congenital heart disease
CLD	chronic lung disease
COVID-19	coronavirus disease 2019
EPAR	European Public Assessment Report
EU	European Union
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IM	intramuscular(ly)
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
PK	pharmacokinetic
RMP	risk management plan
RSV	respiratory syncytial virus
SmPC	Summary of Product Characteristics
TSQ	Targeted Safety Questionnaire
US	United States

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Nirsevimab (MEDI8897)
Pharmacotherapeutic group(s) (ATC Code)	Immune sera and immunoglobulins, antiviral monoclonal antibodies (J06BD08)
Marketing Authorisation Applicant	AstraZeneca AB 15185 Södertälje Sweden
Medicinal products to which this RMP refers	Nirsevimab
Invented name(s) in the European Economic Area (EEA)	Beyfortus®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Recombinant human IgG1κ mAb
	Summary of mode of action: Beyfortus is a recombinant neutralising human IgG1κ long-acting monoclonal antibody to the prefusion conformation of the RSV F protein which has been modified with a triple amino acid substitution (YTE) in the Fc region to extend serum half-life. Nirsevimab binds to a highly conserved epitope in antigenic site Ø on the prefusion protein with dissociation constants KD = 0.12 nM and KD = 1.22 nM for RSV subtype A and B strains, respectively. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion
	Important information about its composition: The antibody has been engineered with a triple amino acid substitution, M252Y/S254T/T256E (YTE) in the Fc region to prolong the terminal half-life, which is expected to provide protection from RSV disease for the duration of the RSV season with a single dose/administration.
Hyperlink to the Product Information	Beyfortus® (see Module 1.3.1)
Indication(s) Dosage for in the EEA	Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season. Beyfortus should be used in accordance with official recommendations.

Table I-1 Product Overview

	The recommended dose of Beyfortus is: • 50 mg IM for infants with body weight < 5 kg • 100 mg IM for infants with body weight ≥ 5 kg. Beyfortus should be administered prior to commencement of the RSV season, or from birth for infants born during the RSV season.
Pharmaceutical form(s) and strengths Is/will the product be subject to additional monitoring in the EU?	Nirsevimab drug product is presented as a sterile, single-use, clear to opalescent, colourless to yellow, pH 6.0 solution in pre-filled syringe, for intramuscular injection. Each single-use 1 mL pre-filled syringe contains 100 mg of Beyfortus. Each single-use 0.5 mL pre-filled syringe contains 50 mg of Beyfortus.
	Yes

EU = European Union; Fc = fragment crystallisable; IgG1κ = immunoglobulin G1 kappa; IM = intramuscular; mAb = monoclonal antibody; RMP = risk management plan.

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

II.1.1 Prevention of RSV

Incidence

Respiratory syncytial virus is the most common cause of LRTI among infants and young children, resulting in largely predictable annual epidemics worldwide (Jain et al 2015 PERCH 2019, Shi et at 2017). In temperate climates, RSV infections have occurred primarily during the autumn, winter, and spring, with a typical season lasting 5 months. However, RSV activity declined during the 2020/2021 season due to COVID-19 mitigation measures that also impacted RSV circulation. As these restrictions lift, RSV infections are being observed with onset outside the traditional season, and it is expected that the upcoming RSV season may be broader and more severe than in previous years, particularly as the susceptible population will include infants and children who did not have the typical level of exposure during the COVID-19 restrictions (CDC 2021a, CDC 2021b, ECDC 2021, Ujiie et al 2021, van Summeren et al 2021).

Respiratory syncytial virus is the major cause of hospital admission, with an estimated 33 million clinical cases and 3.2 million hospitalisations in children less than 5 years of age in 2015 (Shi et at 2017).

In European countries, the hospitalisation rates were highest for infants within the first year of life, 19 to 22 per 1000 children (Jansen et al 2007, van Gageldonk-Lafeber et al 2005, Weigl et al 2001). In England, the highest number of confirmed RSV cases were in children aged < 1 year, which accounted for 46% (1331/2903) of total lower-level care admissions for RSV and 64% (96/150) of intensive care unit/health-dependency unit admissions for RSV (PHE 2021). During 2010 through 2018 seasons, on average 45225 RSV-associated hospitalisations (range: 43715 to 54616) per season was reported in France, 69% among children < 1 year old. This represents 28% of all-cause hospitalisations that occurred among children < 1 year old (Demont et al 2021). Modelling suggests that each year in England, an estimated 352570 acute respiratory general practitioner consultations (12 per 100 population), 26400 hospital admissions (0.9 per 100 population), and 25 deaths in hospital are attributable to RSV in children under 5 years of age (Cromer et al 2017). In addition, RSV hospitalisation rates among German children 0 to 3 years of age were found to be 4 and 9 times greater, respectively, than the hospitalisation rates associated with parainfluenza and influenza viral infections (König et al 2004).

Prevalence:

All infants, including healthy infants born at term, are at risk for severe RSV LRTI with primary RSV infection in infancy. Respiratory syncytial virus LRTI is the most common reason for admission to hospital in infants < 1 year of age (Hall 2001, Hall 2012, Murray et al 2014, Rha et al 2020). The majority of infants admitted to hospital with RSV LRTI are healthy, were born at term, and have no known predisposing risk factors, as illustrated with data from England in Murray et al 2014. This observation is further supported by data series from Europe and North America (Bont 2016, Hall 2012, Murray et al 2014, Rha et al 2020).

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

Respiratory syncytial virus LRTI, clinically characterised as bronchiolitis or pneumonia, represents a serious illness with acute and perhaps long-term consequences to the developing lung and immune system in young children (Wu et al 2008; Blanken et al 2013; Lopez Bernal et al 2013; Escobar et al 2013). Respiratory syncytial virus is estimated to cause between 60% to 80% of childhood bronchiolitis in infants less than 12 months of age (Oymar et al 2014) and up to 40% of paediatric pneumonias (Hall 2001).

Specific risk factors have been evaluated and are associated with severe RSV infection, such as young age, preterm birth ≤ 35 weeks' gestational age, CLD (eg, bronchopulmonary dysplasia, cystic fibrosis), haemodynamically significant CHD, immunodeficiencies, neuromuscular disorders, Down syndrome, birth at the start of or during the RSV season. However due to the complex interaction of multiple risk factors (eg, demographic, physiological, environmental), the risk of severe RSV disease is unpredictable.

The main existing treatment options:

There is no preventive option for RSV for all infants. The only current option available for prevention is an IgG (palivizumab [Synagis]), requiring monthly injections throughout the RSV season, that was licensed in 1998 in the US and since 1999 in EU for infants who are at higher risk for serious RSV sequelae.

There is no specific cure for RSV disease and treatment is generally limited to symptomatic relief (CDC 2021a) Current treatment of serious RSV illness depends on supportive care to ensure adequate hydration and nutrition, with additional oxygen and positive pressure mechanical ventilation as required (Ralston et al 2014). Infants with RSV infection who develop a mild, self-limited illness can usually be treated in outpatient settings with supportive care (Peidimonte and Perez 2015).

An antiviral agent, ribavirin, is licensed for the treatment of RSV infection in the United States and some EU member states; however, it is not recommended in the United States or EU guidelines due to its high cost, drug toxicities, and the lack of reproducible data on efficacy/clinical benefit (Villafana 2017, Barr et al 2019, Hoover 2018).

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

Respiratory syncytial virus usually causes mild, cold-like symptoms. Most infants recover in 1 to 2 weeks, but RSV infection can be serious, especially for infants and older adults. RSV LRTI presenting as bronchiolitis and pneumonia is a more serious disease and may have long-term consequences.

Although hospitalisation is an important consequence of RSV illness, a large percentage of the healthcare burden from RSV occurs outside the hospital (Carroll et al 2008, Hall 2009, Hall 2012, Oymar et al 2014, Paramore et al 2010, Lively 2019), such that office visits and emergency department visits are more frequent than subsequent hospitalisations, especially in healthy term and preterm infants. Respiratory syncytial virus infection could be also associated with both short-term complications in the first year of life and medium- and long-term complications in later life, which result in repeated healthcare visits and contribute to the substantial clinical and economic burden associated with RSV infection. RSV is the principal cause of viral AOM in children, with an estimated 58% of children aged < 3 years in a Finnish cohort (N = 2231) developing AOM as a short-term RSV-related complication.

Important co-morbidities:

Although the target population for nirsevimab is all infants, certain groups, including premature infants and those with CLD/bronchopulmonary dysplasia and CHD, are at higher risk for severe RSV disease (Figueras-Aloy et al 2016, Paes et al 2016, Checchia et al 2017). Evidence also suggests that children immunocompromised through the administration of

anticancer chemotherapy and especially those being transplanted and those with Down syndrome face an increased risk of severe RSV LRTI (Murray et al 2014, Robinson et al 2015, Hutspardol et al 2015, Kristensen et al 2012, Wilkesmann et al 2007).

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of key findings from non-clinical data

Key findings from nonclinical studies and their relevance to human usage are described below. There were no key safety findings in any of the nonclinical studies conducted summarised below:

Toxicity

Key issues identified from acute or repeat-dose toxicity studies

No significant findings were observed from a repeat-dose toxicity study in cynomolgus monkeys (up to 300 mg/kg intravenous or 300 mg IM dose levels which were considered the no-observed-adverse-effect-level).

Reproductive/developmental toxicity

In accordance with ICH S6 (R1), no studies were conducted and no studies are planned to evaluate the effects of nirsevimab on fertility or embryo-foetal and pre/postnatal development because nirsevimab binds a viral-specific target that is not expressed in nonclinical models or in humans, and the intended clinical population (infants and children) does not include women of childbearing potential. In addition, nirsevimab did not show any adverse effects on reproductive tissues in the repeat-dose toxicity study (1468-038) and did not bind to any evaluated human reproductive tissues (including placenta) in the tissue cross-reactivity study (20046491).

Genotoxicity

In accordance with ICH S6 (R1), no genotoxicity testing has been conducted and none is planned because it is not applicable to biotechnology-derived large protein products. Nirsevimab, is a large protein molecule, and is not expected to cross the nuclear or mitochondrial membranes to interact directly with DNA or other chromosomal materials.

Carcinogenicity

In accordance with ICH S6 (R1), no carcinogenicity studies have been conducted with nirsevimab and none are planned given that the target for this product is a virus-specific target, which is not expressed in nonclinical animal models or in humans. Further, the intended clinical administration is not of a chronic nature.

Safety pharmacology

No standalone studies to assess safety pharmacology were conducted. Safety pharmacology of nirsevimab was assessed as a component of the repeat-dose toxicity study in cynomolgus monkeys. No significant findings were observed.

Other toxicity-related information or data

Results from tissue cross-reactivity studies against panels of human tissues, including juvenile, neonatal and foetal tissues, showed no staining of any human tissues, as expected. There were no safety concerns identified on the basis of nonclinical safety data, and no further nonclinical studies were considered necessary.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The nirsevimab clinical development programme consists of the following clinical studies: 2 completed dose-escalation, safety, PK, and ADA studies (D5290C00001 [Study 1] and D5290C00002 [Study 2]), and 3 complementary pivotal studies: MELODY (ongoing), D5290C00003 (Study 3) (complete), and MEDLEY (ongoing).

Study 1, which was conducted in adults, is not included in the summaries below. The remaining studies that were conducted in paediatric subjects are within the scope of this section. Exposure to nirsevimab is summarised in Table II-1, Table II-2, and Table II-3.

Table II-1 Exposure to Nirsevimab

Total exposure	Infants (N)
1 dose[a]	2629
10 mg	8
25 mg	31
50 mg	1750
67 mg[b]	1
100 mg	839
2 doses (Cumulative dose given at 2 timepoints)[c]	11
100 mg	2
150 mg	3
200 mg	6
Time between doses	
< 1 m	3
≥ 1 to < 3 m	4
≥ 3 m	4
Total at proposed dose[d]	2173

[a] Includes all infants treated with nirsevimab in Study 2, Study 3, MELODY Primary Cohort and MEDLEY RSV Season 1.

[b] Dose given in error and is estimated based on in investigator-reported estimate of volume received.

[c] Includes replacement dosing needed after cardiac bypass surgery (N = 8 subjects) and accidental second dose (N = 3 subjects) in MEDLEY.

[d] Includes all infants treated with nirsevimab in Study 3, MELODY Primary Cohort, and MEDLEY with an IM dose of 50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg at the time of dosing.

IM = intramuscular; RSV = respiratory syncytial virus.

Source: Table II-1, ISA, Module 5.3.5.3; Table 11-3, Module 5.3.5.3; Table 2, Module 2.7.4

Table II-2 Exposure by Age Group and Sex

	Infants (N)		
Age group	**M**	**F**	**Total**
Age ≤ 3.0 months	723	648	1371
Age > 3.0 to ≤ 6.0 months	449	418	867
Age > 6.0 months	200	202	402
Total	1372	1268	2640

Includes all infants treated with nirsevimab in Study 2, Study 3, MELODY Primary Cohort and MEDLEY RSV Season 1.

F = female; M = male; RSV = respiratory syncytial virus.

Source: Table II-2, ISA, Module 5.3.5.3

Table II-3 Exposure by Race

Race	Infants (N)
American Indian or Alaska Native	69
Asian	77
Black or African American	570
Native Hawaiian or Other Pacific Islander	18
White	1703
Other	167
Multiple Categories Checked	32
Missing	4
Totals	2640

Includes all infants treated with nirsevimab in Study 2, Study 3, MELODY Primary Cohort and MEDLEY RSV Season 1.

RSV = respiratory syncytial virus.

Source: Table II-4, ISA, Module 5.3.5.3

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Any history of LRTI or active LRTI prior to, or at the time of, randomisation

Reason for exclusion: Infants were excluded to avoid factors that may confound a complete understanding of the efficacy and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile for nirsevimab in subjects with a history of LRTI or active LRTI is different than that of the general target population.

Known history of RSV infection or active RSV infection prior to, or at the time of, randomisation

Reason for exclusion: Infants with known history of RSV infection or active RSV infection were excluded to avoid factors that may confound a complete understanding of the safety and efficacy profile and to ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile for nirsevimab in subjects with a history of RSV infection or active RSV infection prior to, or at time of, randomisation will be different than that of the general target population.

Chronic seizures or evolving or unstable neurologic disorder

Reason for exclusion: Infants were excluded to avoid factors that may confound a complete understanding of the safety profile and to ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile for nirsevimab in subjects with a history of chronic seizures or evolving or unstable neurologic disorder will be different than that of the general target population.

Known hepatic dysfunction including known or suspected active or chronic hepatitis infection

Reason for exclusion: Infants were excluded to ensure the study safety results were not confounded by pre-existing illnesses.

Is it considered to be included as missing information: No

Rationale: IgG mAbs are not primarily cleared via the hepatic pathway, thus change in hepatic function is not expected to influence nirsevimab clearance.

Immunocompromised patients

Reason for exclusion: Infants were excluded to avoid factors that may confound a complete understanding of the safety and efficacy profile.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile of nirsevimab is different in immunocompromised patients. Findings from a Japanese study which evaluated the safety and efficacy of palivizumab in high-risk infants including immunocompromised patients indicated a similar safety profile (Haerskjold et al 2017). There is an ongoing global nirsevimab study (D5290C00008) evaluating immunocompromised children with different underlying causes from different countries to support safety evaluation in a diverse population.

Receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination

Reason for exclusion: Infants were excluded to avoid factors that may confound a complete understanding of the safety and efficacy data of nirsevimab and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: For patients who receive any RSV vaccine, including infants whose mothers received an RSV vaccine (ie, maternal RSV vaccines), there is no scientific rationale to suspect that the safety profile of nirsevimab may differ to that characterised so far for the general target population.

Known renal impairment

Reason for exclusion: Infants were excluded to ensure the study safety results were not confounded by pre-existing illnesses.

Is it considered to be included as missing information: No

Rationale: IgG mAbs are not primarily cleared via the renal pathway, thus change in renal function is not expected to influence nirsevimab clearance. For this reason, it is not anticipated that the safety profile will be different in patients with active or chronic renal impairment compared to that characterised so far in the general target population.

Clinically significant congenital anomaly of the respiratory tract

Reason for exclusion: Infants with clinically significant congenital anomaly of the respiratory tract were excluded to ensure the study results, specifically respiratory findings, were not confounded by pre-existing illnesses.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile in this population is different to that of the general target population. Further characterisation of this population is neither feasible nor warranted.

History of allergy to component of mAb

Reason for exclusion: Infants with a history of allergy to any component of a mAb were excluded as they may be at a higher risk of hypersensitivity (including anaphylactic reaction).

Is it considered to be included as missing information: No

Rationale: Nirsevimab is contraindicated in patients with known hypersensitivity to active substance or excipients; therefore, this population is not relevant as missing information.

Mother with HIV infection (unless the child has been proven to be not infected)

Reason for exclusion**:** Infants born to mothers with HIV infection (unless the infant was proven not to be infected) and those children with known HIV infection were excluded in

order to avoid factors that may confound a complete understanding of the safety and efficacy data of nirsevimab and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile of nirsevimab is different in immunocompromised patients including those with HIV. There is an ongoing global nirsevimab study evaluating the immunocompromised children with different underlying causes (including HIV infection) from different countries to support safety evaluation in a diverse population (D5290C00008).

II.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

II.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Exposure of special populations included or not in the nirsevimab clinical trial development programme is summarised in Table II-4

Table II-4 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women and breast-feeding women	Not relevant for inclusion in the clinical development programme
Patient with relevant co-morbidities:	
• Patients with hepatic impairment	Not included in the clinical development programme
• Patients with renal impairment	Not included in the clinical development programme
• Patients with cardiovascular impairment (congenital heart disease [CHD]/chronic lung disease [CLD])	Included in the clinical development programme
Immunocompromised patients	Not included in the clinical development programme;[a] immunocompromised patients included in study (D5290C0008)

[a] Includes Study 2, Study 3, MELODY Primary Cohort, and MEDLEY RSV Season 1.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

Not applicable.

II.5.1 Method used to calculate exposure

Not applicable.

II.5.2 Exposure

Not applicable.

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

In view of the mechanism of action of nirsevimab and since nirsevimab is administered in a healthcare setting, no potential for misuse for illegal purposes exists.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of safety concerns in the initial RMP submission

II.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP

Known risks that do not impact the risk-benefit profile

- **Injection site reactions**: Injection site reactions have been observed with administration of nirsevimab. There were no serious events related to nirsevimab injection. The reported terms were injection site pain, injection site induration, injection site oedema, injection site reaction, injection site erythema. The majority of events were mild to moderate in intensity and were transient and resolved within 1 or 2 days. These reactions are managed according to standard clinical practice and do not impact the benefit-risk profile of nirsevimab.
- **Rash:** Events of rash have been observed with the administration of nirsevimab. There were no serious events of rash that were considered to be related to nirsevimab. The following events with reported terms rash, rash macular, and rash maculo-papular were assessed as related to nirsevimab administration. These events were mild or moderate in intensity. These reactions are managed according to standard clinical practice and do not impact the benefit-risk profile of nirsevimab.
- **Pyrexia:** Events of pyrexia have been observed with the administration of nirsevimab. There have been no serious events of pyrexia considered to be related to nirsevimab

administration. These reactions are managed according to standard clinical practice and do not impact the benefit-risk profile of nirsevimab.

Potential risks that require no further characterization.

- **Immediate (Type 1) hypersensitivity reactions including anaphylaxis:** Monoclonal antibodies have the potential to cause immediate hypersensitivity reactions including anaphylaxis. Anaphylaxis is a serious allergic reaction that is rapid in onset with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention. Manifestations of anaphylaxis include involvement of skin, mucosal tissue or both (eg, generalised urticaria, pruritus or flushing, angioedema), respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, hypoxemia), hypotension or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence), and gastrointestinal symptoms (eg, crampy abdominal pain, vomiting). There have been no serious adverse events of serious allergic reactions including anaphylaxis attributable to nirsevimab reported in the clinical development programme.

Healthcare professionals are familiar with this risk and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies. Therefore, the risk of allergic reactions including anaphylaxis is considered to be a potential risk not categorised as important for inclusion in the RMP. These reactions are managed as per routine clinical practice and guidance to healthcare professionals provided in the product information (Section 4.4).

Potential risks also not considered important

- **Immune complex disease (Type III hypersensitivity):** Nirsevimab, like other biologics, can induce the development of ADA and the occurrence of such ADA could result in immune complex disease or altered nirsevimab levels or activity. Drug-induced immune complex (type III) hypersensitivity reactions can occur when the host immune system generates antibodies to drug resulting in soluble circulating antigen-antibody complex formation and their deposition in blood vessels. Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. There were a limited number of subjects (n = 110; 5.9%) in the pivotal studies who were ADA positive post baseline. Although the numbers were small and data were limited, ADA did not appear to impact the safety or overall efficacy of nirsevimab. In addition, there have been no events of immune complex disease reported in the nirsevimab clinical development programme. This risk is not considered to alter the risk-benefit profile of nirsevimab. Therefore, the risk of immune complex disease is considered to be a potential risk not categorised as important for inclusion in the RMP.

- **Thrombocytopaenia:** Although severe thrombocytopaenia cases have been reported in post-approval use of Synagis and are included in the product information, similar events have not been observed with nirsevimab. The possible clinical outcomes of thrombocytopaenia include bleeding in the mouth and gums, bruising, nosebleeds, petechiae (pinpoint red spots/rash), the majority of these outcomes were they to occur would not impact benefit risk with the possible exception of severe bleeding Nonserious cases of thrombocytopaenia were observed rarely in the nirsevimab clinical trials but all cases included other confounding factors. There were no investigational product-related serious events of thrombocytopaenia reported in the nirsevimab clinical development programme. For these reasons, thrombocytopaenia is not considered to impact the benefit risk profile of Nirsevimab and routine pharmacovigilance activities and guidance in Section 4.4 of the product information are considered sufficient to manage these events. A follow-up safety questionnaire for thrombocytopaenia events will be implemented to characterize this adverse event of special interest (AESI) which will continue to be closely monitored as part of routine pharmacovigilance activities. There are no additional pharmacovigilance activities or additional risk minimization measures in place and the potential risk of thrombocytopaenia events is not considered important for the inclusion in the RMP.
- **Antibody-dependent enhancement of disease:** ADE is a theoretical risk for mAbs. One of the syndromes of ADE involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells which trigger virus entry. Potential clinical outcomes resulting from ADE include lack of therapeutic effect progressing to unanticipated worsening of RSV, which has not been observed in the clinical trials to date. The potential for ADE of RSV infection was evaluated in a cotton rat model of RSV infection using 1G7, the non-YTE version of nirsevimab. No evidence of enhancement of RSV infection was observed at any dose evaluated, including sub-efficacious doses down to 0.125 mg/kg. For these reasons ADE is not considered to impact the benefit-risk profile of nirsevimab and is therefore not considered to be an important potential risk.
- **Antiviral resistance:** Currently nirsevimab has demonstrated neutralisation activity against both RSV A and RSV B strains through 150 days post dose and the percentage of subjects with any RSV LRTI or non-LRTI event that had an RSV isolate containing resistance-associated substitutions was rare across all treatment groups and reporting periods in the 3 pivotal studies. Potential emergence of neutralisation escape variants that may impact effectiveness of nirsevimab will continue to be monitored closely and characterised through ongoing virologic assessment in RSV molecular surveillance studies (OUTSMART-RSV, INFORM-RSV, and SEARCH-RSV) and post-marketing RSV molecular surveillance activities.

II.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks:

There are no identified risks considered important for inclusion in the list of safety concerns of the initial submission of the RMP of nirsevimab.

Important potential risks:

There are no important potential risks considered important for inclusion in the list of safety concerns of the initial submission of the RMP of nirsevimab.

Missing information:

Long term safety:

Risk Benefit Impact:

While there is currently no evidence, based on the mechanism of action and the half-life of the medicinal product, to suggest that the safety profile after long-term use might be different to that established to date, safety follow-up data beyond 360 days is limited.

II.7.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

II.7.3 Details of important identified risks, important potential risks and missing information

II.7.3.1 Presentation of important identified risks and important potential risks

Not applicable. There are no important identified or important potential risks

II.7.3.2 Presentation of missing information

Missing information: Long term safety.

Evidence Source:

While there is currently no evidence, based on the mechanism of action and the half-life of the medicinal product, to suggest that the safety profile after long-term use might be different to that established to date, safety follow-up data beyond 360 days is limited.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the safety concerns

A summary of the safety concerns for nirsevimab is presented in Table II-5

Table II-5 Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Long term safety

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

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities

AstraZeneca undertakes routine pharmacovigilance activities consistent with the International Council for Harmonisation (ICH) E2E Pharmacovigilance Planning Guideline. Routine pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to rapidly assess the ongoing safety profile of Nirsevimab throughout clinical development and in the post-authorization period in order to characterize and communicate pertinent safety data appropriately. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

Specific adverse reaction follow-up questionnaires:

There are no follow-up questionnaires for safety concerns for Nirsevimab. However, there are follow-up questionnaires in place for thrombocytopaenia (refer to Section SVII.1.1).

Other forms of routine pharmacovigilance activities:

Continuous and thorough reviews of thrombocytopaenia as an AESI (refer to Section SVII.1.1) will be conducted as part of the close monitoring of this topic. Data from these reviews will be summarized in the PSURs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Melody (D5290C00004)

A Phase 3 Randomized, Double- blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants

Rationale and study objectives:

Subjects will be followed-up for long term safety from Day 362 to Day 511, for disease incidence of medically attended lower respiratory tract infection (LRTI) and enhanced disease

Milestones:

Final Report Q42023.

MEDLEY (D5290C00005)

A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children.

Rationale and study objectives:

Subjects receiving nirsevimab in both seasons will be followed for long term safety after Day 361 post initial Season 1 treatment. Assessments will include treatment emergent adverse events (non-serious and serious).

milestones:

Final Report Q42023.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The following additional pharmacovigilance activities planned for Nirsevimab are shown in Table III-1.

Table III-1 Ongoing and planned additional pharmacovigilance activities

Study [Status]	Summary of objectives	Safety concerns addressed	Milestones	Due dates for EMA
Category 1 - Not applicable				
Category 2 – Not applicable				
Category 3 - Required additional pharmacovigilance activities				
A Phase 3 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants (MELODY). **Study Code:** D5290C00004. **Status:** Ongoing	To evaluate safety and efficacy of MEDI8897.	Long term safety	Final report	Q4 2023
A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY). **Study Code:** D5290C00005. **Status:** Ongoing	To evaluate safety and tolerability of MEDI8897 compared to palivizumab.	Long term safety	Final report	Q4 2023

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This section is not applicable as no post-authorization efficacy studies are planned.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Long term safety	None

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term Safety	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • MELODY (D5290C00004) • MEDLEY (D5290C00005)

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR BEYFORTUS (NIRSEVIMAB)

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

Beyfortus's Summary of Product Characteristics SmPC and its package leaflet give essential information to healthcare professionals and caregivers for infants on how Beyfortus should be used.

This summary of the RMP for Beyfortus 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.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

Beyfortus is indicated for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season (see SmPC for the full indication). Beyfortus contains nirsevimab as the active substance and it is given by IM administration.

Further information about the evaluation of Beyfortus's benefits can be found in Beyfortus's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage (<< link to the EPAR summary landing page to be added when available>>).

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Beyfortus, together with measures to minimise such risks and the proposed studies for learning more about Beyfortus '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 caregiver for infants 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 patient (eg, 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 periodic safety update report 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 Beyfortus is not yet available, it is listed under 'missing information' below.

VI.2.1 List of important risks and missing information

Important risks of Beyfortus are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered (Table VI-1). 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 Beyfortus. 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 (eg, on the long-term use of the medicine).

Table VI-1 List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing Information	Long term safety

VI.2.2 Summary of important risks and Missing Information

Table VI-2 Missing information: Long term safety

Risk minimisation measures	None
Additional pharmacovigilance activities	MELODY (Study D5290C00004) and MEDLEY (D5290C00005)

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

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

VI.2.3.2 Other studies in post-authorisation development plan

Melody (D5290C00004)

A Phase 3 Randomized, Double- blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants

Rationale and study objectives:

Subjects will be followed-up for long term safety from Day 362 to Day 511, for disease incidence of medically attended lower respiratory tract infection (LRTI) and enhanced disease

Milestones:

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MEDLEY (D5290C00005)

A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children.

Rationale and study objectives:

Subjects receiving nirsevimab in both seasons will be followed for long term safety after Day 361 post initial Season 1 treatment. Assessments will include treatment emergent adverse events (non-serious and serious).

Milestones:

Final Report Q42023

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EU RMP Part VII Annex 4

Drug Substance MEDI8897 (Nirsevimab)

EU RISK MANAGEMENT PLAN (RMP) for MEDI8897 (Nirsevimab)

Part VII Annex 4 - specific adverse drug reaction follow-up forms

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1. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following specific adverse reaction follow-up questionnaires will be used to collect further information.

Questionnaire for Thrombocytopenia.

AstraZeneca

Questionnaire for Thrombocytopenia

AZ Date of Receipt:_____
AZ Case ID#: _____

1. Reporter's Information

Reporter's Name: | Is Reporter a healthcare professional? ☐ No ☐ Yes, If yes, please provide specialty: | Telephone #:

Reporter's Address: | Reporter's Signature: | Date *(DD/MM/YY):*

2. Patient's Details

Initials: | Sex: ☐ Male ☐ Female | Date of Birth (*DD/MM/YYYY*): | Age (*years*):

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Other ☐ Refused or Unknown

Ethnic Group: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

3. Adverse Event Details

Adverse Event(s)	Start Date	Stop Date	Outcome	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae. If yes, please specify:
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae If yes, please specify:

In the event of Death, please provide the cause of death (please provide copy of autopsy report, if available). ☐ No ☐ Yes

Please provide details about the thrombocytopenia (bleeding events) (please check all that is applicable. Also provide the date of diagnosis)

Please provide details of bleeding events

☐ Petechiae

☐ Haemmorahage

☐ Contusion

☐ Epistaxis (bleeding from nose)

☐ Ecchymosis

☐ Hematoma

☐ Other signs and symptoms, please list_____:

☐ Kindly provide if a diagnosis if thrombocypenia was confirmed the event is suggestive of Thromocytopenia (platelet count <150 X 10^9/L)

(Date DD/MMM/YYYY):

☐ None (No clinical signs or symptoms

4. Nirsevimab

Dose received: ☐ No ☐ Yes Date and time of nirsevimab dose (DD/MM/YY / hh:mm):
Batch/Lot #:

5. How was the patient treated?

Was treatment provided? ☐ No ☐ Yes

Please specify the details of the treatment (including dose/start date):

☐ Platelet transfusions

☐ Plasma exchange

Others please specify: _____

6. Other Suspect Drugs

Please only include other drugs you consider to be causally related to the adverse event(s) and not concomitant medications.

Suspect Drug Name	Indication	Daily Dosage	Route	Start Date	Stop Date	Was suspect drug
						☐ No ☐ Y
						☐ No ☐
						☐ No ☐

If any of the above drugs were stopped, did the event(s) improve after stopping?

☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Stopped/Altered *(DD/MM/YY)*:
_____

Did the event(s) reoccur after reintroduction?

☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

7. Concomitant Drugs/ Vaccines *(Including RSV/ or anti RSV monoclonal antibodies administered in the last 4 weeks) Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations.*

Concomitant Drug Name/ Concomitant	Indication	For vaccines please enter	Daily Dosage	Route	Start Date (DD/MM/YY)	Stop Date (DD/MM/YY)	Was concomitant
							☐ No ☐ Yes
							☐ No ☐ Yes
							☐ No ☐ Yes

8. Please provide information on Relevant Medical History/Concurrent Diseases/ Treatments

Medical History		Start Date (if applicable) (DD/MM/YY)	Stop date (if applicable) (DD/MM/YY)
History of thrombotic/embolic event	☐ No ☐ Yes		
Any malignancies	☐ No ☐ Yes		
Haemophilia/other coagulation disorders	☐ No ☐ Yes		
History of Heparin induced Thrombocytopenia	☐ No ☐ Yes		
History of Primary immune thrombocytopenia/ Thrombocytopenia	☐ No ☐ Yes		
History of Drug induced immune thrombocytopenia	☐ No ☐ Yes		
Anticoagulation / previous heparin use	☐ No ☐ Yes		
Therapeutic thrombolysis	☐ No ☐ Yes		
Sickle cell disease	☐ No ☐ Yes		

Disseminated intravascular coagulation	☐ No ☐ Yes		
Cancer with disseminated intravascular coagulation	☐ No ☐ Yes		
Cancer with bone marrow infiltration or suppression (eg, lymphoma, leukemia, some solid tumors)	☐ No ☐ Yes		
Renal failure	☐ No ☐ Yes		
Liver failure	☐ No ☐ Yes		
Hypersplenism due to chronic liver disease	☐ No ☐ Yes		
Hypertension	☐ No ☐ Yes		
Valvular heart disease	☐ No ☐ Yes		
Atrial fibrillation	☐ No ☐ Yes		
Atherosclerosis	☐ No ☐ Yes		
Ischaemic heart disease	☐ No ☐ Yes		
Endocarditis	☐ No ☐ Yes		
Sudden hypotension	☐ No ☐ Yes		
Peripheral vascular disease	☐ No ☐ Yes		
Inflammatory vascular disease	☐ No ☐ Yes		
Diabetes mellitus	☐ No ☐ Yes		

Infections (eg HIV, Hepatitis C, Intracellular parasites)	☐ No ☐ Yes		
Sepsis	☐ No ☐ Yes		
Rheumatologic/autoimmune disorders (eg, systemic lupus erythematosus, rheumatoid arthritis)	☐ No ☐ Yes		
Trauma	☐ No ☐ Yes		
Nutrient deficiencies (eg, vitamin B12, folate, copper)	☐ No ☐ Yes		
Myelodysplasia	☐ No ☐ Yes		
Surgical procedures	☐ No ☐ Yes		
Other, please specify:			

9. Laboratory Results- Before/During/After Treatment Please provide details of the relevant lab tests as applicable (attach results if available).

Test	Date	Results
Complete blood count (CBC)		
Platelet count (before Nirsevimab		
Platelet count (after Nirsevimab) – please provide details of all the values with dates		
Peripheral blood smear		
Bone marrow biopsy		
Blood group (Rh)		
Direct antiglobulin test		
Erythrocyte sedimentation rate		
Serum C-reactive protein (CRP)		
Prothrombin time (PT)		
Activated partial thromboplastin		
Heparin-induced Thrombocytopenia (HIT) PF4		
Heparin-induced Thrombocytopenia (HIT) PF4		
PF4-serotonin release assay		
D-dimers, fibrinogen levels		
Serum anti-platelet antibodies		
Partial thromboplastin time (PTT)		
INR		

Ultrasound (e.g. carotid, cardiac)		
ECG		
MRI		
CT		
Cerebral angiography		
Other, please specify: Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available:		

Thank you for completing this form.