EU RMP	
Drug Substance	Nirsevimab
Version Number	2
Succession Number	3
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Date of final sign off	See e-signature page

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.

Administrative Information

This RMP covers updates made to the RMP from Version 1 until this Version 2 Succession 3 and includes two Type 2 Variations.

Rationale for Submitting an Updated RMP

Updates from Version 1 through Version 2 Succession 2

This RMP is updated to include information to support the use of nirsevimab for children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season and updates to the exposure table.

Summary of Significant Changes

Part I	Updated to include information related to extended indication (use of nirsevimab for children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season) including dosage and editorial updates
Part II SI:	No updates
Part II SII:	No updates
Part II SIII:	Updated clinical trial exposure
Part II SIV:	Updated special populations included or not included in clinical development programme
Part II SV:	No updates
Part II SVI:	No updates
Part II SVII:	No updates
Part II SVIII:	No updates
Part III:	No updates
Part IV	No updates
Part V	No updates
Part VI	Editorial updates

Updates from Version 2 Succession 2 to Version 2 Succession 3

This RMP is updated to reclassify missing information regarding long-term safety, the obligation for which has now been provided through the completion of the MELODY (D5290C00004) and MEDLEY (D5290C00005) studies.

Summary of Significant Changes

Part I	Editorial updates to align with the Core RMP
Part II SI:	No updates
Part II SII:	No updates
Part II SIII:	No updates
Part II SIV:	No updates
Part II SV:	Updated to include approval status and post-marketing exposure data
Part II SVI:	No updates
Part II SVII:	Updated to reclassify missing information: long-term safety, as completed
Part II SVIII:	Updated to reclassify missing information: long-term safety, as completed
Part III:	Updated additional PV activities with completion of MELODY and MEDLEY studies
Part IV	No updates
Part V	Removal of Table V-1 and Table V-2 to remove long-term safety as missing information
Part VI	Editorial updates in accordance with the other updates made in the RMP. Removal of Table VI-2

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Annex 1- EudraVigilance Interface	Not Applicable
Annex 2 - Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programmes	Included
Annex 3 - Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Included
Annex 4 - Specific Adverse Drug Reaction Follow-up Forms	Not Applicable
Annex 5 - Protocols for Proposed and Ongoing Studies in RMP Part IV	Not Applicable
Annex 6 - Details of Proposed Additional Risk Minimisation Activities	Not Applicable
Annex 7 - Other Supporting Data (Including Referenced Material)	Not Applicable
Annex 8 - Summary of Changes to the Risk Management Plan Over Time	Included

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADA	anti-drug antibody
ADE	antibody-dependent enhancement of disease
AESI	Adverse Event of Special Interest
AOM	acute otitis media
BPD	bronchopulmonary dysplasia
CHD	congenital heart disease
CLD	chronic lung disease
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
F	Female
Fc	Fragment crystallisable
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEMT	Information Exploration Management Team (validated outputs from clinical database)
IgG(1κ)	immunoglobulin G(1 kappa)
IM	intramuscular(ly)
LRTI	lower respiratory tract infection
M	Male
MA	Medically attended
mAb	monoclonal antibody
OR	Odds ratio
RMP	risk management plan
RSV	respiratory syncytial virus
SmPC	Summary of Product Characteristics
US	United States

1 PART I: PRODUCT OVERVIEW

Table 1-1 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)	Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in: • Neonates and infants during their first RSV season. • Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Table 1-1 Product Overview

Dosage in the EEA	<u>Infants entering their first RSV season</u> 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, from birth for infants born during the RSV season. For others born outside the season, BEYFORTUS should be administered ideally prior to the RSV season. <u>Children who remain vulnerable to severe RSV disease entering their second RSV season</u> The recommended dose is a single dose of 200 mg given as two intramuscular injections (2 x 100 mg). Beyfortus should be administered ideally prior to the start of the second RSV season. For individuals undergoing cardiac surgery with cardiopulmonary bypass, an additional dose may be administered as soon as the individual is stable after surgery to ensure adequate nirsevimab serum levels. If within 90 days after receiving the first dose of Beyfortus, the additional dose during the first RSV season should be 50 mg or 100 mg according to body weight, or 200 mg during the second RSV season. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight during the first RSV season, or 100 mg during the second RSV season, to cover the remainder of the RSV season.
Pharmaceutical form(s) and strengths	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. nirsevimab. Each single-use 0.5 mL pre-filled syringe contains 50 mg of. nirsevimab.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

2.1.1 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 al 2017).

Respiratory syncytial virus is the major cause of hospital admission, with an estimated 33 million clinical cases and 3.6 million hospitalisations in children less than 5 years of age in 2019 (Shi et al 2017). This risk extends into the second RSV season, with an RSV attributable hospitalisation rate for respiratory disease of approximately 2.5 per 1000 population estimated in children aged 6 to 23 months in the UK between 1995 and 2009 (Taylor et al 2016). In children 12 to 60 months of age, RSV-associated acute LRTI hospital admission rates of approximately 1.5% were reported globally and across lower, middle-, and higher-income countries (Li et al 2022).

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).

A number of reviews and metanalyses report elevated risk of severe RSV disease in infants and children with underlying diseases, including CLD, CHD, immunocompromised state, Down syndrome, cystic fibrosis, and neurological conditions (Chaw et al 2020a, Chaw et al 2020b, Manzoni et al 2017, Paes et al 2016). In a review of 20 years of data for infants and young children in Western countries, RSV hospitalisation rates in the second year of life were

higher in children with underlying conditions (73/1000 for children with BPD, 18/1000 for children with CHD, and 30/1000 for children aged < 29 weeks gestational age at birth) compared with only 4/1000 for children born at term without underlying conditions (Paes et al 2016).

In a systematic review and metanalysis of data from 29 studies, RSV associated risks were higher among children with BPD compared to those without this condition: RSV hospitalisation (OR 2.6; $p < 0.001$), Intensive Care Unit admission (OR 2.9; $p < 0.001$), need for mechanical ventilation (OR 8.2; $p < 0.001$), and in-hospital case fatality rate (OR, 12.8; $p < 0.001$). In addition, the requirement for oxygen supplementation and mechanical ventilation was increased in patients with BPD compared with those without (Chaw et al 2020a). In a separate review and metanalysis of 39 studies, having CLD or BPD was shown to be an independent risk factor for RSV hospitalisation (OR 2.2 to 7.2) and once hospitalised, children were at risk of a more severe course of disease than children with no RSV (Paes et al 2016).

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 (Ahuja et al 2021, Bont et al 2016, Hall 2012, Murray et al 2014, Rha et al 2020).

Acute respiratory infections have also been identified as a significant burden on infants and children with CHD, associated with higher mortality, costs, and longer length of hospital stay (Ahuja et al 2021, Williams et al 2021). Compared to infants with respiratory infections and non-critical CHD, infants aged < 1 year, with respiratory infections and critical CHD had higher mortality (4.5% vs 2.3%, $p < 0.001$) and longer mean length of stay (20.1 days vs 15.5 days, $p < 0.001$). In addition, a review of US National inpatient data from 1997 to 2013 reported a 1.5% mortality rate in children aged 12 to 23 months of age with CHD who were hospitalised for RSV, compared to 0.1% in those without CHD (Friedman et al 2017), again showing that the risk of serious outcomes from RSV extends beyond the first year of life.

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).

Due to the complex interaction of multiple risk factors (eg, demographic, physiological, environmental), the risk of severe RSV disease is unpredictable. 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, BPD, cystic fibrosis), haemodynamically significant CHD, immunodeficiencies, neuromuscular disorders, Down syndrome, birth at the start of or during the RSV season.

In an extensive literature review, Down syndrome, CHD, immunocompromised state, cystic fibrosis, and neurologic conditions were all associated with a significantly increased risk of RSV hospitalisation, and a number of other congenital malformations and chronic conditions are also associated with severe RSV disease (Manzoni et al 2017).

The Main Existing Treatment Options:

There is no specific cure for RSV disease and treatment is generally limited to symptomatic relief (CDC 2021) 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 (Piedimonte and Perez 2015).

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

Approval in the EEA for Beyfortus was received on 31 October 2022 for the prevention of RSV lower respiratory tract infection in neonates and infants during their first RSV season. Nirsevimab has the potential to provide an improvement over the current standard of care by offering a convenient and effective prophylactic treatment for the broad range of children who remain at risk for severe RSV disease in their second RSV season.

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 et al 2009, Hall 2012, Oymar et al 2014, Paramore et al 2010, Lively et al 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/BPD 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).

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

2.2.1 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.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The nirsevimab clinical development programme consists of the following clinical studies: 2 completed dose-escalation, safety, pharmacokinetic, and ADA studies (D5290C00001 [Study 1] and D5290C00002 [Study 2]), 3 complementary pivotal studies: MELODY (complete), D5290C00003 (Study 3) (complete), and MEDLEY (complete); and an open-label study in immunocompromised infants and children (MUSIC [Study D5290C00008]) (complete).

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 2-1, Table 2-2,Table 2-3, Table 2-4, Table 2-5, and Table 2-6

Table 2-1 Exposure to Nirsevimab (Season 1)

Total exposure	Infants (N)
1 dose [a]	3686
10 mg	8
25 mg	31
50 mg	2153
67 mg [b]	1
100 mg	1493
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 < 5 m	8
≥ 5 to < 12 m	0
≥ 12	0
Total	3697
Total at proposed dose [c]	3230

[a] Includes all infants treated with nirsevimab in Study 2, Study 3, MELODY, MEDLEY Season 1, and MUSIC Season 1 (MUSIC Season 1 includes all subjects < 12 month at time of dosing).

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

[c] Includes all infants treated with nirsevimab in Study 3, MELODY, MEDLEY, and MUSIC 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.

Table 2-2 Exposure to Nirsevimab (Season 2)

Total exposure	Infants (N)
1 dose [a]	272
100 mg	2
150 mg	2
200 mg	268
2 doses (Cumulative dose given at 2 timepoints)	2
300 mg	2
Time between doses	
< 1 m	1
≥ 1 to < 5 m	1
≥ 5 to < 12 m	0
≥ 12	0
Total	274

[a] Includes all infants treated with nirsevimab in MEDLEY Season 2 and MUSIC Season 2.

Source: Validated Program Output IEMT_158

Table 2-3 Exposure by Age Group and Sex (Season 1)

	Infants (N)		
Age group	**M**	**F**	**Total**
Preterm newborn infants (≤ 35 weeks gestational age)	882	819	1701
Term newborn infants (0 to 27 days)	318	294	612
Infants and toddlers (≥ 28 days to < 12 months)	1623	1462	3085
Total	2823	2575	5398

Includes all infants treated with nirsevimab in Study 2, Study 3, MELODY, MEDLEY Season 1, and MUSIC Season 1 (MUSIC Season 1 includes all subjects < 12 month at time of dosing).

Source: Validated Program Output IEMT_158

Table 2-4 Exposure by Age Group and Sex (Season 2)

	Infants (N)		
Age group	**M**	**F**	**Total**
Toddlers (< 24 months)	159	115	274
Childrens (≥ 24 months)	0	0	0
Total	159	115	274

Includes all infants treated with nirsevimab in MEDLEY Season 2 and MUSIC Season 2.

Source: Validated Program Output IEMT_158

Table 2-5 Exposure by Race (Season 1)

Race	Infants (N)
American Indian or Alaska Native	105
Asian	165
Black or African American	592
Native Hawaiian or Other Pacific Islander	27
White	2246
Other	519
Multiple Categories Checked	39
Missing	4
Totals	3697

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

Source: Validated Program Output IEMT_158

Table 2-6 Exposure by Race (Season 2)

Race	Infants (N)
Asian	26
Black or African American	22
Native Hawaiian or Other Pacific Islander	1
White	213
Other	57
Multiple Categories Checked	45
Totals	274

Includes all infants treated with nirsevimab in MEDLEY Season 2 and MUSIC Season 2

Source: Validated Program Output IEMT_158

2.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

2.4.1 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 from pivotal clinical trials ie, Study 3, MELODY, and MEDLEY 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). Findings from the completed global nirsevimab study (MUSIC) evaluating immunocompromised children with different underlying causes from different countries to support safety evaluation in a diverse population also indicated a similar safety profile.

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. This is supported by findings from the completed global nirsevimab study evaluating immunocompromised children with different underlying causes (including HIV infection) from different countries to support safety evaluation in a diverse population (MUSIC), which indicated a similar safety profile.

2.4.2 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.

2.4.3 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 2-7.

Table 2-7 Exposure of Special Populations Included or not in Pivotal 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 (MUSIC)

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

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Method Used to Calculate Exposure

Not applicable.

2.5.2 Exposure

Approval on the EEA for Beyfortus was received on 31 October 2022 for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.

At the data lock point of this RMP, no global post-marketing patient exposure data were available.

2.6 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.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

2.7.1.1 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 are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers.

- **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). 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 characterise this AESI which will continue to be closely monitored as part of routine pharmacovigilance activities. There are no additional pharmacovigilance activities or additional risk minimisation 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. Increased binding efficiency of virus-antibody complexes to Fc receptor-bearing cells and excessive Fc-mediated effector functions may promote increased viral entry into cells (ADE of infection) and enhanced inflammation (ADE of disease), respectively. Antibody-dependent enhancement (ADE) could potentially occur when non-neutralising antibodies or antibodies in sub-neutralising concentrations bind to viral antigens without blocking or clearing infection (Lee et al 2020). 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. 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. Additionally, the incidence of any medically attended RSV LRTI in the second year for MELODY study subjects (in the setting of low serum concentration of nirsevimab from Day 361 to 511 post dose), was low and balanced across nirsevimab and placebo groups to suggest no evidence of ADE in clinical trials. 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 were 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.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The Following Topics were Classified as Safety Concerns in the Initial EU RMP and will not be Updated:

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.

2.7.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Long-term safety previously classified as missing information is removed from the list of safety concerns.

During review of the marketing authorisation application (EMEA/H/C/005304/0000), long-term safety was added as “missing information” and MELODY (D5290C00004) and MEDLEY (D5290C00005) were included as additional pharmacovigilance activities. Final long-term safety data from these studies are consistent with data up to Day 360, with no change to the favourable safety profile described in the previous submissions. Safety results from the second RSV season (Day 362 to 511) in MELODY did not show any increase in the cases of MA RSV LRTI and no increased severity of disease for infants administered nirsevimab compared with infants administered placebo.

2.7.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

2.7.3.1 Presentation of Important Identified Risks and Important Potential Risks

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

2.7.3.2 Presentation of Missing Information

Not applicable. There is no safety concern considered missing information.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the Safety Concerns

A summary of the safety concerns for nirsevimab is presented in Table 2-8.

Table 2-8 Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

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

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities

AstraZeneca undertakes routine pharmacovigilance activities consistent with the 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-authorisation period in order to characterise 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 2.7.1.1).

Other Forms of Routine Pharmacovigilance Activities:

Continuous and thorough reviews of thrombocytopaenia as an AESI (refer to Section SVII 2.7.1.1) will be conducted as part of the close monitoring of this topic. Data from these reviews will be summarised in the PSURs.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The following additional pharmacovigilance activities planned for nirsevimab are shown in Table 3-1.

Table 3-1 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 – Not applicable				

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

5 PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

Not applicable.

5.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable

6 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 SmPC and its package leaflet give essential information to healthcare professionals and caregivers for infants and children 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 EPAR.

6.1 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 and children up to 24 months of age who remain vulnerable to severe RSV disease through their second 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 https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf

6.2 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.

6.2.1 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 6-1). 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.

Table 6-1 List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	None
Missing Information	None

6.2.2 Summary of Important Risks and Missing Information

Not applicable.

6.2.3 Post-authorisation Development Plan

6.2.3.1 Studies Which are Conditions of the Marketing Authorisation

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

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

NOT APPLICABLE