EU RISK MANAGEMENT PLAN (RMP) FOR

Clesrovimab Intramuscular Injection

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 08-May-2024

Date of final sign off: 11-Sep-2025

Rationale for submitting an updated RMP:

Not applicable

Summary of significant changes in this RMP:

Not applicable

Other RMP versions under evaluation:

Not applicable

QPPV name*:* Peter De Veene, MD

QPPV signature: see signature page

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ATC	Anatomical Therapeutic Chemical classification system
CI	Confidence interval
CHD	Congenital heart disease
CLD	Chronic lung disease
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GLP	Good Laboratory Practice
ICH	International Conference on Harmonization
ICU	Intensive care unit
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
LRTI	Lower respiratory tract infection
mAb	Monoclonal antibody
N/A	Not Applicable
PAES	Post-authorization Efficacy Study
PK	Pharmacokinetics
PD	Pharmacodynamic
QPPV	Qualified Person for Pharmacovigilance
RBC	Red blood cells
RMP	Risk Management Plan
RSV	Respiratory syncytial virus
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) (INN or Generic name)	Clesrovimab
Pharmacotherapeutic group(s) (ATC Code)	J06BD10
Marketing Authorisation Applicant	Merck Sharp & Dohme B.V.
Number of medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	ENFLONSIA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody
	Summary of mode of action: Clesrovimab is a fully human immunoglobulin G1 kappa (IgG1κ) neutralizing monoclonal antibody with a triple amino acid substitution (YTE) in the Fc region which increases binding to the neonatal Fc receptor leading to an extended serum half-life. Clesrovimab provides passive immunity by targeting the RSV outer membrane fusion (F) protein to prevent viral entry into cells. Clesrovimab binds to a conserved epitope on antigenic site IV on the fusion F protein. Clesrovimab binds to RSV pre-fusion F glycoprotein and post-fusion F glycoprotein with equilibrium dissociation constant values (K_D) of 71 pM and 480 pM, respectively.
	Important information about its composition: Clesrovimab is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Full list of excipients: Histidine Histidine hydrochloride monohydrate Arginine hydrochloride Sucrose Polysorbate 80 (E433) Water for injections
Hyperlink to the Prescribing Information	See proposed Prescribing information in Module 1.3.1
Indication(s) in the EEA	ENFLONSIA is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.

Table I.1: Product Overview

Dosage in the EEA	Neonates and infants: first RSV season The recommended dose is 105 mg administered as a single 0.7 mL intramuscular (IM) injection. For neonates and infants born during the RSV season, ENFLONSIA should be administered starting from birth. For infants born outside the RSV season, it should be administered once prior to the start of their first RSV season (see section 5.1).
Pharmaceutical form(s) and strengths	Solution for injection in a pre-filled syringe Clear to slightly opalescent, colourless to slightly yellow solution, with a pH of 5.5 – 6.5, and an osmolality of 320 – 420mOsm/kg. Each pre-filled syringe contains 105 mg of clesrovimab in 0.7mL.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

Indication

ENFLONSIA is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.

Incidence

RSV is the most common cause of bronchiolitis, lower respiratory tract infections (LRTIs), and hospitalization in infants. Most infants hospitalized with RSV infection have no predisposing risk factors and are healthy [Ref. 5.4: 03R4JG]. A prospective observational cohort study followed children for 24 months from birth in 8 countries around the globe and found an incidence rate of 7.4, 5.5, and 2.9 cases/100-person-years for first episode of RSV-LRTI among children 0-5, 6–11, and 12–23 months of age, respectively [Ref. 5.4: 08LRDB]. Although incidence rates varied by country and by age group, overall, rates tended to be higher in the youngest age group and in lower-income settings. Globally, and based on 2019 worldwide population estimates, 33.0 million (95% CI: 25.4 – 44.6) episodes of RSV occur annually in children under 5 years of age, including 3.6 million (95% CI: 2.9 – 4.6) resulting in hospitalization; 61% of these hospitalizations occur in infants [Ref. 5.4: 087V3J].

RSV is estimated to cause 28% of acute LRTIs and 13% to 22% of deaths from acute LRTIs in children under 5 years of age worldwide [Ref. 5.4: 04Q7DF]. Mortality associated with RSV infection is significant, with an estimated 101,400 (95% CI: 84,500 – 125,200) childhood deaths worldwide annually [Ref. 5.4: 087V3J]. The overwhelming majority of these deaths occur in low- and middle-income countries, where underreporting and at-home deaths are more common; therefore, the number of deaths due to RSV worldwide is likely higher [Ref. 5.4: 087V3J].

In the European Union (EU), it is estimated that about 245,244 (95% CI: 224,688 – 265,799) RSV-associated hospitalizations occur every year in children under 5 years of age, with most cases observed in children aged under 1-year (75%), followed by those aged 1–2 years of age (21%) [Ref. 5.4: 08MWJT]. The higher RSV-associated hospitalization rates (71.6 per 1000 population) are observed among the youngest age group (0 to 2 months of age), and rates decrease as children get older (38.9 per 1000 among those 3 to 5 months old, 17.6 per 1000 among those 6 to 11 months old, 5 per 1000 among those 12 to 35 months old and 1 per 1000 among those 36 to 59 months old). Overall, it is estimated that 10 out of 1000 children aged 0 to 59 months living in the EU are hospitalized due to RSV every year. Approximately 60% of the estimated annual RSV-associated hospitalizations in children <5 years in the EU occur in France, the United Kingdom, Germany, and Italy [Ref. 5.4: 08MWJT].

In the US, RSV causes approximately 2.1 million outpatient visits, between 58,000 to 80,000 hospitalizations, and 100 – 300 deaths in children <5 years of age annually, with most cases in the younger age groups [Ref. 5.4: 03R4JG, 05JB5D, 08CGH8, 08CGHY]. During the 2014 – 2015 RSV season, it was estimated that 49,000 – 59,000 RSV-associated

hospitalizations occurred in children <2 years of age in the US, with higher hospitalization rates observed in younger age groups [Ref. 5.4: 08PL98]. Furthermore, among children <5 years of age, those <1 year experienced a higher RSV-associated mortality rate compared to those 1 to 4 years of age (3.1 vs 0.1 deaths per 100,000 person-years) [Ref. 5.4: 04Q9DN].

Beyond hospitalizations, RSV infection is a significant driver of outpatient health care utilization in infants. In a prospective cohort of approximately 1,000 full-term healthy infants born between July 1, 2017 and April 1, 2020 in Spain, Finland, England, Scotland, and the Netherlands, Wildenbeest et al (2023) estimated an incidence rate of 12.1 per 1,000 infants per month for RSV-associated medical attendance [Ref. 5.4: 08N5LM]. Furthermore, during the 2022 – 2023 RSV season, a community-based surveillance study implemented among 55 primary care pediatricians from five Italian regions showed that 38% (246/650) of children under five years of age with acute respiratory symptoms tested positive for RSV by RT-qPCR [Ref. 5.4: 08N5LL].

Prevalence

RSV may cause frequent reinfections because of the lack of long-term immunity after infection. It is estimated that RSV has infected ~90% of children at least once within their first 2 years of life. Infants are especially vulnerable to developing LRTIs with ~40% of primary infection presenting as bronchiolitis or pneumonia [Ref. 5.4: 08NPDM, 03PFZR, 04Q7HH]. In addition, children who had RSV-associated bronchiolitis or pneumonia may have a higher risk of subsequently developing chronic conditions such as allergic rhino-conjunctivitis [Ref. 5.4: 04HFQT], recurrent wheezing, and asthma [Ref. 5.4: 04HFSP, 08BK86, 0503JQ, 08MY0J, 08MY0K].

Demographics in the proposed indication and risk factors for the disease

RSV is one of the most common respiratory viruses that infects children around the world. Younger age is a risk factor identified for severe disease [Ref. 5.4: 08NPBV, 03R4JG]. Infants under 6 months of age, and especially those under 2 months of age, present the highest incidence of RSV-associated hospitalization (14.7 (95% CI: 13.6 – 15.9) hospitalized per 1000 children <6 months old and 18.9 (95% CI: 17.0 – 20.9) per 1000 children <2 months old) [Ref. 5.4: 05JB5D]. Studies have also identified risk factors associated with higher morbidity and mortality. Specifically, prematurity, congenital heart disease, and chronic lung disease account for high-risk groups with increased risk of complications including RSV-associated hospitalization; RSV-associated mortality in children with these conditions is also high [Ref. 5.4: 08NPDZ, 04Q7H4]. For instance, one study showed that infants with RSV-associated disease had twice the risk of death for those born premature (≤35 weeks gestational age) and/or with low birth weight (<2500g) as compared to infants born at ≥37 weeks gestational age and weighing ≥2500g [Ref. 5.4: 03Q5XJ].

The main existing treatment options

There is no specific treatment for RSV; however, passive immunization with a neutralizing monoclonal antibody (mAb) against the RSV F protein is a proven prophylaxis approach in infants [Ref. 5.4: 04HGVB, 08HM0F]. Currently, two anti-F protein mAbs are approved for use:

1) Palivizumab (Synagis®) is approved in the EU, US, and other countries [Ref. 5.4: 08PG23, 08PG24, 04HGV6] for the prevention of serious LRTI caused by RSV in infants and children with medical conditions that place them at risk of complications from this disease. Palivizumab is administered monthly during the RSV season via IM injections. Palivizumab has only been studied in children <2 years of age with underlying health conditions (e.g., children born with a history of premature birth ≤35 weeks, children ≤2 years of age with chronic lung disease [CLD] or congenital heart disease [CHD]).

2) Nirsevimab (Beyfortus™) has been approved in the EU, US, and other countries for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season [Ref. 5.4: 08PG0X, 08PG0Z, 082WC8, 082W2Z].

In addition to passive immunoprophylaxis with mAbs, a vaccine containing RSV stabilized prefusion F proteins (Abrysvo®) has been approved in the EU, US, and other countries for prevention of RSV in infants through maternal immunization during pregnancy (timing of administration may vary by region) [Ref. 5.4: 08PG34, 08PG0T].

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

RSV spreads via respiratory droplets from person to person. The incubation period ranges from 2 to 8 days, depending on factors such as age or previous exposure to the virus. After inoculation into the nasopharyngeal or conjunctiva mucosa, the virus enters the respiratory tract targeting epithelial cells. Approximately 30–40% of infants infected with RSV will have disease progression involving the lower respiratory tract by aspiration of RSV infected epithelial cells or by cell to cell spread of the virus. LRTI is characterized by difficulty breathing, cough, tachypnea, wheezing, crackles, use of accessory muscles, and nasal flaring [Ref. 5.4: 04Q7HH, 08NPDM, 08NPBV].

LRTI often involves hospitalization and hospitalization may have a variable course of illness. A median RSV-associated hospital length of stay ranges from 2 to 5 days [Ref. 5.4: 05JB5D, 08PL98]. Globally, rates of hospitalization for RSV-associated acute LRTI peaked in children aged 0-3 months (especially at 28 days to 3 months of age) [Ref. 5.4: 087V3J]. RSV-associated complications during hospitalization include ICU admission, use of ventilatory support or oxygen supplementation, or even death.

A study report of age-specific incidence rates of RSV-related disease in Europe estimated that infants required more ICU admission compared to other age-groups [Ref. 5.4: 04Q7HH, 08NPDM, 08NPBV, 08NPCV]. Among children <5 years of age hospitalized for acute LRTI in the US, frequency of supplemental oxygen use, ICU admission, and mechanical ventilation were higher among those who tested positive for RSV than those who tested negative [Ref. 5.4: 08P7W4]. Substantial unmeasured burden of RSV-associated mortality exists in the world as one in every 50 deaths in children aged 0–60 months and one in every 28 deaths in children aged 28 days–6 months could be attributed to RSV [Ref. 5.4: 087V3J]. RSV-associated in-hospital deaths are also estimated to be higher in infants born in low-income countries compared to high or upper middle-income countries (including EU) [Ref. 5.4: 087V3J].

Important co-morbidities

Preterm infants, and those with underlying medical conditions, are predisposed to severe RSV infection. Specifically, children at increased risk for severe RSV disease include those born preterm irrespective of other co-morbidities (especially those born before 29 weeks gestation), those born preterm with CLD, and infants with hemodynamically significant CHD [Ref. 5.4: 05JB5D, 04HGV6, 058F0Y, 03Q5XB, 056MHC, 03R4JC]. Studies have demonstrated that infants born before 29 weeks have 2 to 4 times higher rates of RSV-associated hospitalization compared to later preterm infants [Ref. 5.4: 05JB5D, 058F0Y, 03Q5XB, 056MHC]. Data from the New Vaccine Surveillance Network (2016-2020) showed that among children <2 years of age, RSV-associated hospitalization rates among those born at 32-34 weeks of gestation (17.5 [95% CI: 14.8–20.2] per 1000 children), 29-31 weeks of gestation (19.3 [95% CI: 14.7–23.7] per 1000 children), and <29 weeks of gestation (24.9 [95% CI: 19.3–30.6] per 1000 children) were 2.33, 2.57, and 3.32 times higher than those born at ≥37 weeks of gestation (7.5 [95% CI: 7.2–7.9] per 1000 children), respectively [Ref. 5.4: 08P7W4]. Furthermore, children with CLD have high rates of RSV hospitalization until 2 years of age (388 and 73 RSV hospitalizations per 1000 children during their first and second year of life, respectively). CLD was identified as the strongest risk factor (incidence rate ratio of 10.7; 95% CI: 8.4–13.6) for RSV-associated hospitalization in a multivariate analysis adjusted for medical and demographic characteristics in children under 1 year of age. For children with CLD and CHD in their second year of life, there is a 20-fold (95% CI: 11.1–33.7) and 5-fold (95% CI: 3–7.9) increased risk of RSV hospitalization, respectively, as compared to low-risk children [Ref. 5.4: 03Q5XB].

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

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

The nonclinical testing strategy of clesrovimab has been adequately characterized through a variety of in vitro and in vivo studies consistent with ICH S6(R1) guidance: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. The safety and local tolerance of clesrovimab was evaluated in 2 pivotal GLP studies, including a 2-week IV and IM repeat dose toxicity study in rats, and a single dose IM local tolerance study in rats. Clesrovimab was well tolerated in rats, with no systemic toxicity. Local tolerance following IV or IM administration was consistent with a well-tolerated formulation. Additionally, clesrovimab did not bind to other antigens in in vitro off target binding assays in whole blood (RBCs and platelets) and the lack of specific staining by clesrovimab in adult, juvenile, or neonatal human tissues in cross-reactivity studies identified no concerns for off-target binding. Developmental and reproductive toxicity, juvenile toxicity, genotoxicity, phototoxicity, and carcinogenicity studies were not conducted as there was no cause for concern identified, and these studies are not required for biotechnology-derived products directed against foreign targets (i.e., bacterial, viral, etc.).

Overall, there were no key safety findings in any of the nonclinical studies conducted with clesrovimab.

Table SII.1: Summary of Important Safety Findings from Nonclinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
None	Not Applicable

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The clesrovimab pediatric clinical development program consists of 4 clinical studies (2 completed and 2 ongoing) as of the data lock point of this RMP.

The 2 completed studies include:

- MK-1654-002: Phase 1b/2a study that evaluated the safety and PK of single ascending doses of clesrovimab in healthy preterm and full-term infants

- MK-1654-008: Phase 1 study that evaluated the safety and tolerability of a single dose of clesrovimab in Chinese infants, children, and adults

The 2 ongoing studies include:

- MK-1654-004: a Phase 2b/3 placebo-controlled study evaluating the safety, efficacy, and PK of clesrovimab in healthy preterm and full-term infants;

- MK-1654-007: a Phase 3 palivizumab-controlled study evaluating the safety, efficacy, and PK of clesrovimab in infants and children at increased risk for severe RSV disease.

Overall, these 4 studies enrolled and randomized a diverse population of 4637 preterm and full-term infants entering their first RSV season across approximately 284 clinical study sites in 34 countries. A total of 2947 healthy infants and infants at increased risk for severe RSV disease received clesrovimab, including >2500 infants with at least 240 days of safety follow-up post Dose 1 in RSV Season 1. This 240-day duration represents approximately 5 half-lives of clesrovimab in infants. The safety database represents a robust dataset that allows for a comprehensive assessment of safety to support an RSV Season 1 indication for neonates and infants.

Exposure to clesrovimab is summarized in Table III-1, Table III-2, and Table III-3.The summaries include information from the pediatric studies and cohorts that inform the proposed indication, including MK-1654-002 (Panels D and E – infants received 100 mg dose), MK-1654-008 (Panel C – infants received 105 mg dose), MK-1654-004 (infants received 105 mg dose) and MK-1654-007 (infants received 105 mg dose).

Table SIII.1: Age Group and Gender

Age Group	Participants		
	Male	Female	Total
0 to <28 days	200	185	385
≥28 days to <6 months	1,022	979	2,001
≥6 months to <9 months	222	222	444
≥9 months to ≤12 months	54	63	117
Total	1,498	1,449	2,947

Participants randomized and dosed with clesrovimab in RSV season 1 from ongoing and completed studies: MK-1654-002 (Panels D and E), MK-1654-004 (Data cut-off =04Mar2024), MK-1654-007 (Data cut-off= 05Feb2024), MK-1654-008 (Panel C).

Table SIII.2: Dose

Dose of Exposure	Participants
100 mg IM	64
105 mg IM	2,883
Total	2,947

Participants randomized and dosed with clesrovimab in RSV season 1 from ongoing and completed studies: MK-1654-002 (Panels D and E), MK-1654-004 (Data cut-off =04Mar2024), MK-1654-007 (Data cut-off= 05Feb2024), MK-1654-008 (Panel C).

In studies MK-1654-002 and MK-1654-008, participants were dosed with Process 1 formulation. In studies MK-1654-004 and MK-1654-007, participants were dosed with Process 2 formulation.

In study MK-1654-002 (Panels D and E), infants received a 100 mg IM dose of MK-1654 and in studies MK-1654-004, MK-1654-007 and MK-1654-008 (Panel C), infants received a 105 mg IM dose of MK-1654.

Table SIII.3: Race Origin

Race	Participants
American Indian Or Alaska Native	57
Asian	753
Black Or African American	422
Multiple	366
Native Hawaiian Or Other Pacific Islander	6
White	1,332
Missing	11
Total	2,947

Participants randomized and dosed with clesrovimab in RSV season 1 from ongoing and completed studies: MK-1654-002 (Panels D and E), MK-1654-004 (Data cut-off =04Mar2024), MK-1654-007 (Data cut-off= 05Feb2024), MK-1654-008 (Panel C).

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

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Recipients of any vaccine or mAb for the prevention of RSV, including receipt of maternal RSV vaccination during the mother's pregnancy	To avoid confounding the evaluation of the safety and efficacy of clesrovimab.	No	For individuals who received an RSV mAb or any RSV vaccine, including infants whose mothers received an RSV vaccine, it is not anticipated that the safety and efficacy profile of clesrovimab would differ.
Known hypersensitivity to any component of clesrovimab	These infants may be at higher risk of hypersensitivity reactions upon exposure.	No	The product labeling describes that clesrovimab is contraindicated in infants with known hypersensitivity to any of its components.
Participants with a life expectancy <6 months	To avoid confounding the evaluation of the safety and efficacy of clesrovimab.	No	It is not anticipated that the safety profile of clesrovimab would differ in these individuals.
Participants with renal impairment	To ensure the study safety results were not confounded by pre-existing illnesses.	No	As IgG mAb are not cleared by the kidney, it is not anticipated that the safety profile of clesrovimab would differ in these individuals.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Participants with bleeding disorder contraindicating intramuscular administration	To ensure the study safety results were not confounded by pre-existing illnesses.	No	The risk of bleeding in persons with underlying coagulation disorders exists for any product that is administered intramuscularly [Ref. 5.4: 05MBMT], is well characterized, and considered common medical knowledge, as is medical management of this risk.
Participants with hepatic impairment	To ensure the study safety results were not confounded by pre-existing illnesses.	No	As IgG mAb are not cleared by the liver, it is not anticipated that the safety profile of clesrovimab would differ in these individuals.
Chronic seizure disorder	To ensure the study safety results were not confounded by pre-existing illnesses.	No	It is not anticipated that the safety profile of clesrovimab would differ in these individuals.
Patients who had a recent illness with rectal temperature ≥100.5°F (≥38.1°C) or axillary temperature ≥100.0°F (≥37.8°C) within 72 hours predose.	To avoid confounding the evaluation of the safety and efficacy of clesrovimab.	No	It is not anticipated that the safety and efficacy profile of clesrovimab would differ in these individuals.
Severe immunodeficiency or severely immunocompromised patients	To avoid confounding the evaluation of the safety and efficacy of clesrovimab.	No	It is not anticipated that the safety and efficacy profile of clesrovimab would differ in these individuals.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

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.

Based on a sample size of 2947 infant participants who received clesrovimab in the clinical development program, there is a 95% chance of observing an adverse reaction with an underlying incidence of 0.1% (1/1000) or greater. Adverse reactions that occur at a lower incidence, or with a latency greater than 12 months, are less likely to be detected.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not relevant to be included in the clinical development program as clesrovimab is intended to be indicated for infants.
Breastfeeding women	
Individuals with relevant comorbidities:	
• Individuals with hepatic impairment	Not included in the clinical development program
• Individuals with renal impairment	Not included in the clinical development program
• Immunocompromised individuals	Individuals with severe immunodeficiency or severely immunocompromised were not included in the clinical development program, including but not limited to: AIDS (CD4 percentage <25%, or history of AIDS-Defining Condition), leukemia, myeloproliferative disorder, or other malignancy and receiving or expected to receive chemotherapy during the study, status post solid-organ or bone marrow transplantation and on a systemic immunosuppressive regimen, severe combined immunodeficiency.
• Individuals with congenital heart disease (CHD)	In MK-1654-007, a total of 101 (11.3%) participants had CHD.
• Individuals with chronic lung disease (CLD)	In MK-1654-007, a total of 250 (27.9%) participants had CLD.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

As of the DLP, this product is not marketed in any country worldwide.

SV.1.1 Method Used to Calculate Exposure

Not applicable

SV.1.2 Exposure

Not applicable

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

Potential for Misuse for Illegal Purposes

Clesrovimab is available only through prescribing physicians and other health care providers with prescriptive authority. Neither clesrovimab nor its components are known to possess addictive properties.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

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

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

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

- Injection site erythema, injection site swelling, injection site pain, urticaria, rash[1]

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

- Serious hypersensitivity reactions including anaphylaxis

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

Table SVII.1.2.1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety concern	Benefit risk impact
Important identified risks	
None	N/A
Important potential risks	
None	N/A
Missing information	
None	N/A

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

Not applicable

[1] defined by the following grouped preferred terms: rash, rash erythematous, rash papular, rash maculo-papular, rash vesicular, dermatitis allergic, drug eruption

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

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

There are no safety concerns identified for clesrovimab.

SVII.3.2 Presentation of the Missing Information

Not applicable

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

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

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

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Not applicable

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance studies that are required for clesrovimab.

III.3 Summary Table of Additional Pharmacovigilance Activities

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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
N/A	N/A	N/A	N/A	N/A

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for clesrovimab.

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

Risk Minimisation Plan

There are no safety concerns identified for clesrovimab as described in Part II Module SVII Summary of the Safety Concerns of this Risk Management Plan. Routine risk minimisation activities are conducted as for all Company products.

V.1 Routine Risk Minimisation Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
None	N/A

V.2 Additional Risk Minimisation Measures

This section is not applicable as there are no safety concerns for clesrovimab.

V.3 Summary of Risk Minimisation Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
None	N/A	N/A

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for ENFLONSIA (clesrovimab)

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

ENFLONSIA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and caregivers for infants on how ENFLONSIA should be used.

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

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

I. The Medicine and What it is Used for

ENFLONSIA is authorised for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season (see SmPC for the full indication). It contains clesrovimab as the active substance and it is given by intramuscular injection.

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

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

Important risks of ENFLONSIA, together with measures to minimise such risks and the proposed studies for learning more about ENFLONSIA'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 caregivers of 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 (e.g., with or without prescription) can help to minimise its risks.

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

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

II.A List of Important Risks and Missing Information

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

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks and Missing Information

There are no important identified risks, important potential risks or missing information for ENFLONSIA.

II.C Post-Authorisation Development Plan

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

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

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

There are no studies required for ENFLONSIA.

REFERENCES

[Ref. 5.4: 03PFZR] Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. AJDC 1986;140:543-6.

[Ref. 5.4: 03Q5XB] Boyce TG, Mellen BG, Mitchel EF Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000;137:865-70.

[Ref. 5.4: 03Q5XJ] Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr 2003;143:S127-S132.

[Ref. 5.4: 03R4JC] Chang R-KR, Chen AY. Impact of palivizumab on RSV hospitalizations for children with hemodynamically significant congenital heart disease. Pediatr Cardiol 2010;31(1):90-5.

[Ref. 5.4: 03R4JG] Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360(6):588-98.

[Ref. 5.4: 04HFQT] Diez-Domingo J, Perez-Yarza EG, Melero JA, Sanchez-Luna M, Aguilar MD, Blasco AJ, et al. Social, economic, and health impact of the respiratory syncytial virus: a systematic search. BMC Infect Dis. 2014 Oct 30;14:544.

[Ref. 5.4: 04HFSP] Polack FP. The changing landscape of respiratory syncytial virus. Vaccine. 2015 Nov 25;33(47):6473-8.

[Ref. 5.4: 04HGV6] American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014 Aug;134(2):e620-38.

[Ref. 5.4: 04HGVB] Graham BS, Modjarrad K, McLellan JS. Novel antigens for RSV vaccines. Curr Opin Immunol. 2015 Aug;35:30-8.

[Ref. 5.4: 04Q7DF] Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD. et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017 Jul 6. pii: S0140-6736(17)30938-8.

[Ref. 5.4: 04Q7H4] Figueras-Aloy J, Manzoni P, Paes B, Simoes EA, Bont L, Checchia PA, et al. Defining the risk and associated morbidity and mortality of severe respiratory syncytial virus infection among preterm infants without chronic lung disease or congenital heart disease. Infect Dis Ther. 2016 Dec;5(4):417-452.

[Ref. 5.4: 04Q7HH] Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001 Jun 21;344(25):1917-28.

[Ref. 5.4: 04Q9DN] Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003 Jan 8;289(2):179-86.

[Ref. 5.4: 0503JQ] Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med. 2013 May 9;368(19):1791-9. Erratum in: N Engl J Med. 2016 Jun 16;374(24):2406.

[Ref. 5.4: 056MHC] Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks gestation or earlier: hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med. 2000 Jan;154:55-61.

[Ref. 5.4: 058F0Y] Hall CB, Weinberg GA, Blumkin AK, Edwards KM, Staat MA, Schultz AF, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics. 2013 Aug;132(2):e341-8.

[Ref. 5.4: 05JB5D] Rha B, Curns AT, Lively JY, Campbell AP, Englund JA, Boom JA, et al. Respiratory syncytial virus-associated hospitalizations among young children: 2015-2016. Pediatrics. 2020 Jul;146(1):e20193611.

[Ref. 5.4: 05MBMT] Makris M, Conlon CP, Watson HG. Immunization of patients with bleeding disorders. Haemophilia. 2003;9:541-6.

[Ref. 5.4: 082W2Z] Domachowske J, Madhi SA, Simoes EAF, Atanasova V, Cabanas F, Furuno K, et al. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity [correspondence]. N Engl J Med. 2022 Mar 3;386(9):892-4.

[Ref. 5.4: 082WC8] Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med. 2022 Mar 3;386(9):837-46.

[Ref. 5.4: 087V3J] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022 May 28;399:2047-64.

[Ref. 5.4: 08BK86] Rosas-Salazar C, Chirkova T, Gebretsadik T, Chappell JD, Peebles RS, Dupont WD, et al. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study. Lancet. 2023 May 20;401:1669-80.

[Ref. 5.4: 08CGH8] McLaughlin JM, Khan F, Schmitt HJ, Agosti Y, Jodar L, Simoes EAF, et al. Respiratory syncytial virus-associated hospitalization rates among US infants: a systematic review and meta-analysis. J Infect Dis. 2022 Mar 15;225:1100-11.

[Ref. 5.4: 08CGHY] Hansen CL, Chaves SS, Demont C, Viboud C. Mortality associated with influenza and respiratory syncytial virus in the US, 1999-2018. JAMA Netw Open. 2022 Feb 28;5(2):e220527.

[Ref. 5.4: 08HM0F] Jones JM, Fleming-Dutra KE, Prill MM, Roper LE, Brooks O, Sanchez PJ, et al. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the advisory committee on immunization practices - United States, 2023. MMWR Morb Mortal Wkly Rep. 2023 Aug 25;72(34):920-5.

[Ref. 5.4: 08LRDB] Langley JM, Bianco V, Domachowske JB, Madhi SA, Stoszek SK, Zaman K, et al. Incidence of respiratory syncytial virus lower respiratory tract infections during the first 2 years of life: a prospective study across diverse global settings. J Infect Dis. 2022 Aug 1;226:374-85.

[Ref. 5.4: 08MWJT] Del Riccio M, Spreeuwenberg P, Osei-Yeboah R, Johannesen CK, Fernandez LV, Teirlinck AC, et al. Burden of respiratory syncytial virus in the European Union: estimation of RSV-associated hospitalizations in children under 5 years. J Infect Dis. 2023 Dec 1;228:1528-38.

[Ref. 5.4: 08MY0J] Mauskopf J, Margulis AV, Samuel M, Lohr KN. Respiratory syncytial virus hospitalizations in healthy preterm infants: systematic review. Pediatr Infect Dis J. 2016 Jul;35(7):e229-38.

[Ref. 5.4: 08MY0K] Shi T, Ooi Y, Zaw EM, Utjesanovic N, Campbell H, Cunningham S, et al. Association between respiratory syncytial virus-associated acute lower respiratory infection in early life and recurrent wheeze and asthma in later childhood. J Infect Dis. 2020;222(Suppl 7):S628-33.

[Ref. 5.4: 08N5LL] Scarpaci M, Bracaloni S, Esposito E, De Angelis L, Baglivo F, Casini B, et al. RSV disease burden in primary care in Italy: A multi-region pediatric study, winter season 2022-2023. Influenza Other Respir Viruses. 2024;18:e13282.

[Ref. 5.4: 08N5LM] Wildenbeest JG, Billard MN, Zuurbier RP, Korsten K, Langedijk AC, van de Ven PM, et al. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. Lancet Respir Med. 2023 Apr;11:341-53.

[Ref. 5.4: 08NPBV] Meissner HC. Principles and practice of pediatric infectious diseases. 4th ed. Long SS, Pickering LK, Prober CG, editors. London (United Kingdom): Elsevier Inc.; c2012. Chapter 33, Bronchiolitis; p. 231-5.e4.

[Ref. 5.4: 08NPCV] Arinze JT and Verhamme K. DARWIN EU - age-specific incidence rates of RSV-related disease in Europe. Rotterdam (Netherlands): DARWIN EU Coordination Centre; 2024 Mar. 96 p.

[Ref. 5.4: 08NPDM] Jain H, Schweitzer JW, Justice NA. Respiratory syncytial virus infection in children [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan [Cited 2024 Sep 10]. 6 p. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459215/.

[Ref. 5.4: 08NPDZ] Meissner HC. Selected populations at increased risk from respiratory syncytial virus infection. Pediatr Infect Dis J. 2003 Feb;22(2):S40-5.

[Ref. 5.4: 08P7W4] Curns AT, Rha B, Lively JY, Sahni LC, Englund JA, Weinberg GA, et al. Respiratory syncytial virus-associated hospitalizations among children <5 years old: 2016 to 2020. Pediatrics. 2024 Mar;153(3):e2023062574.

[Ref. 5.4: 08PG0T] U.S. Prescribing Information: ABRYSVO (respiratory syncytial virus vaccine) for injection, for intramuscular use: Aug 2024.

[Ref. 5.4: 08PG0X] E.U. Summary of Product Characteristics: Beyfortus 50 mg solution for injection in pre-filled syringe, Beyfortus 100 mg solution for injection in pre-filled syringe; AstraZeneca AB, Sodertalje, Sweden: [date available online only]. Available from: https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf.

[Ref. 5.4: 08PG0Z] U.S. Prescribing Information: BEYFORTUS (nirsevimab-alip) injection, for intramuscular use: Aug 2024.

[Ref. 5.4: 08PG23] E.U. Summary of Product Characteristics: Synagis 50 mg/0.5 ml solution for injection, Synagis 100 mg/1 ml solution for injection; AstraZeneca AB, Sodertalje, Sweden: [date available online only]. Available from: https://www.ema.europa.eu/en/documents/product-information/synagis-epar-product-information_en.pdf.

[Ref. 5.4: 08PG24] U.S. Prescribing Information: SYNAGIS (palivizumab) injection, for intramuscular use: Nov 2021.

[Ref. 5.4: 08PG34] E.U. Summary of Product Characteristics: Abrysvo powder and solvent for solution for injection, Respiratory syncytial virus vaccine (bivalent, recombinant); Pfizer Europe MA EEIG, Bruxelles, Belgium: [date available online only]. Available from: https://www.ema.europa.eu/en/documents/product-information/abrysvo-epar-product-information_en.pdf.

[Ref. 5.4: 08PL98] Arriola CS, Kim L, Langley G, Anderson EJ, Openo K, Martin AM, et al. Estimated burden of community-onset respiratory syncytial virus-associated hospitalizations among children aged <2 years in the United States, 2014-15. J Pediatric Infect Dis Soc. 2020 Nov;9(5):587-95.

ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

This RMP Annex is not applicable.

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

This RMP Annex is not applicable.