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**The evolving science of Clesrovimab: pharmacological insights and clinical implications**

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**Key words:** Clesrovimab (MK-1654); Respiratory Syncytial Virus (RSV); monoclonal antibody; RSV prophylaxis; Lower Respiratory Tract Infection (LRTI).

**Abstract**

Clesrovimab (MK-1654) is a next-generation monoclonal antibody (mAb) engineered for the prophylaxis of Respiratory Syncytial Virus (RSV or HRSV), a major etiological agent of lower respiratory tract infections in newborns, the elderly, and immunocompromised individuals. Having received regulatory approval in the United States and the United Arab Emirates in 2025, and currently under review in additional global markets, Clesrovimab has demonstrated robust immunoprophylactic efficacy in clinical trials. A single-dose administration provides durable protection, a significant reduction in RSV-associated infections and hospitalizations versus placebo,

and a favorable safety profile with a lower incidence of adverse events (AEs) compared with existing standard-of-care interventions. This narrative review summarizes Clesrovimab's molecular characteristics and clinical development, outlining key improvements observed in late-phase trials. Relevant data were identified through a literature search of PubMed, Scopus, and ClinicalTrials.gov (2018–2025) using the keywords "Clesrovimab," "MK-1654," and "respiratory syncytial virus". A comparative analysis is presented with currently approved RSV-targeting mAbs, such as Palivizumab and Nirsevimab. The aim is to highlight Clesrovimab's potential as a novel preventive strategy against RSV infection, emphasizing its enhanced binding affinity for the viral fusion (F) protein, superior biodistribution within the respiratory tract, and capacity to provide more effective and sustained protection. These features support its promising role in reducing RSV-related morbidity and mortality among high-risk populations.

## Introduction

Clesrovimab (MK-1654) is an extended half-life IgG1 monoclonal antibody (mAb), derived from the fully human parental antibody RB1. Developed by Merck in 2023, it entered Phase III clinical trials in November 2024, demonstrating potent prophylactic and neutralizing activity against neonatal Lower Respiratory Tract Infections (LRTIs) caused by Respiratory Syncytial Virus (RSV), including in high-risk populations such as preterm infants and those with severe comorbidities. It provides immediate, complete, and durable passive immunization, with a safety and tolerability profile superior to that of various RSV vaccine candidates and other contemporary mAbs.[1]

Respiratory Syncytial Virus (RSV) is a non-segmented, negative-sense, single-stranded RNA virus with a lipid envelope, classified within the family Pneumoviridae and the genus *Orthopneumovirus*. It exhibits a seasonal distribution, with infection peaks typically occurring during the winter months in temperate climates, while maintaining continuous circulation in tropical regions. However, factors beyond climate, such as population immunity and social behavior, can influence both the onset and progression of RSV outbreaks, potentially altering established seasonal patterns. Notably, the COVID-19 pandemic has significantly impacted RSV epidemiology, leading to delayed outbreak peaks and modulating disease severity.[2,3] RSV is transmitted via airborne droplets or through contact with contaminated surfaces and is particularly prevalent in high-density environments such as pediatric hospitals. Following an incubation period of 4–6 days, the virus typically causes influenza-like symptoms affecting the Upper Respiratory Tract (URTI), but may progress to more severe forms involving the Lower Respiratory Tract (LRTI), such as bronchiolitis and pneumonia. These conditions are characterized by respiratory distress, initially presenting with rhinorrhea followed by a dry cough and wheezing, often accompanied by subcostal, intercostal, and supraclavicular retractions. In severe cases, due to significant respiratory distress, hospitalization in intensive care units may be required, where oxygen therapy or, in extreme situations, mechanical ventilation is administered.[4]

The most vulnerable populations include preterm infants, those younger than six months of age, individuals with chronic pulmonary disease, immunocompromised patients, and those with congenital heart defects.[4,5] RSV is recognized as the second leading cause of infant mortality beyond the neonatal period, with 99% of RSV-related deaths occurring in low- and middle-income countries.[5] Nonetheless, the majority of RSV-related hospitalizations occur in term-born infants and otherwise healthy children without prior comorbidities. Moreover, infection is not limited to the acute phase; approximately 70% of infants who experience severe RSV infection during the first

year of life go on to develop recurrent wheezing or bronchial asthma. In healthy adults, RSV usually results in mild symptoms; however, in elderly individuals with underlying health conditions, it can lead to severe respiratory complications.[5]

The RSV genome is approximately 15.2 kb in length and encodes 11 proteins, including three structural surface glycoproteins: G, F, and SH. The G glycoprotein is responsible for viral attachment and adherence to the host cell. The F (fusion) glycoprotein is essential for the fusion of the viral envelope with the host cell membrane of ciliated respiratory epithelial cells. It also determines the fusion of infected cells with neighboring cells, resulting in the formation of multinucleated syncytia.[6,7]

The virus is classified into two subtypes, RSV-A and RSV-B, primarily distinguished by antigenic variability in the G glycoprotein. In contrast, the F glycoprotein is highly conserved across both subtypes, making it the principal target for vaccine and mAb development.[2] The F glycoprotein exists in two forms: pre-fusion and post-fusion, with the transition occurring during viral membrane fusion with the host cell membrane. This change is triggered by specific signals, such as receptor interactions on the surface of respiratory epithelial cells or exposure to acidic environments.[8] Early RSV vaccines and therapeutic mAbs targeted antigenic sites present in the post-fusion conformation. However, it was not until 2011 that a stabilized pre-fusion conformation of the F protein was successfully achieved. This form elicited significantly higher titers of neutralizing antibodies *in vivo* due to the presence of more accessible and immunodominant antigenic sites. Once the protein undergoes conformational transition to its post-fusion state, these critical epitopes become structurally inaccessible.[9] Several antigenic sites have been identified on the pre-fusion F protein. Among these, site Ø is a highly maintained epitope and represents the primary therapeutic target for most current immunological interventions. Other key sites include site II and site IV. Notably, site IV demonstrates the lowest mutation rate among known antigenic regions of the F

protein, with 99.8% sequence identity across over 15,000 RSV-A and RSV-B isolates reported in GenBank.[10,11]

Given the persistent global burden of RSV disease and the recent advancements in immunoprophylaxis, particularly with the emergence of next-generation mAb, this narrative review aims to comprehensively summarize the molecular characteristics and clinical development of Clesrovimab. Specifically, it will outline key improvements observed in late-phase clinical studies and present a comparative analysis with currently approved RSV-targeting mAbs, such as Palivizumab and Nirsevimab. The ultimate objective is to highlight Clesrovimab's potential as a novel and highly effective preventive strategy against RSV infection.

To achieve these aims, a comprehensive literature search was performed in PubMed, Scopus, and ClinicalTrials.gov using the keywords "Clesrovimab," "MK-1654," "respiratory syncytial virus," and "RSV prophylaxis." Articles published between 2018 and May 2025 were considered, with emphasis on original research, clinical trials, and comprehensive reviews relevant to Clesrovimab's development and comparative efficacy.

### *Innovation and early clinical study results for RSV*

Clesrovimab is designed to be administered as a single-dose passive immunizing agent for high-risk individuals. Engineered to recognize and bind to antigenic site IV of the pre-fusion F-RSV glycoprotein, it has demonstrated the ability to neutralize various RSV strains expressing the F glycoprotein *in vitro*. Furthermore, it maintains a prolonged serum half-life due to modifications made to the parental RB1 mAb, specifically the substitution of three amino acids (YTE mutations) in the Fc fragment.[9,12] This mutation enhances binding to the neonatal Fc receptor (FcRn), reducing antibody degradation in lysosomes and promoting its recycling. This results in extended protection

against viral infection over an entire RSV season, as antibody titers typically decrease within months following natural exposure. Unlike other treatments that require multiple doses, Clesrovimab provides sustained immunity with a single Intramuscular (IM) administration.[1]

Factors such as safety, tolerability, and pharmacokinetics of Clesrovimab were assessed in two double-blind, placebo-controlled Phase I studies involving 152 healthy adult volunteers, randomized 3:1 to receive a single dose of MK-1654 or placebo in five cohorts, followed by experimental RSV inoculation. Doses ranging from 100 to 300 mg IM and 3000 mg Intravenously (IV) were administered, with participants being monitored and evaluated over the course of one year.[13] The results demonstrated that Clesrovimab was well tolerated, with a safety profile comparable to placebo. Serum concentrations increased in a dose-dependent manner, corresponding to elevated neutralizing antibody titers against the inoculated RSV strain. MK-1654 exhibited a prolonged serum half-life in adults, ranging from 73 to 91 days, with approximately 69% bioavailability at the 300 mg IM dose and a low Anti-Drug Antibody (ADA) response (2.6%) without associated Adverse Events (AEs). Recent studies also showed a half-life of approximately 44.9 days in both preterm and term-born healthy newborns.[14,15] In adults, the pharmacokinetics of MK-1654 was best described by a two-compartment model with first-order elimination. IM absorption followed a first-order rate process incorporating a lag time. Interindividual variability was included for key parameters such as clearance, central volume of distribution, and absorption rate constant (Ka). In the pediatric population, the population pharmacokinetic model indicated that the apparent terminal half-life in a typical infant is shorter than in adults. This difference is likely attributable to the rapid somatic growth occurring during the treatment period, which affects both the apparent volume of distribution and the overall elimination rate of the antibody.[16]

One of the most innovative aspects of Clesrovimab is its ability to penetrate the Epithelial Lining Fluid (ELF), the primary site of RSV infection.[13] Studies in human models have confirmed that the

drug neutralizes the virus directly within the respiratory tract, providing immediate and additional protection, superior to existing mAbs. This finding facilitated progression to Phase II/III trials, comparing Clesrovimab with placebo (NCT04767373) and with Palivizumab (NCT04938830).[10]

***Clinical efficacy of Clesrovimab***

The Phase IIb/III study MK-1654-004 involved 3,614 healthy newborns, both preterm and term-born, randomized 2:1 to receive a single 105 mg IM dose of Clesrovimab or placebo.[10]

The primary endpoint, as defined in the study protocols, was the incidence of Medically-Attended Lower Respiratory Tract Infections (MALRI) associated with RSV during the first 150 days post-administration. MALRI included clinically confirmed cases requiring outpatient or hospital care, providing a clinically meaningful measure of RSV disease burden and aligning with regulatory expectations for prophylactic efficacy in high-risk pediatric populations. The results demonstrated that Clesrovimab significantly reduced the incidence of MALRI and hospitalizations compared to placebo, with a favorable safety profile. The efficacy of Clesrovimab was 60.4% (95% Confidence Interval: 44.1, 71.9, $p<0.001$) and it reduced RSV-related hospitalizations (secondary endpoint) and RSV-related Lower Respiratory Infections (LRI) hospitalizations (tertiary endpoint) up to day 150 (5 months) by 84.2% (95% CI: 66.6, 92.6, $p<0.001$) and 90.9% (95% CI: 76.2, 96.5), respectively, compared to placebo. The incidence of AEs and Serious Adverse Events (SAEs) was comparable between the Clesrovimab and placebo groups, and no treatment- or RSV-related deaths occurred during the studies.[17,18]

A further Phase III study (MK-1654-007) compared the efficacy and safety of Clesrovimab with Palivizumab, the first mAb approved for RSV prevention. The study involved 896 newborns at increased risk for severe RSV disease, including those with Chronic Lung Disease (CLD),

Congenital Heart Disease (CHD), or prematurity (≤35 weeks), who were eligible for Palivizumab prophylaxis.[19] After randomization (1:1), participants received either a single IM dose of Clesrovimab (105 mg) or monthly doses of Palivizumab, with safety follow-up for up to 365 days after the first administration. Eligible patients who entered the second part of the study received Clesrovimab 210 mg IM, followed by 180 days of safety observation.

The primary endpoint of the study was to evaluate the safety and tolerability of Clesrovimab compared with Palivizumab, assessed by the proportion of participants experiencing Treatment-Emergent Adverse Events (TEAEs) and SAEs. Secondary endpoints included the incidence of RSV-associated MALRI and RSV-related hospitalizations through day 150 post-dose. As shown in Table 1, both treatments exhibited a comparable safety profile, with no treatment-related deaths or unexpected adverse events. The incidence of MALRI and RSV-related LRI requiring hospitalization was similar between Clesrovimab (3.6% and 1.3%, respectively) and Palivizumab (3.0% and 1.5%, respectively) up to day 150. Since a classic non-inferiority trial in high-risk newborns would have required an exceedingly large sample size in a limited population, the study employed a Pharmacokinetic (PK) bridging approach, supported by efficacy data estimated within the study itself, to assess the treatment's efficacy against RSV in high-risk newborns (preterm, CLD, or CHD). This approach demonstrated that PK exposures in healthy newborns were comparable to those in high-risk newborns, allowing extrapolation of treatment efficacy without the need to adjust dosing.[20]

The goal is to make Clesrovimab available by the 2025-26 RSV season; it could become the first-line treatment for high-risk newborns and children, revolutionizing RSV prevention and significantly reducing the incidence of infections and hospitalizations in the most vulnerable pediatric patients.

***The role of mAbs in RSV prevention***

MAbs against RSV represent one of the key therapies for preventing severe RSV infection, especially in newborns.[21] Palivizumab (Synagis®, AstraZeneca) was the first mAb approved, targeting antigenic site II of the pre-fusion F glycoprotein of RSV, which prevents the virus from fusing with respiratory cells. Approved by the FDA in 1998 and by the EMA in 1999, it is administered monthly (15 mg/kg) for 5 months to cover the RSV epidemic season. Although it significantly reduces hospitalizations in high-risk newborns, its short half-life (approximately 20 days) requires repeated administrations, making it less practical and accessible.[22,23] A systematic review of five clinical trials, including 3,343 participants, demonstrated that at a 2-year follow-up, the Risk Ratio (RR) for hospitalization due to RSV in the treated group was 0.44 (95% CI 0.3-0.64), corresponding to approximately 43 hospitalizations per 1,000 treated newborns compared to 98 per 1,000 in the placebo group, with no significant differences in mortality between the treated and untreated groups. The drug led to a significant reduction in overall respiratory hospitalizations (RR 0.78, 95% CI 0.62-0.97), as well as a reduction in RSV infections (RR 0.33, 95% CI 0.2-0.55) and days with wheezing (RR 0.39, 95% CI 0.35-0.44).[24] Further studies on healthy preterm newborns suggested that Palivizumab treatment resulted in a 61% reduction in wheezing days during the first year of life.[25]

The high cost of Palivizumab and the need for monthly administrations make it inaccessible for universal distribution, limiting its use to high-risk patients, such as newborns with congenital heart disease (CHD) or chronic lung disease, who are at a higher risk of developing severe RSV infections.[26] However, Palivizumab paved the way for new therapies, such as the attempt to develop an alternative intranasal formulation (Narsyn), which unfortunately failed due to a lack of efficacy, or Motavizumab (Numax®, AstraZeneca), a modified derivative version developed to improve efficacy and reduce the number of required doses. However, in 2010, the FDA rejected its approval

as it failed to demonstrate significant clinical advantage over Palivizumab and showed risks of hypersensitivity reactions.[27,28]

Currently, the only mAb approved for broader use in newborns is Nirsevimab (Beyfortus®), developed by AstraZeneca and Sanofi, authorized by the EMA in 2022 and by the FDA in 2023. It is a recombinant human IgG1-k mAb that binds to the antigenic site Ø of the pre-fusion F protein for both RSV subtype A and B strains, maintaining the protein in its pre-fusion conformation and preventing viral entry into cells. Using the YTE mutation technique, Nirsevimab enhances its affinity for FcRn at lower pH, thus avoiding lysosomal degradation and ensuring a half-life of about 69 days, providing protection throughout the entire RSV epidemic season with a single IM dose. Nirsevimab has demonstrated high efficacy in preventing RSV-associated MALRI through efficacy and safety profiles in multicenter, placebo-controlled clinical trials.[23-29]

The phase 2B study (NCT02878330) demonstrated that in healthy preterm newborns (29-35 week's gestation), there was a 70.1% reduction (95% CI, 52.3-81.2) in RSV-associated MALRI with prophylaxis compared to placebo, and a 78.4% reduction (95% CI, 51.9-90.3) in hospitalization for RSV-associated LRTI. The pharmacokinetics showed a half-life of 59.3 days, and 97.9% of newborns had effective serum concentrations of Nirsevimab, with a safety profile similar to that of placebo, with no related deaths.[30,31]

Subsequently, the MELODY study (phase III), conducted in 21 countries, involved 1,490 healthy newborns (≥ 35 week's gestation) to assess the incidence of MALRI confirmed by reverse transcription polymerase chain reaction (RT-PCR), primarily characterized as bronchiolitis or pneumonia, up to 150 days after a single injection of Nirsevimab or placebo. MALRI occurred in 12 newborns (1.2%) in the Nirsevimab group and in 25 newborns (5.0%) in the placebo group; these results correspond to an efficacy of 74.5% (95% CI, 49.6 to 87.1; $p < 0.001$) for Nirsevimab, with similar efficacy in both preterm and term newborns. The study also demonstrated a reduction in

RSV-associated LRTI hospitalization with an efficacy of 62.1% (95% CI, -8.6 to 86.8; p = 0.07). Furthermore, the pharmacokinetic analysis showed that the half-life of Nirsevimab is 68.7 days (about 10 days longer than the phase 2B outcome), with ADA detected in a small percentage of patients; the studies also confirmed that the incidence of AEs and SAEs was similar between the Nirsevimab and placebo groups, with common AEs such as injection site pain, fever, and irritability.[30,32,33] The MEDLEY study (Phase II/III) compared Nirsevimab with Palivizumab, with the primary objective of evaluating the safety and tolerability of the drug in preterm infants with a gestational age of less than 35 weeks and in infants with Congenital Heart Disease (CHD) and/or Chronic Lung Disease (CLD) who were eligible for Palivizumab. Conducted on a total of 925 infants, Nirsevimab demonstrated a safety profile similar to that of Palivizumab, showing efficacy and protection throughout the entire RSV season with a single administration. For this reason, it has been introduced in several countries with good acceptance, demonstrating significant reductions in hospitalizations and length of stay.[30,34,35]

***Comparative analysis and adverse events***

From the comparative analysis of clinical, pharmacokinetic, and therapeutic characteristics, it can be highlighted that Clesrovimab represents a promising future option for the prevention of RSV, showing encouraging results compared to Palivizumab and exhibiting characteristics comparable to those of Nirsevimab.[15,36] Despite all three mAb acting with the same mechanism of action and targeting the same viral target, the pre-fusion F glycoprotein, they differ in the recognized antigenic sites and their binding affinity. Clesrovimab, by binding to antigenic site IV, which is highly preserved between RSV-A and RSV-B, would ensure not only an extremely strong and selective binding but also a binding resistant to potential mutations of the virus that could reduce the efficacy of other mAbs.[8] It should be noted that a single dose would provide passive immunization coverage

for approximately 45 days in newborns, protecting them throughout the entire RSV epidemic season. This would make it superior to Palivizumab, which has a shorter half-life and requires monthly administration cycles.[37] While Nirsevimab, with the substitutions of the three amino acids (tyrosine, threonine, glutamic acid), also achieves a longer half-life (69 days), this superiority is not evident from the half-life alone.[29] In fact, the difference in plasma half-life between Clesrovimab and Nirsevimab after administration could be attributed to a difference in their tissue distribution, as supported by pharmacokinetic analyses, where the intravascular distribution volume determined by the plasma volume was found to be higher for Clesrovimab.[13] Indeed, positively charged antibodies are retained more in human tissues, which naturally have a negative charge.[38] The isoelectric point (pI) of Clesrovimab is 8.52, compared to ≤ 7.0 for Nirsevimab, giving it a higher net charge and promoting greater retention in tissues, especially at mucosal sites (nose, lungs), which are the primary sites of RSV infection. This would explain the greater tissue penetration capacity of the antibody into the nasal epithelial fluid observed in healthy adults, enhancing protection at the mucosal sites in the upper and lower respiratory tracts compared to Nirsevimab.[12,15]

The simulations obtained from Meta-Analyses Based on Modeling Approaches (MBMA), conducted prior to current clinical trials, to explore the connection between Serum Neutralization Antibody titers (SNA) and clinical endpoints, such as the prevention of severe respiratory infections (such as MALRI), hospitalizations, or other clinical manifestations, had already predicted that a single 100 mg dose of Clesrovimab would have an efficacy ≥ 76% in preventing MALRI up to 150 days post-administration.[39] To date, this is consistent with the data obtained from the MK-1654-004 protocol, showing an efficacy of 84.2% (95% CI: 66.6-92.6%),[10] demonstrating a significant advantage over Palivizumab and comparable to Nirsevimab.

Clesrovimab has demonstrated a competitive safety profile compared to other mAbs, with a low incidence of AEs. In the MK-1654-004 and MK-1654-007 studies, the drug was well tolerated in

both healthy and high-risk newborns, with the percentage of participants experiencing AEs, including solicited AEs and drug-related Adverse Reactions (ADRs), generally comparable between the intervention groups (both placebo and Palivizumab). The majority of AEs were of grade 1 or 2 toxicity, and most participants (≥ 96%) in both groups had a maximum temperature ≤ 38°C.[10,17,19] Considering the safety profile of Palivizumab, based on data from clinical trials and post-marketing surveillance, the most common reactions observed included fever, local reactions at the injection site, and rashes, as well as rarer events such as apnea, urticaria, and thrombocytopenia. There have been some reports of more severe adverse effects, such as anaphylaxis and anaphylactic shock which, while rare, still required more frequent monitoring.[22,40] Nirsevimab has also shown a safety profile comparable to that of Palivizumab, as evidenced by the MEDLEY study and consistent with the safety profile demonstrated in both the phase 2b study and the MELODY study. The most common adverse reactions were mild to moderate skin rashes (0.7%), occurring fourteen days after the first administration. SAEs were similar between Nirsevimab and placebo, although 4 AEs involved hypersensitivity reactions and fever in 4 patients within 7 days of receiving Nirsevimab.[33,34]

It is important to consider that individuals treated with mAbs may develop a humoral immune response with the formation of ADA specific to either the Fab or Fc portion of the mAb itself. These antibodies could modify therapeutic efficacy not only by affecting pharmacokinetics (leading to a faster elimination of the compound) but in the case of Clesrovimab, no neutralizing antibodies against the mAb were observed, indicating no direct loss of therapeutic effect.[37] Furthermore, immune reactions of hypersensitivity type III may develop, both locally and systemically.[41] The formation of anti-palivizumab antibodies was observed in approximately 1% of patients monitored in the Impact-RSV study during the first treatment cycle. However, this phenomenon was found to be transient, with low ADA titers and no impact on the safety or efficacy of Palivizumab.[21]

Similarly, for Clesrovimab and Nirsevimab, the frequency of ADA formation is quite comparable.[15,28,42,43] A recent study analyzed the development of ADAs at later time points in the phase 1b/2a clinical trial of Clesrovimab, showing that showing that only 36.7% of treated infants developed ADAs without impacting pharmacokinetics or safety up to day 150.[37] However, after 365 days (with negligible Clesrovimab serum concentrations), 26% of ADA-positive infants had anti-RSV antibody (RSV-SNA) titers 4-8 times higher than ADA-negative infants, suggesting that a potential natural exposure to the virus (confirmed by subsequent epidemiological data) between day 150 and 365 may have triggered a secondary immune response. After 545 days, 36.1% of the infants analyzed showed elevated ADA titers, predominantly directed against the Ø site of the RSV F protein, confirming the hypothesis of natural virus exposure during the second epidemic season. This trend suggests that sub-therapeutic levels of Clesrovimab may promote an immune response against RSV upon re-exposure to the virus after day 150, specifically driving an immune response both against the virus (RSV-SNA) and the drug (anti-YTE titers).[15,37] A similar behavior was observed with Nirsevimab, where the frequency of ADAs was higher one year after administration. However, as with Clesrovimab, the low ADA titers detected did not impact pharmacokinetic characteristics or therapeutic efficacy of Nirsevimab in RSV prevention.[29]

One final distinguishing factor that makes Clesrovimab superior to Palivizumab and comparable to Nirsevimab is its potential impact on the healthcare system. The extended efficacy of Clesrovimab reduces the number of required administrations, directly impacting the reduction of healthcare costs associated with treatment. Although the initial cost of a single administration may be higher than for Palivizumab, the need for fewer visits and monthly doses more than compensates for this economic difference. Additionally, the lower risk of hospitalization and ADRs contributes to a reduction in the costs associated with managing respiratory complications in high-risk newborns and children.[26] The comparative characteristics are illustrated in Table 2.

## Discussion

The introduction of mAbs for prophylaxis against RSV represents a significant advancement, particularly for high-risk pediatric populations.[4,7,36] In this context, Clesrovimab (MK-1654) emerges as a promising option, thanks to distinctive molecular characteristics and clinical profiles that warrant a comparative analysis with other approved mAbs.[1,6,9,11]

Available clinical data indicate that Clesrovimab offers significant efficacy and a favorable safety profile.[15] Its single-dose administration ensures protection for the entire RSV season, representing a practical advantage over Palivizumab, which requires monthly administrations due to its short half-life.[21,22] This convenience can reduce the logistical burden and costs associated with repeated visits, thereby increasing therapeutic adherence.

The comparison with Nirsevimab highlights further differences. While Nirsevimab binds to antigenic site Ø of the pre-fusion F protein,[29,31,32] Clesrovimab distinguishes itself by targeting site IV, which is highly conserved between RSV-A and RSV-B subtypes (99.8% identity).[9] This antigenic specificity suggests more stable protection against various viral variants, a relevant aspect in evaluating the long-term efficacy of prophylactic strategies.[28]

Pharmacokinetic properties and tissue distribution represent an additional distinctive point. Despite having an extended plasma half-life, Clesrovimab demonstrates greater local retention in the respiratory mucosa, the primary sites of RSV infection. This characteristic, correlated with a higher isoelectric point (pI 8.52 vs ≤7.0 for Nirsevimab), favors penetration into the ELF, allowing for more direct virus neutralization. This suggests that prophylactic efficacy depends not only on plasma half-life but also on the mAb's ability to persist at the site of infection.[1,16,38,41]

Studies on MK-1654-004 and MK-1654-007 confirm Clesrovimab's high efficacy in reducing the incidence of MALRI and RSV-related hospitalizations, in both healthy and high-risk newborns.[15,17,19] The reduction rates are comparable to or superior to Nirsevimab and superior to Palivizumab. The safety profile is favorable, with a low rate of adverse events. No treatment- or RSV-related deaths occurred during the studies. Although ADA were observed in some patients, they did not affect the pharmacokinetics or therapeutic efficacy of Clesrovimab, consistent with observations for Nirsevimab.

The clinical and healthcare implications are significant. Seasonal protection with a single dose can improve therapeutic adherence and reduce indirect costs.[7,36] While considering a possibly higher initial cost, the prevention of hospitalizations and severe RSV complications can lead to overall savings, supporting Clesrovimab as an effective and sustainable prophylactic strategy.

It should be noted that this review is narrative in nature; therefore, the selection of literature may involve subjective interpretations. Furthermore, much of the data on Clesrovimab comes from pre-registrational clinical trials; its efficacy and safety in real-world settings will need to be confirmed by future pharmacovigilance studies, once approval and commercialization in Europe are also granted.

For the future, direct and long-term comparative studies between Clesrovimab and Nirsevimab will be useful to better evaluate the advantages related to site IV binding and tissue distribution, especially considering the emergence of new RSV variants. The systematic collection of future real-world data will be fundamental to confirm clinical impact and cost-effectiveness. Further research could explore the potential role of sub-therapeutic levels of Clesrovimab in modulating the natural immune response to RSV, as suggested by ADA and anti-RSV antibody data.

**Conclusions**

In light of the findings of this review, we can state that the introduction of mAbs in the therapeutic landscape for respiratory infections caused by RSV represents a modern and effective prophylaxis, particularly in the pediatric population. Based on the studies presented, Clesrovimab emerges as a promising mAb in the near future, superior to Palivizumab in terms of greater specificity, long-lasting seasonal protection, therapeutic safety, and clinical practicality. At the same time, its tissue distribution suggests better control of the infection at primary viral replication sites, potentially making it more advantageous than Nirsevimab. The possibility that it can directly replace and passively stimulate the immune system at the primary site of infection would provide additional protection for newborns, eventually leading to a reduction in RSV-related morbidity and mortality in the future.

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**Table 1. Detailed clinical study data for Clesrovimab.[10,19]**

| Characteristic/Endpoint | Study MK-1654-004 (Healthy Newborns) | Study MK-1654-007 (High-Risk Newborns vs Palivizumab) |
|---|---|---|
| Population type | 3,614 healthy newborns (preterm and term-born). | 896 high-risk newborns for severe RSV disease (including CLD, CHD, prematurity ≤35 weeks). |
| Study design | Phase IIb/III, randomized 2:1 Clesrovimab (105 mg IM, single dose) *vs* Placebo. | Phase III, randomized 1:1 Clesrovimab (105 mg IM, single dose) vs Palivizumab (monthly doses).<br>Second part: Clesrovimab 210 mg IM. |
| Primary endpoint | Reduction in the incidence of MALRI associated with RSV within the first 150 days post-administration. | Safety and tolerability assessed by proportion of participants experiencing TEAEs and SAEs. |
| Primary efficacy results | Clesrovimab Efficacy: 60.4% (95% CI: 44.1, 71.9, p<0.001) reduction in MALRI incidence. | Incidence of RSV-associated MALRI or RSV-related LRI requiring hospitalization comparable between Clesrovimab (MALRI 3.6%; LRI hosp. 1.3%) and Palivizumab (MALRI 3.0%; LRI hosp. 1.5%) up to day 150. |
| Secondary/Tertiary endpoints | Reduction in RSV-related hospitalizations (secondary endpoint).<br>Reduction in RSV-related LRI hospitalizations (tertiary endpoint). | Incidence of RSV-associated MALRI (secondary endpoint).<br>Incidence of RSV-related LRI requiring hospitalization (secondary endpoint). |
| Secondary/Tertiary efficacy results | RSV Hospitalizations: reduced by 84.2% (95% CI: 66.6, 92.6, p<0.001) up to 150 days. | Results showed comparable efficacy between the two treatments. The study employed a PK bridging approach to assess efficacy in high-risk newborns, demonstrating that pharmacokinetic (PK) exposures |

| | | |
|---|---|---|
| | RSV-LRI Hospitalizations: reduced by 90.9% (95% CI: 76.2, 96.5) up to 150 days. | in healthy newborns were comparable to those in high-risk newborns, allowing for extrapolation of treatment efficacy. |
| Safety profile | The incidence of adverse events (AEs) and SAEs was comparable between the Clesrovimab and placebo groups. No treatment- or RSV-related deaths occurred during the study. | Both treatments showed a similar safety profile. Safety follow-up up to 365 days (in the initial part). |
| Key conclusions | Clesrovimab significantly reduced the incidence of MALRI and hospitalizations in healthy newborns, with a favorable safety profile. | Clesrovimab demonstrated comparable safety and efficacy to Palivizumab in a high-risk population. PK bridging data supports efficacy in this population. |

RSV, Respiratory Syncytial Virus; CLD, Chronic Lung Disease; CHD, Congenital Heart Disease; IM, Intramuscular; MALRI, Medically-Attended Lower Respiratory Tract Infection; TEAE, Treatment-Emergent Adverse Event; SAE, Serious Adverse Event; CI, Confidence Interval; LRI, Lower Respiratory Infection; PK, Pharmacokinetic.

**Table 2. Comparative table of anti-RSV mAbs: Palivizumab, Nirsevimab, and Clesrovimab.[26]**

| Feature | Palivizumab (Synagis®) | Nirsevimab (Beyfortus®) | Clesrovimab |
|---|---|---|---|
| **Mechanism of action** | mAb that binds to a conserved epitope of the RSV F-fusion protein. | Long half-life mAb that binds to a conserved epitope of the RSV F-fusion protein. | Long half-life mAb that binds to antigenic site IV of the RSV F-fusion protein, highly conserved between RSV-A and RSV-B, ensuring strong, selective binding resistant to potential mutations. |
| **Target population** | Preterm infants and children with bronchopulmonary dysplasia, hemodynamically significant congenital heart disease, or other | All infants born during or entering their first RSV season, and children up to 24 months with high risk in their second RSV season. | Designed for all healthy infants (preterm and term-born) and, in the future, as a first-line treatment for high-risk infants and children (e.g., with CLD, CHD, prematurity). |

| | | | |
|---|---|---|---|
| | high-risk medical conditions. | | |
| **Dose and frequency** | 15 mg/kg IM, once a month throughout the RSV season (typically 5 doses). | Single IM dose (50 mg for infants <5 kg; 100 mg for infants ≥5 kg) before or during the RSV season. | In clinical development; current data suggest a single IM dose (105 mg) for healthy infants. |
| **Half-life** | Short (approx. 20-28 days). Requires monthly doses. | Long (approx. 60-70 days). Allows for full-season protection with a single dose. | Very long, designed to surpass Nirsevimab and Palivizumab, allowing full-season protection with a single dose (studies suggest protection up to 5 months/150 days). |
| **Efficacy** | Demonstrated reduction in RSV-related hospitalizations in the high-risk group. | High efficacy in reducing RSV-related LRTIs and hospitalizations. | Preliminary data show high potency and long-duration potential. Clinical studies are ongoing to confirm efficacy and safety. |
| **Key advantages** | Only preventive option for decades; well-established safety profile. | Single dose per season; broad applicability to all infants. Greater convenience and potential for wider coverage. | Single dose with extended protection and high efficacy in both healthy and high-risk infants. Binding to the highly conserved site IV may offer greater resistance to viral mutations. Potential to become the first-line treatment for RSV prevention. |
| **Key disadvantages** | Need for monthly doses (burden for parents/healthcare system); high cost; limited applicability. | High cost; not yet widely available or reimbursed. | Currently in development; not immediately available; final efficacy and safety still to be established in large-scale studies. |
| **Safety profile** | Generally well-tolerated; injection site reactions, fever, rash. | Generally well-tolerated; injection site reactions. | Favorable and comparable to placebo in studies of healthy infants. Comparable to Palivizumab in studies of high-risk infants. No treatment- or RSV-related deaths reported. |
| **Status** | Approved and in use for many years. | Approved in Europe, USA, and other countries. Rolling out. | Approved in the USA and United Arab Emirates and is currently under review in several other countries globally. |

mAb, Monoclonal antibody; RSV, Respiratory Syncytial Virus; CLD, Chronic Lung Disease; CHD, Congenital Heart Disease; IM, Intramuscular; Lrtis, Lower Respiratory Tract Infections.

Contributions:

Conflict of interest: the authors declare no conflict of interest.

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