Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761432
Priority or standard	Priority
Submit date(s)	10/10/2024
Received date(s)	10/10/2024
PDUFA goal date	6/10/2025
Division/office	Division of Antivirals (DAV)
Review completion date	6/5/2025
Established/proper name	Clesrovimab-cfor
(Proposed) proprietary name	ENFLONSIA
Pharmacologic class	Monoclonal antibody
Other product name(s)	MK-1654
Applicant	Merck Sharp & Dohme LLC
Dosage form(s)/formulation(s)	Solution for intramuscular (IM) injection
Dosing regimen	Single intramuscular dose of 105 mg
Applicant-proposed indication(s)/ population(s)	Prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season.
SNOMED CT code for proposed indication disease term(s)[1]	55735094 Respiratory Syncytial Virus Infection (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	105 mg administered as a single intramuscular (IM) injection
Approved indication(s)/ population(s) (if applicable)	Prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season.
SNOMED CT code for approved indication disease term(s)[1]	55735094 Respiratory Syncytial Virus Infection (disorder)

[1] For internal tracking purposes only.
Abbreviations: LLC, limited liability company; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AAP	American Academy of Pediatrics
ADA	antidrug antibody
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APaT	all-participants as-treated
ARI	acute respiratory infection
ATCC	American-type culture collection
AUC	area under the concentration-time curve
$AUC_{0\text{-}150d}$	area under the concentration-time curve from Day 1 to Day 150
BLA	biologics license application
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CHD	congenital heart disease
CL	clearance
CLD	chronic lung disease
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
CPB	cardiopulmonary bypass
CV	coefficient of variation
DART	developmental and reproductive toxicology
DNA	deoxyribonucleic acid
DS-Cav1	prefusion F protein
EC_{50}	half-maximal effective concentration
EC_{90}	90% effective concentration
ECMO	extracorporeal membrane oxygenation
eDMC	external data monitoring committee
F protein	fusion protein
Fab	fragment antigen-binding
FAS	full analysis set
FBS	fetal bovine serum
FDA	Food and Drug Administration
GA	gestational age
GFP	green fluorescent protein
GLP	good laboratory practice
GOF	goodness-of-fit
HEp-2	human epidermoid carcinoma #2

HER2	human epidermal growth factor receptor 2
HPLC-MS/MS	high-performance liquid chromatography tandem mass spectrometry
IA	interim analysis
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IgG1κ	immunoglobulin G1 kappa
IM	intramuscular(ly)
IND	investigational new drug
iPSP	initial Pediatric Study Plan
IS	immunogenicity specimen
ISTD	internal standard
IV	intravenous(ly)
K_a	absorption rate constant
K_D	dissociation constant
LALA	Fc substitutions L234A and L235A
LC-MS/MS	liquid chromatography tandem mass spectrometry
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
MALRI	medically attended lower respiratory infection
NCI-CTCAE	National Cancer Institute–Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NOAEL	no-observed-adverse-effect level
NP	nasopharyngeal
OCMQ	OND Custom Medical Query
OKT3	Muromonab-CD3
OND	Office of New Drugs
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PD	pharmacodynamic
PFU	plaque-forming units
PI	Prescribing Information
PK	pharmacokinetic
PIND	pre-investigational new drug
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population pharmacokinetic(s)
PPE	per-protocol efficacy
PT	preferred term
RADT	rapid antigen diagnostic test
RNA	ribonucleic acid
RP1	respiratory panel 1
RRR	relative risk reduction
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction

SAE	serious adverse event
SEE	substantial evidence of effectiveness
SNA	serum-neutralizing antibody
SOC	system organ class
SUR	Safety Update Report
TCID	tissue culture infectious dose
TCR	tissue cross-reactivity
TGN1412	theralizumab
T_{max}	time to maximum concentration
URI	upper respiratory infection
USPI	United States Prescribing Information
VAF	variant allele frequency
Vc/F	apparent central volume of distribution
Vp/F	apparent peripheral volume of distribution
WRO	Written Response Only
WT	wild-type
YTE	M252Y/S254T/T256E (amino acid substitution)

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

This new biological license application (BLA) for clesrovimab (MK-1654) for intramuscular use was submitted by Merck and was reviewed by the FDA interdisciplinary review team. The proposed proprietary name, ENFLONSIA, has been conditionally granted. Clesrovimab is a fully human immunoglobulin G (IgG)1 monoclonal antibody which binds to respiratory syncytial virus (RSV) fusion (RSV F) protein preventing cell entry and has three M252Y/S254T/T256E (YTE) amino acid substitutions in the Fc region, which leads to longer serum half-life and duration of coverage over an RSV season. The intended indication for clesrovimab is for the prevention of RSV lower respiratory tract disease (LRTD) in neonates and infants who are born during or entering their first RSV season.

The Applicant submitted the original investigational new drug (IND) application on December 7, 2016, for the prevention of RSV in infants. Fast track designation was granted on August 27, 2018. See Section 12 for further information.

No discipline (clinical, clinical virology, clinical pharmacology, pharmacometrics, pharmacology/toxicology, statistics, chemistry, or regulatory) identified any issues that preclude approval, and the Agency recommends approval. Refer to the Approval Letter for further details.

To support the proposed indication, the Applicant conducted two pivotal clinical trials: one Phase 2/3 efficacy and safety trial in healthy infants ages ≥29 weeks (with two cohorts, 29 to <35 weeks and ≥35 weeks gestational age), and one Phase 3 trial of safety, efficacy and pharmacokinetics in infants and children at increased risk for severe RSV disease (with chronic lung disease, congenital heart disease, or prematurity with gestational age ≤35 weeks).

Trial MK-1654-004 was a Phase 2/3 randomized (2:1), double-blinded, placebo-controlled, two cohort design trial (Phase 2 lead cohort of 300 participants, ages >2 weeks to 1 year of age and Phase 3 cohort of 2700 participants from birth to 1 year of age). Trial MK-1654-004 was ongoing at the time of the BLA submission. As of the 90-Day Safety Update Report submitted on January 7, 2025, all participants had completed 365 days of follow-up and study follow-up was complete for Trial MK-1654-004.

The primary efficacy endpoint for Trial MK-1654-004 was the incidence of RSV-associated medically attended lower respiratory infection (MALRI) from Days 1 through 150 postdose. RSV-associated MALRI was defined as the following: cough or difficulty breathing; and one or more of the following: wheezing, chest wall indrawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms; and an RSV-positive reverse transcription–polymerase chain reaction (RT-PCR) nasopharyngeal (NP) sample. A key secondary endpoint included RSV-associated hospitalization from Days 1 through 150. A subgroup of 1518 participants (1016 in the clesrovimab group and 502 in the placebo group) were followed into RSV Season 2 (through Day 515 postdose) without additional study

intervention, for additional monitoring for incidence of RSV-associated MALRI, RSV-associated hospitalization, and serious adverse events (SAEs) to assess for any increase in RSV frequency or severity in RSV Season 2 resulting from clesrovimab administration in RSV Season 1.

Trial MK-1654-007 is an ongoing Phase 3 randomized (1:1), double-blind, open-label, active-controlled study. The primary endpoint is evaluation of safety; efficacy and pharmacokinetic (PK) assessments are secondary endpoints. Trial MK-1654-007 enrolled infants and children at increased risk for severe RSV disease (due to comorbid conditions such as chronic lung disease, congenital heart disease, or prematurity with gestational age ≤35 weeks). Infants who were born during or entering their first RSV season were randomized 1:1 to receive clesrovimab (105 mg intramuscularly [IM]) or palivizumab (as five monthly IM doses of 15 mg/kg). In Part 1 (double-blind), participants were to receive two blinded doses of either clesrovimab 105 mg (Dose 1) and placebo (Dose 2), or palivizumab (Dose 1 and 2), prior to being unblinded at the Day 60 visit. In Part 2 (open-label), participants in the palivizumab group received three to five single doses of palivizumab in RSV Season 1, depending on the timing of enrollment relative to the RSV season. Participants in the clesrovimab group received no additional study drug in Part 2, with rare exceptions where an additional dose was administered following extracorporeal membrane oxygenation (ECMO) or cardiac surgery requiring cardiopulmonary bypass (CPB). Eligible participants in either treatment group who continued to be at increased risk of RSV and were entering their second RSV season (approximately 300 infants/children) were administered clesrovimab at the start of the second RSV season (RSV Season 2).

The proposed dosage for clesrovimab is 105 mg administered once by IM injection in infants born during or entering their first RSV season. For infants and children undergoing cardiac surgery with cardiopulmonary bypass, an additional dose of clesrovimab is recommended as soon as the child is stable after surgery to ensure adequate postoperative clesrovimab serum levels.

The available efficacy data from the clinical trials have demonstrated that clesrovimab is effective for its intended use. In Trial MK-1654-004, which enrolled healthy infants, for the primary efficacy endpoint of RSV-associated MALRI from Days 1 through 150, administration of clesrovimab reduced the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose compared with placebo, with observed efficacy of 60.4% (95% CI: 44.1%, 71.9%; $p<0.001$). The statistical criterion for success was met, with the lower bound of the 95% CI >25%. For the key secondary efficacy endpoint of RSV-associated hospitalization from Days 1 through 150 (with Type-1 error control), administration of clesrovimab was associated with a relative risk reduction of 84.2% (95% CI: 66.6%, 92.6%, $p<0.001$), with the lower bound of the 95% CI >0%, which met the statistical criterion for success.

In Trial MK-1654-007, the incidence rates of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose were generally comparable between the clesrovimab group (incidence rate =3.6%, 95% CI: 2.0%, 6.0%) and the palivizumab group (incidence rate =3.0%, 95% CI: 1.6%, 5.3%). The incidence rates of RSV-associated hospitalizations from Days 1 through 150 postdose were also generally comparable between the clesrovimab group (incidence rate =1.3%, 95% CI: 0.4%, 3.0%) and the palivizumab group (incidence rate =1.5%, 95% CI: 0.6%, 3.3%). As noted, Trial MK-1654-007 was not powered to detect differences between the treatment groups. PK exposures were comparable between Trial MK-1654-004 and Trial MK-

1654-007, allowing for PK extrapolation of efficacy from healthy infants enrolled in Trial MK-1654-004 to infants at increased risk for severe RSV disease (Trial MK-1654-007). Based on the similarity in the pathophysiology of RSV infection between infants with and without certain medical comorbidities, as well as the drug's mechanism of action, the exposure-response analysis from healthy infants in Trial MK-1654-004 is supportive of the proposed dosing regimen for infants at high risk of severe RSV.

The available safety data from the clinical trials demonstrate that clesrovimab is safe for its intended use. In the clinical trials, clesrovimab was generally well-tolerated, though higher rates of injection site reactions and rash were observed in the clesrovimab arm compared to the comparator arm in both pivotal trials (Trials MK-1654-004 and MK-1654-007). Key safety concerns with clesrovimab are those observed with use of other monoclonal antibodies, including the potential risk of serious hypersensitivity reactions such as anaphylaxis, and serious skin reactions/rashes. Severe or serious hypersensitivity reactions and serious skin reactions were not reported in the clesrovimab clinical trials. One participant in the clesrovimab group (Trial MK-1654-004) experienced an anaphylaxis/hypersensitivity adverse event of special interest (AESI) of bronchospasm (Grade 2) on Day 3 postdose. This event was not serious and was assessed as not related to study intervention by the Investigator. The Agency concludes that the risks identified in the review of the clinical trial data can be mitigated through the Prescribing Information and further evaluated through a pharmacovigilance strategy with surveillance for postmarketing safety events.

Based upon review of all available efficacy and safety data, the benefits of clesrovimab outweigh the risks when used for the prevention of RSV LRTD in neonates and infants who are born during or entering their first RSV season. For detailed information supporting the basis for the benefit-risk assessment, refer to the details in this Integrated Assessment document.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

The Applicant submitted one adequately designed Phase 2/3 trial in healthy infants, Trial MK-1654-004, that provided compelling evidence of effectiveness for the proposed indication. Confirmatory evidence of effectiveness was provided by the Phase 3 trial, Trial MK-1654-007, in which efficacy against RSV-associated MALRI was evaluated as a secondary endpoint among infants at increased risk of severe RSV disease. Although Trial MK-1654-007 was not powered for the assessment of efficacy, the incidence rates of RSV-associated MALRI were comparable between the clesrovimab and palivizumab arms, thereby supporting the effectiveness of clesrovimab. Additionally, the Applicant submitted non-clinical data that provide further confirmatory evidence of efficacy. In cell culture, sub-nanomolar activity of clesrovimab was demonstrated against diverse clinical RSV isolates, with similar activities reported against RSV A and RSV B isolates. In a cotton rat model of RSV infection, the prophylactic antiviral activity of clesrovimab parental antibody RB-1 was assessed alongside a palivizumab comparator, and RB-1 showed greater potency than palivizumab, with reductions in viral titer in lung and nasal tissue that were dose-dependent. In conclusion, the totality of the available data from the clinical

trials and non-clinical studies have demonstrated that clesrovimab is effective for its intended use.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	Respiratory syncytial virus (RSV) • RSV is an enveloped RNA virus that causes respiratory tract infection. • RSV occurs in annual outbreaks each fall and winter in the majority of the United States. Most children and adults with symptomatic RSV infection have self-limited disease with signs and symptoms limited to the upper respiratory tract. However, RSV can present as a lower respiratory tract disease (LRTD), particularly in very young children and older adults. Because of annual RSV outbreaks, almost all children have been infected with RSV by 2 years of age. • RSV is the most common cause of lower respiratory tract infection (LRTI) in infants and young children both in the United States and worldwide. Approximately 20% to 30% of infants with RSV develop LRTD with their first RSV infection. RSV LRTD usually presents as bronchiolitis and/or pneumonia. The Centers for Disease Control and Prevention (CDC) estimates that RSV infection results in 2.1 million outpatient visits yearly among children younger than 5 years of age (CDC 2024b). Based on CDC's New Vaccine Surveillance Network (NVSN) analysis, it is estimated that RSV infections in pediatric patients <24 months of age results in 472,000 visits to Emergency Departments each year (Lively et al. 2019). • RSV LRTI/LRTD is the most common cause of hospitalization for infants in the United States. Approximately 1% to 3% of all children in the United States will be hospitalized due to severe RSV disease. In children younger than 5 years of age, RSV infection results in 58,000 to 80,000 hospitalizations each year in the United States (American°Lung°Association 2025). The majority of children hospitalized with RSV infection improve with supportive care and are discharged in 2 to 3 days.	RSV virus is one of the most common causes of viral respiratory tract infection in infants and young children. While most experience mild upper respiratory tract infection, certain populations are at risk of lower respiratory tract disease, including pneumonia and bronchiolitis. RSV can lead to severe or serious disease in infants, including healthy term and preterm infants. Extremely preterm infants (e.g., <29 weeks of GA) and infants/children with certain underlying medical conditions are at the greatest risk for severe or serious disease, including death.

	• According to CDC, all infants (children ≤12 months of age), particularly those 6 months of age or younger, are at increased risk of hospitalization (CDC 2024a). While some studies have shown that the highest risk for severe RSV infection in otherwise healthy infants is for infants in the second month of life, the risk of hospitalization continues through at least 6 months of age. In a study by (Hall et al. 2009), 58% of children hospitalized with RSV LRTD were 0 to <6 months of age, and 17% were from 6 to <12 months of age. Hospitalizations due to RSV LRTD were not reported in children older than 5 years of age. • Severe RSV disease and hospitalization are more common in certain pediatric populations. The CDC defines children at high risk of severe RSV LRTD as infants and young children (the younger the age, the higher the risk), those who were born prematurely, have chronic lung disease (CLD) of prematurity or hemodynamically unstable congenital heart disease (CHD), have weakened immune systems, or have neuromuscular disorders, including those with difficulty swallowing or clearing mucus secretions (CDC 2024a). The risk of severe RSV LRTD in infants born prematurely increases with decreasing gestational age (GA). Although the increased risk of severe RSV LRTD has been reported for all premature infants born at <35 weeks GA, the American Academy of Pediatrics (AAP) determined that the majority of studies show that the greatest risk for severe RSV LRTD is in infants born before 29 weeks GA (Caserta et al. 2023). • According to the CDC, RSV infection leads to 100 to 300 deaths in children younger than 5 years of age in the United States each year (CDC°NCIRD 2023). The Global Burden of Diseases, Injuries, and Risk Factors reported that there were more than 41,000 deaths due to RSV worldwide in 2016 in children <5 years of age (Cohen and Zar 2022). It was estimated per a meta-analysis that globally in 2019, there were 101,400 RSV-associated deaths in children <5 years of age (Li et al. 2022).	
Current treatment options	The following products are FDA-approved for the prevention of RSV infection in infants and young children: Nirsevimab • Nirsevimab-alip (Beyfortus) is a human monoclonal antibody, RSV F protein-directed fusion inhibitor, approved by FDA in July 2023 for	Clesrovimab offers an additional option in the RSV prevention armamentarium for healthy infants and infants/children who are at increased risk for severe RSV disease, including those with extreme

	the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and children up to 24 months of age who remain vulnerable to severeRSV disease through their second RSV season. RSV vaccine for injection • RSV Vaccine (ABRYSVO) is composed of RSV recombinant stabilized prefusion F proteins and was approved by FDA in August 2023 for active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age. Palivizumab • Prior to the approval of nirsevimab-alip (Beyfortus), palivizumab (Synagis®) was the only drug product approved by FDA for the prevention of serious lower respiratory tract disease caused by RSV. Palivizumab is a monoclonal antibody directed against a conserved epitope on the RSV fusion protein. Palivizumab is indicated for the prevention of serious RSV LRTD in pediatric patients: – With a history of premature birth (less than or equal to 35 weeks GA) and who are 6 months of age or younger at the beginning of RSV season – With bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season – With hemodynamically significant CHD and who are 24 months of age or younger at the beginning of RSV season • Palivizumab is administered by intramuscular injection; the first dose is administered prior to the start of the RSV season and the remaining four doses are administered monthly during the RSV season.	prematurity or with certain underlying medical conditions. Products requiring a single dose administration, such as clesrovimab, may increase compliance and potentially decrease the frequency of adverse reactions associated with multiple intramuscular injections.
Benefit	Effectiveness of clesrovimab for the prevention of RSV LRTD in neonates and infants born during or entering their first RSV season was primarily established through a randomized placebo-controlled trial, Trial MK-1654-004 • In Trial MK-1654-004, for the primary efficacy endpoint of the incidence of RSV-associated MALRI[1] from Day 1 through Day 150	Reduction in the incidence of RSV-associated MALRI is a primary efficacy endpoint that demonstrates meaningful clinical benefit. Prospective, population-based surveillance studies have described the burden of RSV in infants by documenting the increased rates of both RSV

	postdose, administration of clesrovimab demonstrated efficacy of 60.4% (95% CI: 44.1%, 71.9%; p<0.001), with the lower bound of the 95% CI >25%, meeting the statistical criterion for success. • For the secondary endpoint of the incidence of RSV-associated hospitalization from Days 1 through 150 postdose, the relative risk reduction of clesrovimab compared with placebo was 84.2% (95% CI: 66.6%, 92.6%, p<0.001), with a lower bound of the 95% CI >0%, meeting the statistical criterion for success. • The exposure-response relationship analysis using data from Trial MK-1654-004 showed a flat exposure-response relationship, indicating efficacy is on the plateau. Additional efficacy and exposure-response analyses by body weight and age support administration of the same dosage in RSV Season 1 regardless of body weight or age. Supportive evidence of effectiveness from Trial MK-1654-007 • Supportive evidence came from Trial MK-1654-007, in which safety was the primary endpoint and efficacy and pharmacokinetics were secondary endpoints. The efficacy of clesrovimab in pediatric participants at high risk of severe RSV-associated MALRI was concluded based on PK extrapolation from Trial MK-1654-004. • The incidence of RSV-associated MALRI was evaluated as a secondary endpoint in high-risk infants in Trial MK-1654-007. The incidence rates of RSV-associated MALRI from Days 1 through 150 postdose were generally comparable between the clesrovimab group (incidence rate of 3.6% [95% CI: 2.0%, 6.0%]) and the palivizumab group (incidence rate of 3.0% [95% CI: 1.6%, 5.3%]). Note that Trial MK-1654-007 was not powered to detect any difference between the treatment groups. Uncertainty regarding the potential effectiveness of a second dose of clesrovimab in RSV Season 2 • In Trial MK-1654-007, eligible participants who continue to be at increased risk and are entering their second RSV season were administered open-label clesrovimab at a dose of 210 mg up to 4 weeks prior to the start of the second RSV season. • At the time of this BLA review, the data to support the potential benefit of a second dose administered in Season 2 are not available.	hospitalization and RSV outpatient visits (Hall et al. 2009). Infants with RSV LRTD are less likely to be hospitalized today than they were in the past, when palivizumab was studied. Therefore, RSV-associated MALRI, which is inclusive of both outpatient visits and hospitalization, is a reasonable and clinically meaningful endpoint for evaluating clesrovimab for the prevention of RSV LRTD. The clinical data submitted to the BLA provide substantial evidence of clesrovimab efficacy to support the proposed indication of prevention of respiratory syncytial virus lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. Results from MK-1654-004 demonstrated that a single 105 mg IM dose was superior to placebo in reducing the incidence of RSV-associated MALRI in preterm and term infants across age and weight bands in RSV Season 1. Although Trial MK-1654-007 was not designed for inferential statistical analysis, the incidence rates of RSV-associated MALRI were comparable between the clesrovimab and palivizumab arms, thereby supporting the effectiveness of clesrovimab. Based on the similarity in the pathophysiology of RSV infection between infants with and without certain medical comorbidities, as well as the drug's mechanism of action, the exposure-response analysis from healthy infants in MK-1654-004 is supportive of the proposed dosing regimen for the prevention of RSV lower respiratory tract disease in neonates and infants at high risk of severe RSV.

		Submission of the final CSR from Trial MK-1654-007, including data regarding the potential benefit of a dose in Season 2 for participants who remain at increased risk for severe RSV disease, will be issued as a PREA PMR.
Risk and risk management	Safety summary • Clesrovimab demonstrated an overall favorable safety profile in the clinical trials. • The safety database included 2,947 pediatric participants at the proposed (to-be-marketed) dose, of which 2,858 were enrolled in the pivotal studies, Trials MK-1654-004 and MK-1654-007. • Summary of Trial MK-1654-004 safety: – Injection site reactions were reported in 9.3% of clesrovimab recipients versus 9.7% of placebo recipients; most were Grade 1 or 2 in severity. – Solicited systemic AEs (i.e., irritability, somnolence, and appetite loss) were reported in 26.2% of clesrovimab recipients and 28.0% of placebo recipients; most were Grade 1 or 2 in severity. – Deaths: In Trial MK-1654-004, a total of 10 deaths were reported, 0.3% (7/2409) in the clesrovimab group and 0.2% (3/1202) in placebo group. No deaths were considered by the Investigator to be related to study intervention. No pattern was observed in AEs leading to death or the timing of death relative to study intervention, and the AE PTs varied across multiple SOCs. – AESIs: For the AESIs of hypersensitivity/anaphylaxis, one participant (in the clesrovimab group) experienced an anaphylaxis/hypersensitivity AESI of bronchospasm (Grade 2) on Day 3 postdose. This event was not serious and was assessed as not related to study intervention by the Investigator. Analyses of rash AEs occurring within 14 days of study intervention showed that a higher proportion of participants in the clesrovimab group versus the placebo group experienced rash AEs (2.3% versus 1.9%, in the clesrovimab and placebo groups, respectively). All events were nonserious with Grade 1 to 2 toxicity, and most events were not considered to be related to study intervention per the Investigator's assessment.	The size of the safety database for otherwise healthy infants and high-risk infants is adequate. No major safety issues related specifically to clesrovimab have been identified. In general, clesrovimab had a similar adverse event profile compared to placebo or palivizumab in the pivotal clinical trials. As serious hypersensitivity reactions, including anaphylaxis, have been observed with other human immunoglobulin G1 monoclonal antibodies, this risk will be included as a Warning and Precaution in the Prescribing Information and a focus of postmarket surveillance. Overall, no adverse events consistent with a severe or serious allergic reaction to clesrovimab were reported in clinical trials of clesrovimab. Local injection site reactions were common, but generally mild. The risk of injection site reactions will be conveyed in Section 6 of the USPI. Rash events were reported more frequently in the clesrovimab group versus the comparator control group. The imbalance in rash AEs/AESIs will be described in Section 6 of the USPI. While numerically more deaths were reported among participants who received clesrovimab, the causes of death were varied, suggesting lack of organ-specific toxicity. No pattern was observed in the AEs leading to death or the timing of death relative to study intervention. None of the deaths

	• Summary of Trial MK-1654-007 RSV Season 1 safety: – Injection site reactions (Days 1 through 5 following Dose 1) were reported in 9.4% of participants in the clesrovimab group and 6.2% in the palivizumab group. Most were Grade 1 or 2 in severity. – Solicited systemic reactions (i.e., irritability, somnolence, and appetite loss) (Days 1 through 5 following Dose 1) were reported at a higher frequency in the clesrovimab group (29.7%) versus the palivizumab group (24.2%). Most were Grade 1 or 2 in severity. – AESI: Within 42 days Postdose 1, 3 participants (0.7%) in the MK-1654 group and 1 participant (0.2%) in the palivizumab group experienced rash AESI; all rash AESI were Grade 1. There were no anaphylaxis/hypersensitivity events reported. – Deaths: a total of 12 deaths occurred: 8 (1.8%) in the MK-1654 group, 4 (0.9%) in the palivizumab group. No deaths were considered related to study intervention. No pattern was observed in AEs leading to death or timing of death relative to administration of study intervention, and the AE preferred terms varied across multiple SOCs. Uncertainties • Theoretical concerns have been raised regarding potential long-term adverse outcomes, including antibody dependent enhancement of RSV disease, and/or the potential for shifting of severe RSV LRTD to the child's second RSV season. However, among the subset of MK-1654-004 participants who were followed through their second RSV season without receiving an additional study drug dose, there did not appear to be an increased rate of RSV-associated MALRI or hospitalization among participants who had received clesrovimab in Season 1 compared to those who received placebo in Season 1. Additionally, the available data from the second RSV season of a Phase 3 trial of nirsevimab (an FDA-approved monoclonal antibody with a similar indication and mechanism of action to clesrovimab), did not show evidence of antibody-dependent enhancement of infection or disease severity in nirsevimab versus placebo recipients (Dagan et al. 2024). • The future efficacy of clesrovimab could be impacted by naturally occurring variants which harbor F protein polymorphisms associated with reduced susceptibility to clesrovimab, or by selection of	appeared to be related to study drug. This slight imbalance is concluded to be due to chance. Postmarket virologic surveillance for resistant variants is planned, and variants/substitutions of interest will continue to be identified and evaluated phenotypically.

	resistant variants following breakthrough infection. In Trial MK-1654-004, binding-site substitutions were seen in 15/156 (9.6%) breakthrough infections in clesrovimab-treated participants through Day 180, compared with 2/150 (1.3%) in placebo participants.	

[1.] RSV-associated MALRI, seen in an outpatient or inpatient clinical setting, was defined as the following:

- Cough or difficulty breathing
- One or more of the following: wheezing, chest wall in drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms
- RSV-positive RT-PCR NP sample.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; CSR, clinical study report; MALRI, medically attended lower respiratory infection; PMR, postmarketing requirement; PREA, Pediatric Research Equity Act; SOC, system organ class; USPI, United States Prescribing Information

2.2. Conclusions Regarding Benefit-Risk

RSV is the most common cause of lower respiratory tract infection (LRTI) in infants and young children both in the United States and worldwide. RSV lower respiratory tract disease is a serious and potentially life-threatening illness in infants and young children. Approximately 20% to 30% of infants with RSV develop LRTD with their first RSV infection (Committee°on°Infectious°Diseases 2024). RSV LRTD usually presents as bronchiolitis and/or pneumonia. Approximately 1% to 3% of children <12 months of age in the United States are hospitalized each year due to RSV (Committee°on°Infectious°Diseases 2024). According to the Centers for Disease Control and Prevention (CDC), there are 100 to 300 deaths per year in children younger than 5 years of age in the United States (CDC°NCIRD 2023). In one retrospective review of deaths from 1999 to 2018 in the United States, the mean mortality rate for RSV in infants <12 months of age was 96 per 100,000 (Hansen et al. 2022).

There are currently two FDA-approved drugs for the prevention of RSV LRTD, nirsevimab-alip and palivizumab, which are both monoclonal antibodies against the RSV fusion (F) protein (MedImmune 1998; ASTRAZENECA°AB 2023). Palivizumab is administered IM monthly throughout the RSV season. Although palivizumab is approved for use in preterm infants <35 weeks gestational age (GA), those with bronchopulmonary dysplasia (now known as chronic lung disease of prematurity), and those with hemodynamically significant congenital heart disease, the use of palivizumab is only recommended by the American Academy of Pediatrics (AAP) in infants born at <29 weeks GA and those with certain underlying medical conditions (American°Academy°of°Pediatrics 2014; AAP 2022). In addition, palivizumab requires monthly intramuscular injections during the RSV season. For these reasons, palivizumab is not widely used. Nirsevimab was approved on July 17, 2023, for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

On August 21, 2023, the FDA approved the RSVpreF vaccine for active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age (Pfizer°Inc. 2023).

Clesrovimab, a monoclonal antibody against RSV fusion (F) protein, has demonstrated clinical benefit in the prevention of RSV-associated MALRI in healthy infants in their first RSV season in a large, placebo-controlled trial. Exposure-response analyses as well as various subgroup efficacy analyses from this trial support the administration of the same clesrovimab dose in RSV Season 1 regardless of body weight or age. The efficacy of clesrovimab in preventing RSV-associated MALRI in infants and children at increased risk for severe RSV disease due to risk factors such as chronic lung disease, congenital heart disease, or prematurity with gestational age ≤35 weeks during their first RSV season was assessed in a phase 3 trial of clesrovimab versus palivizumab. Efficacy was extrapolated from healthy infants based on the similarity of RSV disease pathophysiology and clesrovimab's mechanism of action, and after similar PK exposures of clesrovimab were demonstrated between the two populations. While this trial was not designed for inferential statistical analysis, the incidence rates of RSV-associated MALRI were comparable between the clesrovimab and palivizumab arms and supportive of efficacy in this patient population.

The safety database for clesrovimab is adequate for the proposed indication, dosing regimen, and population. Overall, clesrovimab has a favorable safety profile. Key safety concerns with clesrovimab are the potential for hypersensitivity reactions, including anaphylaxis and rash (based on experience with other monoclonal antibodies). There was one AESI of "anaphylaxis/hypersensitivity" reaction (bronchospasm, Grade 2) in a participant in the clesrovimab group (Trial MK-1654-004) which was nonserious, occurred on Day 3 after dosing, and was unlikely to be related to clesrovimab administration. The overall incidence of rash in the trials of clesrovimab was low but was observed at a slightly higher frequency in the clesrovimab group versus the placebo group. Severe or serious skin reactions were uncommon in the trials of clesrovimab.

One area of uncertainty is the potential for clesrovimab to result in adverse long-term outcomes not seen in clinical trials, for example, antibody-dependent enhancement of RSV disease or shifting of severe RSV LRTD to children's second RSV season. In Trial MK-1654-004, in the subgroup of participants followed from Days 365 through 515 postdose without redosing, the incidences of RSV-associated MALRI and RSV-associated hospitalization were similar between the clesrovimab and placebo groups. The incidence rates of RSV-associated MALRI over 5 months of Season 2 were 0.055 (95% CI: 0.041, 0.071) in the clesrovimab group and 0.054 (95% CI: 0.035, 0.079) in the placebo group; the incidence rates of RSV-associated hospitalization over 5 months of Season 2 were 0.003 (95% CI: 0.001, 0.009) in the clesrovimab group and 0.004 (95% CI: 0.000, 0.014) in the placebo group. These data, while limited, provide some reassurance regarding the potential concern for antibody dependent enhancement of RSV disease or shifting of severe RSV LRTD to the second RSV season.

Another issue of concern is the potential for efficacy of clesrovimab to be impacted by naturally occurring variants which harbor F protein polymorphisms associated with reduced susceptibility to clesrovimab, or by selection of resistant variants following breakthrough infection. While the surveillance programs conducted in support of this application indicate a high level of conservation of the clesrovimab epitope, clinical data indicate a potential for variants with reduced susceptibility to clesrovimab to be selected in breakthrough infections. Also, because RSV is continually evolving, the possibility that variants with reduced susceptibility to clesrovimab may emerge and become prevalent in the future should be considered, hence continued surveillance programs will be important with the approval of clesrovimab.

In the FDA's decision to approve clesrovimab, we considered the available safety and efficacy data and the recommendation for approval by all review disciplines. The overall benefit-risk profile of clesrovimab is favorable to support an indication for prevention of RSV LRTD in neonates and infants who are born during or entering their first RSV season.

II. Interdisciplinary Assessment

3. Introduction

Human RSV is an orthopneumovirus in the family *Pneumoviridae*, with a negative sense, nonsegmented ribonucleic acid (RNA) genome and lipid envelope. RSV consists of two antigenic subtypes, RSV A and RSV B, which vary in relative prevalence across seasons, and are further subdivided into different clades. The RSV fusion (F) surface protein mediates fusion between viral and host cell membranes, an essential step in the viral entry process. Clesrovimab targets antigenic Site IV on the prefusion conformation of F protein which locks the F protein in the prefusion state, preventing the conformation change and virus-cell membrane fusion needed for cell entry.

RSV occurs in annual outbreaks each fall and winter in most of the United States. Most children and adults with symptomatic RSV infection have self-limited disease with signs and symptoms limited to the upper respiratory tract. However, RSV can present as LRTD, particularly in very young children and older adults. Because of annual RSV outbreaks, almost all children have been infected with RSV by 2 years of age (CDC 2024a; Committee°on°Infectious°Diseases 2024).

RSV is a common cause of bronchiolitis and viral pneumonia in infants and young children, both in the United States and worldwide, and is the leading cause of infant hospitalizations in the United States (Ektare et al. 2022; Suh et al. 2022). Approximately 20 to 30% of infants with RSV develop LRTD with their first RSV infection. The CDC estimates that RSV infection results in 2.1 million outpatient visits yearly among children younger than 5 years of age. Investigators have estimated that RSV infections in pediatric patients results in 472,000 visits to emergency departments each year in children <2 years of age. Approximately 1% to 3% of children in the United States are hospitalized in the first 12 months of life due to severe RSV disease (Committee°on°Infectious°Diseases 2024). RSV disease is associated with a mortality of 1 to 3% in hospitalized infants (Munoz et al. 2003; Hall et al. 2013). In children younger than 5 years of age, RSV LRTD results in 58,000 to 80,000 hospitalizations each year in the United States (CDC°NCIRD 2023). The majority of children hospitalized with RSV LRTD improve with supportive care and are discharged in 2 to 3 days (Committee°on°Infectious°Diseases 2024). However, there are 100 to 300 deaths due to RSV LRTD in children younger than 5 years of age annually in the United States (Centers for Disease Control and Prevention 2022; CDC°NCIRD 2023).

According to CDC, all infants (children ≤12 months of age), particularly those 6 months of age or younger, are at increased risk of hospitalization (CDC 2024a). Although RSV hospitalization rates are highest within the first 3 months of life (with a peak at 2 to 3 months of age), the risk of RSV-associated LRTD and hospitalization continues to at least 12 months of age (Munoz et al. 2003). In a study by Hall et al., 58% of children hospitalized with RSV LRTD were 0 to <6 months of age, and 17% were from 6 to <12 months of age. Hospitalizations due to RSV LRTD were not reported in children older than 5 years of age (Hall et al. 2009).

Severe RSV disease and hospitalization are more common in pediatric patients born prematurely and in those with certain underlying conditions (CDC 2024a)). However, healthy infants 0 to 6 months of age are also at significant risk for morbidity and mortality (Munoz et al. 2003). The CDC defines children at high risk of severe RSV LRTD as infants and young children (the younger the age, the higher the risk), those who were born prematurely, have chronic lung disease or congenital heart disease, have weakened immune systems, or have neuromuscular disorders, including those with difficulty swallowing or clearing mucus secretions (CDC 2024a). The risk of severe RSV LRTD in infants born prematurely increases with decreasing GA. Although the increased risk of severe RSV LRTD has been reported for all premature infants born at <35 weeks of gestation, AAP determined that most studies supported an increased risk of severe RSV LRTD in infants born before 29 weeks of gestation (American°Academy°of°Pediatrics 2014).

The hospitalization rates for RSV decrease after the first year of life; approximately 75% of hospitalizations for RSV occur in the first year of life (Hall et al. 2009). However, some comorbidities, such as chronic lung disease (CLD) of prematurity with continued requirement for medical intervention and hemodynamically significant congenital heart disease (CHD), place children at risk of severe RSV disease in the second year of life (American°Academy°of°Pediatrics 2014; AAP 2022).

Two drugs are currently approved by the FDA for the prevention of RSV lower respiratory disease: palivizumab (MedImmune 1998) and nirsevimab-alip (ASTRAZENECA°AB 2023). Palivizumab (MedImmune 1998) is indicated for the prevention of serious RSV lower respiratory tract disease in high-risk infants. This indication was supported by trials in premature infants born at <35 weeks of gestation, infants with chronic lung disease of prematurity, and infants with hemodynamically significant congenital heart disease. The efficacy of palivizumab was assessed in two trials in which the primary efficacy endpoint was the incidence of RSV-associated hospitalization. In the first trial, there was a 55% relative reduction in RSV-associated hospitalizations; and in the second, there was a 45% relative reduction in RSV-associated hospitalizations. Palivizumab, like nirsevimab and clesrovimab, is a recombinant humanized monoclonal antibody directed against a conserved epitope on the RSV fusion (F) protein. Because palivizumab is not modified to extend its serum half-life, a monthly intramuscular injection is required. The first dose of palivizumab is administered prior to the start of the RSV season and the remaining four doses are administered monthly during the RSV season. Nirsevimab-alip (ASTRAZENECA°AB 2023) is a human monoclonal antibody, RSV F protein-directed fusion inhibitor, approved by the FDA in July 2023 for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Due to its extended half-life, a single dose of nirsevimab provides protection through an RSV season.

Aerosolized ribavirin is the only drug or biologic product approved for the treatment of RSV disease (BAUSCH 1985). However, use of aerosolized ribavirin is limited due to its teratogenic effects and administration challenges, including risk of environmental spread. Aerosolized ribavirin must be administered in a hospital setting and is generally administered using an oxygen tent.

Multiple vaccines are under development to prevent RSV disease. (b) (4)

(b) (4). One RSV vaccine, the RSVpreF vaccine (Pfizer°Inc. 2023) was approved by the FDA in 2023 for active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Efficacy of a Single Clesrovimab 105-mg Dose for All Participants, Regardless of Chronological Age and Weight

The Applicant proposed an indication for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. The results of Trial MK-1654-004 provide compelling evidence that clesrovimab reduces the risk of MALRI in the first year of life. However, the appropriateness of the same 105-mg dose of clesrovimab for all chronological age groups and weight bands within the first year of life warrants careful assessment.

3.1.1.2. Duration of Protection Following a Single Dose of Clesrovimab

Efficacy was assessed through Day 150 postdose as the primary endpoint and through Day 180 postdose as a secondary endpoint. Kaplan-Meier curves for the overall population as well as for key subgroups were analyzed to determine if efficacy was maintained through the entire 150-day period and to assess what, if any, conclusions could be drawn regarding efficacy beyond Day 150.

3.1.1.3. The Need for a Second Clesrovimab Dose for Infants Undergoing ECMO or CPB

For infants undergoing ECMO or cardiac surgery requiring CPB during or entering their first RSV season, the Applicant proposed an additional 105-mg dose, regardless of time of ECMO or CPB relative to the Season-1 dose as soon as the infant is stable after surgery to ensure adequate clesrovimab serum levels. The necessity and appropriateness of the proposed recommended dosage was evaluated.

3.1.1.4. Efficacy by RSV Subtype

While the primary efficacy endpoint of relative risk reduction (RRR) of RSV-associated MALRI Days 1 through 150 was met in Trial MK-1654-004, potential inconsistencies were observed between the RRR estimates for the RSV A and RSV B subtypes. In particular, we note that subgroup analysis of efficacy by RSV subtype suggested potential decreased efficacy against RSV A compared to that observed for RSV B, though a favorable trend toward a decreased

incidence rate of MALRI through Day 150 was still observed for RSV A among participants receiving clesrovimab (0.012) compared to placebo (0.022), with an RRR and 95% CI of 44.4% and (5.5%, 67.3%), respectively.

3.1.1.5. Impact of the Presence of Antidrug Antibodies on Clesrovimab Efficacy

There was a trend of lower efficacy in antidrug antibody (ADA)-positive participants compared to ADA-negative participants in Trials MK-1654-004 and MK-1654-007.

3.1.1.6. Potential for Reduced Susceptibility to Clesrovimab Through Natural Variability/Polymorphisms

The clinical efficacy of clesrovimab against RSV could be impacted by naturally occurring variants which harbor F protein polymorphisms associated with reduced susceptibility to clesrovimab.

3.1.1.7. Potential for Treatment-Emergent Resistance to Clesrovimab

Prophylaxis with clesrovimab could theoretically select for variants with amino acid substitutions which reduce susceptibility and result in a breakthrough infection. Breakthrough infections could potentially result in worse disease outcomes and transmission of resistant virus. The assessment of resistance emergence following prophylaxis with clesrovimab is critical to understanding the overall risk-benefit profile of clesrovimab.

3.1.2. Key Safety Review Issues

3.1.2.1. Hypersensitivity Reactions, Including Anaphylaxis and Rash

Immune-mediated adverse reactions, including anaphylaxis and hypersensitivity skin reactions, are known potential adverse reactions associated with the use of monoclonal antibodies (Pintea et al. 2021). These adverse reactions have been reported with the use of palivizumab and with nirsevimab, monoclonal antibodies against the RSV fusion protein with similar mechanisms of action to clesrovimab.

3.1.2.2. Potential for Interference With RSV Rapid-Test Assays

Rapid antigen testing is typically used in the clinic for the diagnosis of RSV infection. Because these types of assays use antibodies targeting the F protein for detection, there is a potential for interference by clesrovimab in samples from individuals who have received this product, as has been reported for palivizumab (Deming et al. 2013).

3.1.2.3. Pharmacovigilance

If approved, clesrovimab has the potential for widespread use for the prevention of RSV lower respiratory tract disease in neonates and infants. The pharmacovigilance strategy is important for continued assessment and risk characterization once clesrovimab is licensed for marketing.

3.2. Approach to the Clinical Review

Table 3 provides an overview of the clinical trials to support the benefit-risk assessment of clesrovimab for the prevention of RSV in neonates and infants who are born during or entering their first RSV season. Data from six clinical trials were submitted to support licensure of clesrovimab (MK-1654) for the proposed indication: three Phase 1 trials (MK-1654-001 and MK-1654-003 in healthy adults; and MK-1654-008 in healthy adults, children, and infants), one Phase 1b/2a trial (MK-1654-002 in healthy preterm and term infants), one Phase 2b/3 trial (MK-1654-004 in healthy preterm and term infants), and one Phase 3 trial (MK-1654-007 in infants and children at increased risk for severe RSV disease). The results of Trials MK-1654-004 and MK-1654-007 provided the primary data to support the safety, efficacy, and pharmacokinetics of clesrovimab in pediatric patients. An additional (seventh) trial, MK-1654-005, was a human challenge study in adults (b) (4) and only enrolled 16 adult participants who received a relevant dose of 900 mg intravenously (IV) (the closest dose based on allometric scaling to the 105-mg IM dose for infants). Data from the Phase 1 trials and the Safety Update Report were also reviewed and contributed to the benefit-risk assessment of clesrovimab.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

1. Verbatim indication:

   Prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season.

2. SEE was established with

   a. Adequate and well-controlled clinical investigation(s):

      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**

      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

OR

c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[2]

3. Complete response, if applicable

a. ☐ SEE was established
b. ☐ SEE was not established

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (January 2020)

[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (August 2018)

[3] FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (November 2023)

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Clesrovimab

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Participants Planned; Actual Randomized	Number of Centers and Countries
MK-1654-001	Healthy male and female participants of nonchildbearing potential between 19 and 59 years old.	Phase 1, pharmacokinetics and safety Control type: placebo Randomization: standard randomization Randomization ratio: 3:1 Blinding: double-blind Biomarkers: no biomarkers Innovative design features: none	Drug (established name): clesrovimab (MK-1654) Dose: • 100 mg IM • 300 mg IM • 300 mg IV • 1000 mg IV • 3000 mg IV Number treated: Total MK-1654: 114 Placebo: 38 Duration (quantity and units): single dose on Day 1, and 365 days of safety follow-up	Primary: • Safety • Serum pharmacokinetics of MK-1654 ($AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$) Secondary: • $AUC_{0\text{-}inf}$ and C_{max} (to evaluate absolute bioavailability of single IM dose of 300-mg MK-1654) • Incidence and magnitude of ADA to MK-1654	Planned: 152 Actual: 152	Centers: 1 Countries: 1 (United States)
MK-1654-003	Japanese male participants between the ages of 20 to 55 years.	Phase 1, pharmacokinetics and safety Control type: placebo Randomization: standard randomization	Drug (established name): clesrovimab (MK-1654) Dose: • 100 mg IM • 300 mg IM • 300 mg IV • 1000 mg IV Number treated:	Primary: Safety Secondary: • Serum pharmacokinetics of single IV and IM doses of MK-1654 ($AUC_{0\text{-}inf}$, C_{max}, C_{150d}, T_{max}, and $t_{1/2}$) • Proportion of participants who develop ADA	Planned: 44 Actual: 44	Centers: 1 Countries: 1 (Japan)

		Randomization ratio: 3:1 Blinding: double-blind Biomarkers: no biomarkers Innovative design features: none	MK-1654 (N=33) Placebo (N=11) Duration (quantity and units): single dose (follow-up to Day 365)			
MK-1654-008	Panel A: male adults aged ≥18 to ≤55 years Panel B: male or female children aged ≥2 to ≤8 years Panel C: male or female healthy preterm (≥29 to <35 weeks gestational age) and full-term infants (≥35 weeks gestational age) ≥2 weeks to ≤1 year	Phase 1, pharmacokinetics, and safety Control type: none (single-arm) Blinding: unblinded open-label Biomarkers: no biomarkers Innovative design features: none	Drug (established name): clesrovimab (MK-1654) Dose: • 105 mg IM Number treated: MK-1654 (N=75) • Panel A (N=25) • Panel B (N=25) • Panel C (N=25) Duration (quantity and units): single dose (follow-up to Day 365)	Primary: Safety	Planned: 75 Actual: 75	Centers: 2 Countries: 1 (China)

MK-1654-002 (NCT03524118)	Healthy preterm (29 to 35 weeks gestational age) and full-term (over 35 weeks gestational age) infants aged 2 weeks to 8 months	Phase 1/2, pharmacokinetics and safety Control type: placebo Randomization: stratified randomization Randomization ratio: 4:1 Blinding: double-blind Biomarkers: no biomarkers Innovative design features: none	Drug (established name): clesrovimab (MK-1654) Dose: • 20 mg IM • 50 mg IM • 75 mg IM • 100 mg IM Number treated: MK-1654 (N=143) Preterm infants: • 20 mg IM (N=8) • 50 mg IM (N=31) • 75 mg IM (N=40) • 100 mg IM (N=32) Full-term infants • 100 mg IM (N=32) Placebo (N=38) Duration (quantity and units): single dose (follow-up to Day 365 or Day 545)	Primary: Safety Secondary: • Serum pharmacokinetics of MK-1654 ($AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, C_{7d}, C_{14d}, C_{90d}, C_{150d}, and C_{365d}) • Proportion of participants who develop ADA	Planned: 183 Actual: 181	Centers: 34 Countries: 6
MK-1654-004 (NCT04767373)	Healthy preterm and term infants from birth up to 1 year entering first RSV season	Phase 2b/3, safety, efficacy, pharmacokinetics Control type: placebo Randomization: stratified randomization Randomization ratio: 2:1	Drug: clesrovimab (MK-1654) Dose: 105 mg Number treated: MK-1654 (N=2412) Placebo (N=1202) Duration (quantity and units):	Primary: • Number of participants with RSV-associated MALRI (outpatient and inpatient), from Days 1 through 150 postdose, defined as: ○ Cough or difficulty breathing ○ One or more of the following: wheezing, chest wall in-drawing/retractions, rales/crackles,	Planned: 3300 Actual: 3632 (2421 clesrovimab, 1211 placebo)	Centers: 192 Countries: 22

		Blinding: double-blind Biomarkers: no biomarkers Innovative design features: none	Single dose, follow-up to Day 365 or Day 515 postdose	hypoxemia, tachypnea, dehydration due to respiratory symptoms ○ RSV-positive RT-PCR NP sample • Safety Secondary: • Number of participants with RSV-associated hospitalization from Days 1 through 150 postdose, defined as the following: ○ Hospital admission for respiratory illness ○ RSV-positive RT-PCR NP sample • Number of participants with RSV-associated MALRI (outpatient and inpatient), defined as above, from Days 1 through 180 postdose.		
MK-1654-007-Part 1 (NCT04938830)	Infants at increased risk for severe RSV disease from birth up to 1 year entering their first RSV season: 1. Early/moderate preterm infants ≤35 weeks 2. Infants with chronic lung	Phase 3, safety, pharmacokinetics, efficacy Control Type: Active (palivizumab) Randomization: Stratified randomization	Drug (established name): Clesrovimab (MK-1654) Dose: MK-1654 105 mg Palivizumab 15 mg/kg Number treated: MK-1654 (N=445) Palivizumab (N=450)	Primary: Safety Secondary: • Number of participants with RSV-associated MALRI occurring from Days 1 through 150 postdose 1 in RSV Season 1 (outpatient and inpatient), defined as the following seen in clinical setting:	Planned: 1000 Actual: 901 (450 clesrovimab, 451 palivizumab)	Centers: 109 Countries: 27

disease (CLD) of prematurity/ hemodynamically significant congenital heart disease (CHD)	Randomization Ratio: 1:1 Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Duration (quantity and units): MK-1654: Single dose Day 1 and placebo Day 28. Palivizumab: One dose Day 1 and one dose Day 28. Safety follow-up until Day 42. Double-blinded until Day 60.	○ Cough or difficulty breathing; and ○ One or more of the following: wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms; and ○ RSV-positive RT-PCR NP sample • Number of participants with RSV-associated hospitalizations occurring from Days 1 through 150 postdose 1 in RSV Season 1, defined as the following: ○ Hospital admission for respiratory illness; and ○ RSV-positive RT-PCR NP sample • Serum pharmacokinetics of MK-1654 (C_{7d}, C_{150d}, C_{240d})

Source: Clinical Study Report and adsl.xpt
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
Abbreviations: ADA, antidrug antibodies; $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated from time 0 to infinity; C_{max}, maximum plasma concentration; C_{7d}, serum concentration on Day 7; C_{14d}, serum concentration on Day 14; C_{90d}, serum concentration on Day 90; C_{150d}, serum concentration on Day 150; and C_{365d}, serum concentration on Day 365; IM, intramuscular; IV, intravenous; MALRI, medically attended lower respiratory infection; NP, nasopharyngeal; RSV, respiratory syncytial virus; RT-PCR, reverse transcription–polymerase chain reaction; T_{max}, time to reach C_{max}; $t_{1/2}$, terminal half-life

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

The mechanism of action and quantification of activity of clesrovimab were evaluated in nonclinical studies, including RSV fusion protein binding assays and cell culture models of RSV neutralization. Potential effectiveness and contribution of Fc effector functions were assessed in animal models of RSV prevention. These studies are described in detail in Section 20.

Mechanism of Action

Clesrovimab is a recombinant human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that preferentially binds the prefusion conformation of the RSV fusion (F) protein. The Fc

region of the precursor mAb to clesrovimab, RB-1, was modified with three amino acid substitutions (YTE) to extend the serum half-life in humans. YTE substitutions reduce binding by Fcγ receptors and Fc effector function activity (Dall'Acqua et al. 2006).

Co-crystallography studies of RB-1 fragment antigen-binding (Fab) with prefusion F protein showed that RB-1 binds to antigenic Site IV, which likely locks the protein in its prefusion state and prevents the irreversible conformational change to the more stable postfusion conformation. The postfusion F protein brings viral and host membranes together prior to viral entry and is an essential process in the viral replication cycle. The crystallography studies identified 12 discontinuous amino acid positions within the F1 subunit of F protein as contact residues for RB-1: 426-429, 432-433, 440-441, 443, and 445-447. The location of the binding epitope was confirmed using alanine scanning mutagenesis and sequencing of resistant variants that were selected in cell culture.

Binding Activity

The binding activities of clesrovimab and its parental antibody RB-1 were evaluated against prefusion and postfusion trimeric conformations of RSV A F protein using surface plasmon resonance. Clesrovimab bound to RSV prefusion and postfusion F proteins with affinities (dissociation constant [K_D] values) of 71pM and 480pM, respectively. Binding to the postfusion conformation of F protein had a slower off-rate compared with binding to the prefusion version.

Cell Culture Neutralization Activity

The neutralization activity of clesrovimab against laboratory strains and clinical isolates of RSV A and RSV B was evaluated in cell culture. For the laboratory strains, the average half-maximal effective concentration (EC_{50}) values against RSV A Long and RSV B 18537 were 40pM (6.0 ng/mL) and 20pM (3.0 ng/mL), respectively.

Against a panel of 47 historical clinical isolates, collected from 1987 to 2016, clesrovimab neutralized RSV A isolates with a median EC_{50} value of 25pM (3.71 ng/mL) (n=24; range of 1.2 to 74pM [0.18 to 11.11 ng/mL]), and each of the RSV B isolates with a comparable median EC_{50} value of 30pM (4.48 ng/mL) (n=23; range of 4 to 198pM [0.59 to 29.65 ng/mL]).

Against a panel of 12 contemporary clinical isolates, collected from 2016 to 2021, clesrovimab neutralized each of the six RSV A isolates with a median EC_{50} value of 121pM (18.02 ng/mL) (n=6; range of 59 to 186pM [8.79 to 27.74 ng/mL]), and each of the six RSV B isolates with a median EC_{50} value of 130pM (19.41 ng/mL) (n=6; range of 95 to 153pM [14.22 to 22.92 ng/mL]). While the median EC_{50} values for RSV A and RSV B isolates are approximately 5-fold and 4-fold higher, respectively, than those for the larger panel of historical isolates, the EC_{50} values for the RSV A and RSV B reference strains were also 2- to 3-fold higher in the experiments with the contemporary isolates compared with those of the historical isolates, so the difference may be accounted for by assay variability, particularly considering the experiments were conducted several years apart.

Animal Models of RSV Infection and Evaluation of Effector Function

A nonlethal cotton rat model of RSV infection was used to assess the prophylactic antiviral activity of clesrovimab parental antibody RB-1, and the influence of the effector function of RB-1 on antiviral activity.

To determine antiviral activity, RB-1 and D25 control antibodies were assessed at doses of 2.5, 0.83, 0.28, 0.09, 0.03 mg/kg in groups of five female cotton rats, along with a control group (n=5) with no mAb administered. On Day 0, mAbs were administered IM, and animals were challenged intranasally on Day 1 with $1x10^5$ plaque-forming units (PFU) RSV A2 or RSV B 18537 strains in 100-µL volume. Animals were euthanized 4 days following viral challenge, and lung and nasal RSV titers were determined by plaque assay. For RB-1 tested against RSV A2, 90% effective concentration (EC_{90}) values of 69nM (10.3 µg/mL) and 151nM (22.6 µg/mL) were determined for lung and nose tissue, respectively, and for RSV B 18537, EC_{90} values of 43nM (6.4 µg/mL) and 136nM (20.4 µg/mL), respectively. For D25, similar titers were obtained, but approximately 2-fold higher against RSV B.

A modified version of RB-1 was generated to include Fc substitutions L234A and L235A (LALA), which reduce binding to IgG Fcγ receptors and C1q (Wilkinson et al. 2021). RB-1 and RB-1-LALA were assessed at 0.03, 0.09, 0.28, 0.83, or 2.5 mg/kg in groups of five female cotton rats, along with a control group (n=5) which did not receive antibody treatment. Antibody was administered IM on Day 0, and on Day 1, blood samples taken for determining serum antibody concentrations. Following blood collection, each animal was intranasally dosed with $1x10^5$ PFU RSV A2 in 100-µL volume. At 4 days postchallenge, lung and nose tissue were collected for assessment of viral titers by plaque assay. RB-1 and RB-1-LALA had similar EC_{50} values for lung and nose tissue, of approximately 7nM (1 µg/mL) and 67nM (10 µg/mL), respectively, indicating that at least for this model, there was no clear impact of the LALA modifications on antiviral activity.

These data indicate that effector function is not necessarily needed for antiviral activity, at least in the cotton rat model. However, there may be differential effects between cotton rat and humans, depending on relative binding to Fcγ and C1q receptors.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Respiratory syncytial virus (RSV) F protein-directed fusion inhibitor
Mechanism of action	Clesrovimab is a neutralizing recombinant human IgG1 kappa (IgG1κ) monoclonal antibody which binds preferentially to the prefusion conformation of the RSV fusion (F) protein. Clesrovimab binds to a conserved epitope in antigenic Site IV on the RSV F protein, preventing fusion of the viral and cellular membranes and virus entry into cells. Clesrovimab is modified with a triple amino acid substitution (YTE) in the Fc region to extend serum half-life.
Active moieties	Clesrovimab
QT prolongation	A clinical thorough QT/QTc study was not conducted as monoclonal antibodies have a low likelihood of direct ion channel interactions.
	General Information
Bioanalysis	Clesrovimab concentrations in human serum were determined with LC-MS/MS methods which were validated in the calibration range of 0.500 (LLOQ) to 500 (ULOQ) mcg/mL. The method involved sample preparation via protein precipitation followed by trypsin digestion to generate peptides. Stable isotope-labeled clesrovimab was used as an internal standard (ISTD). A peptide from the variable region of the antibody that resulted from the digestion served as a surrogate for the analyte quantitation, with a corresponding peptide from the ISTD serving as a surrogate for the ISTD.
Healthy subjects versus patients	Not applicable (N/A). Clesrovimab is not indicated for the treatment of RSV lower respiratory tract disease.

Characteristic	Drug Information
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 6. Clesrovimab Pharmacokinetic Parameters Following a Single 105-mg Dose Administered Intramuscularly, Trials MK-1654-004 and MK-1654-007**

Parameters	MK-1654-004 Season 1 (N=2304)	MK-1654-007 Season 1 (N=434)	Overall Season 1 (N=2738)
$AUC_{0\text{-}150d}$ (mcg*day/mL)			
Mean (SD)	6400 (1350)	7900 (1540)	6640 (1490)
Median [2.5%, 97.5%]	6270 [4150, 9440]	7970 [5080, 10800]	6490 [4190, 9940]
Geo. mean (geo. CV)	6260 (21.2)	7740 (20.4)	6470 (22.6)
C_{150d} (mcg/mL)			
Mean (SD)	10.6 (3.30)	12.1 (3.38)	10.9 (3.35)
Median [2.5%, 97.5%]	10.5 [4.49, 17.2]	11.9 [5.27, 18.8]	10.8 [4.49, 17.8]
Geo. mean (geo. CV)	10.1 (36.4)	11.5 (35.2)	10.3 (36.6)

Source: Ref. 5.3.5.3, 08KHN9, Clesrovimab PopPK Report Table 6-21
Abbreviations: $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; CV, coefficient of variation; C_{150d}, serum concentration on Day 150; geo., geometric; N, number of participants in treatment arm; PopPK, population pharmacokinetic(s); SD, standard deviation

Range of effective dose(s) or exposure	The recommended dosage is 105 mg administered as a single intramuscular (IM) injection
Maximally tolerated dose or exposure	A maximally tolerated dose or exposure was not determined. The highest evaluated dosage in the indicated population (neonates and infants) was 105 mg IM. A single dose of 210 mg IM is currently being evaluated in pediatric participants entering their second RSV season. Single doses up to 300 mg IM or 3000 mg IV have been administered in healthy adult participants.
Dose proportionality	Clesrovimab exhibits linear pharmacokinetics with approximate dose-proportional increases in AUC (and C_{max}) in infants receiving 20 to 105 mg IM and adults receiving 300 mg to 3000 mg IV.
Accumulation	N/A.
Time to achieve steady-state	N/A.
Bridge between to-be-marketed and clinical trial/study formulations	The intended commercial clesrovimab formulation is identical to the formulation (Process 2 formulation) used in the Phase 2b and Phase 3 trials except that the commercial formulation is prepared in a single-use PFS whereas solution in vial presentation was used in the clinical trials.
	Absorption
Bioavailability	The absolute bioavailability in infants is not estimated at this time.
T_{max}	Median [2.5%, 97.5%]: 6.50 [5.90, 7.40] days
Food effect (fed/fasted)	N/A. Clesrovimab is administered IM.
Geometric least square mean and 90% CI	

Characteristic	Drug Information
	Distribution
Volume of distribution (Vd)	The estimated apparent Vd is 830 mL for a typical infant weighing 5 kg, based on PopPK estimate.
Plasma protein binding	N/A.
Drug as substrate of transporters	N/A.
	Elimination
Mass balance results	N/A.
Clearance	The estimated apparent clearance is 19.7 mL/day for a typical infant weighing 5 kg, based on PopPK estimate.
Half-life	Terminal half-life 44.0 days (CV% 13.4)
Metabolic pathway(s)	Clesrovimab is expected to be degraded into peptides and amino acids via catabolic pathways.
Primary excretion pathways (% dose)	N/A.
	Intrinsic Factors and Specific Populations
Body weight	Based on the PopPK analysis, body weight was identified as a significant covariate impacting the pharmacokinetics of clesrovimab. The magnitude of the effect of body weight on clesrovimab exposures in RSV Season 1 is not clinically significant, and thus dose adjustment based on body weight is not necessary.
Age	Based on the PopPK analysis, after accounting for the weight difference, a maturation function was incorporated in the model describing the additional effect of age on clearance.
Renal impairment	No dedicated study was conducted to evaluate the impact of renal impairment. Clesrovimab is a monoclonal antibody with a molecular weight greater than 69 kDa. Therefore, impaired renal function is unlikely to alter pharmacokinetics to a clinically significant degree.
Hepatic impairment	No dedicated study has been conducted to evaluate the impact of hepatic impairment. Clesrovimab is a monoclonal antibody, thus its distribution and elimination are not mediated by cytochrome P450 (CYP) or drug transporters.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	N/A
Inhibition/induction of transporter systems	N/A

Characteristic	Drug Information
	Immunogenicity (if Applicable)
Bioanalysis	Anticlesrovimab antibodies (ADAs) in human serum were assayed using an electrochemiluminescence (ECL) immunoassay.
Incidence	In Trial MK-1654-002, the proportion of infants with positive ADAs was 13.1% at Day 150 and 22.8% through Day 365. In Trial MK-1654-004, the proportion of participants with positive ADA to clesrovimab was 5.7% at Day 150, 12.0% through Day 240, 37.9% through Day 365, and 58.6% through Day 515. In Trial MK-1654-007 RSV Season 1, the proportion of participants with positive ADA to clesrovimab was 4.5% at Day 150 and 13.0% through Day 240.
Clinical impact	The incidence rates of RSV-associated MALRI were numerically higher in ADA+ group compared to ADA- group. The impact of ADA on efficacy is unknown due to the low rates of MALRI and ADA. There was no identified impact of ADA on pharmacokinetics, RSV serum neutralizing activity or safety of clesrovimab during RSV Season 1.

Source: Reviewer generated table.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; IM, intramuscular; IV, intravenous; kDa, kilodalton; LC-MS/MS, liquid chromatography tandem mass spectrometry; LLOQ, lower limit of quantitation; MALRI, medically attended lower respiratory infection; PFS, prefilled syringe; PopPK, population pharmacokinetic(s); QT, QT interval; QTc, corrected QT interval; ULOQ, upper limit of quantitation

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Recommended Dosage

The recommended dosage of clesrovimab for neonates and infants born during or entering their first RSV season is a single dose of 105 mg administered by IM injection. The recommended dosage is identical to the dosage evaluated in two Phase 3 clinical trials, MK-1654-004 and MK-1654-007.

Selection of Dosing Regimen for the Phase 3 Trials

A single 105-mg IM dose of clesrovimab was selected based on PK and safety data from healthy adults in Phase 1 trials (MK-1654-001 and MK-1654-003) and an infant Phase 1b/2a trial (MK-1654-002), and results from a model-based meta-analysis (MBMA). Briefly, the Applicant conducted an MBMA for RSV which describes the relationship between serum neutralization titer of antibodies targeting RSV (palivizumab, motavizumab, nirsevimab, and immunoglobulin products) and the incidence rate of RSV infection. Per the Applicant's MBMA analysis, doses of 75 mg or higher were predicted to provide median efficacy >70%, and efficacy appeared to plateau between doses of 90 to 105 mg. This approach was discussed in detail during the model-informed drug development (MIDD) meetings on February 20, 2020, and June 29, 2020, and the FDA agreed on the approach to dose selections in the Phase 3 trials.

Data Supporting the Proposed Dosing Regimen

Results from Trial MK-1654-004 demonstrated that a single 105-mg IM dose is safe and efficacious in preterm and term infants in RSV Season 1. The exposure-response relationship analysis using data from Trial MK-1654-004 showed a flat exposure-response relationship, indicating efficacy is on the plateau. Additional efficacy and exposure-response analyses by body weight and age support administration of the same dosage in RSV Season 1 regardless of body weight or age (see Section 6.3.1).

The Applicant characterized the relationship between clesrovimab exposure and efficacy endpoints from Trial MK-1654-004, such as RSV-associated MALRI (Days 1 to 150), RSV-A-associated MALRI (Days 1 to 150), RSV-B-associated MALRI (Days 1 to 150) and RSV-associated MALRI (Days 1 to 180). The exposure metrics evaluated were the PK model-derived clesrovimab area under the concentration-time curve (AUC) from Day 1 to Day 150 ($AUC_{0\text{-}150d}$) or Day 180 ($AUC_{0\text{-}180d}$), depending on the endpoint.

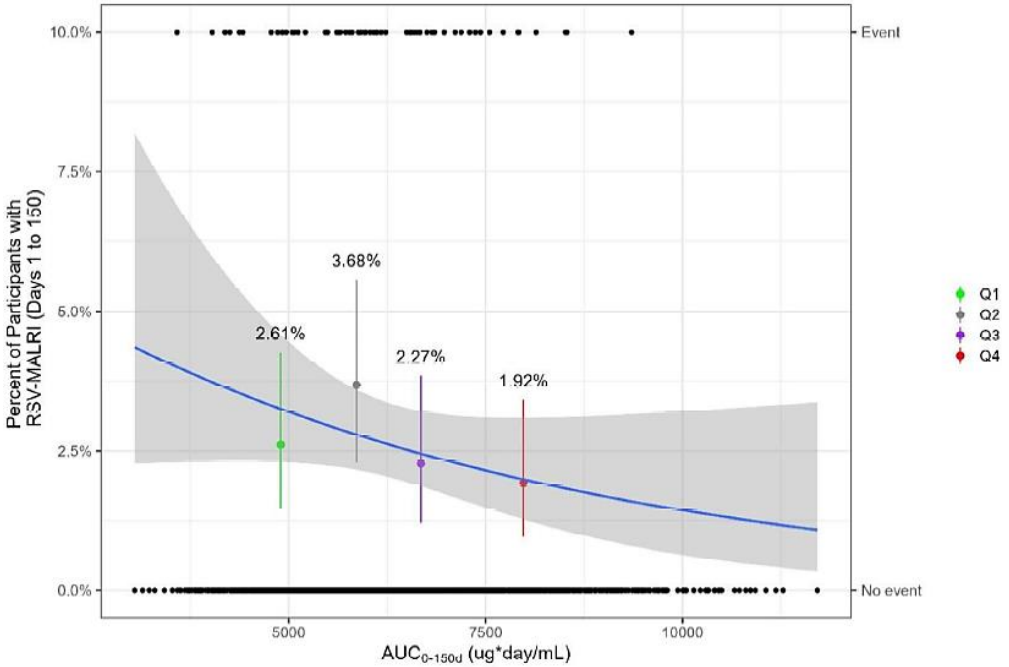
The exposure-response relationship for the primary endpoint, RSV-associated MALRI (Days 1 to 150), versus $AUC_{0\text{-}150d}$ (Figure 1) was relatively flat across the exposure range associated with a single 105-mg IM dose of clesrovimab in Season 1, and the estimated trend of the exposure-response relationship, using a logistic regression, was not found to be statistically significant.

A similarly flat and non-statistically significant relationship was estimated for the endpoints associated with RSV subtypes A and B, and for the relationship between the secondary endpoint

RSV-associated MALRI (Days 1 to 180) and $AUC_{0\text{-}180d}$. Of note, most of RSV-associated MALRI events in the clesrovimab arm occurred before Day 150 (60 events in 2291 participants with evaluable exposure), with four additional events between Day 150 and Day 180. Therefore, exposure-efficacy analyses for the RSV-associated MALRI endpoints up to Day 150 were considered more relevant.

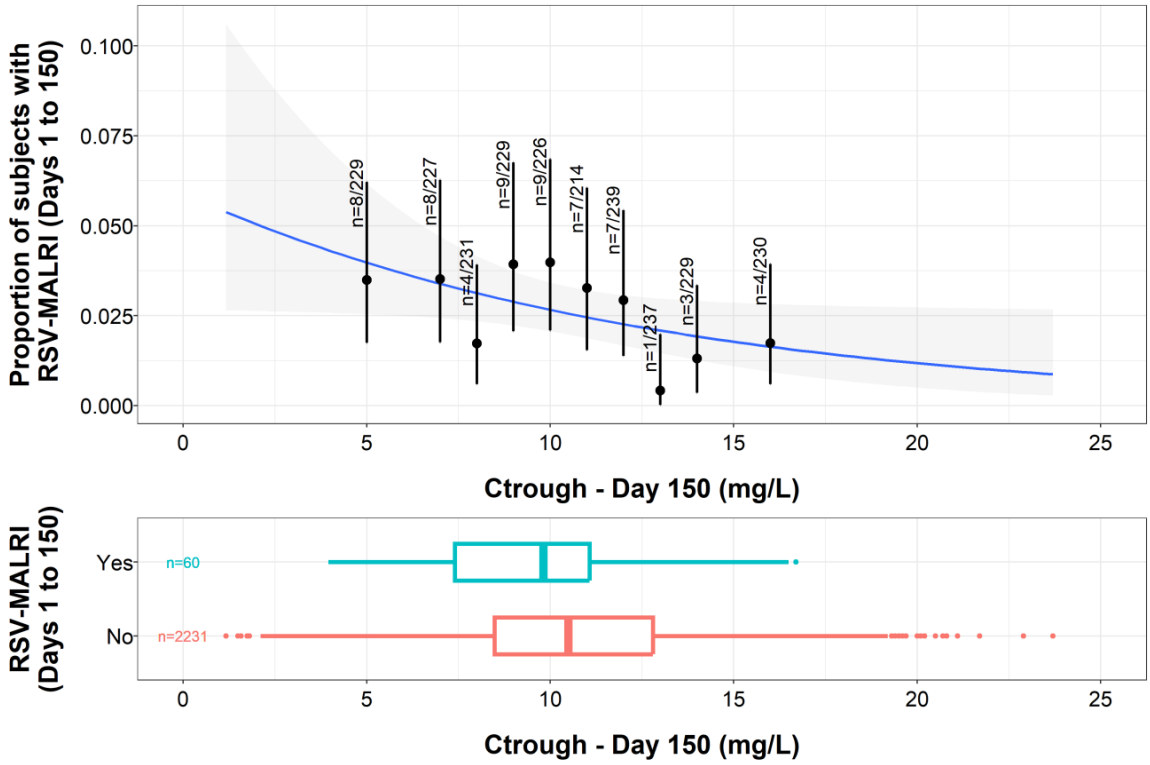
The FDA's assessment of the exposure-efficacy relationship for the primary endpoint, with C_{trough} on Day 150 as the exposure metric (Figure 2), found a statistically significant relationship (p-value of 0.04 for the slope parameter) between C_{trough} and RSV-associated MALRI (Days 1 to 150). Even though there was a trend towards statistical significance for C_{trough}, the relationship was not considered clinically meaningful and does not suggest that other doses would offer improvement in efficacy. Rather, the observations suggest that the 105-mg dose produces exposures in the plateau of response. This conclusion was supported in particular by the largely overlapping C_{trough} values between participants with and without RSV-associated MALRI (Days 1 to 150) events, and the flat relationship when considering the proportion of participants with RSV-associated MALRI (Days 1 to 150) events across most of the quantiles of clesrovimab C_{trough} (representing more than 75% of C_{trough} observations), except for eight participants with C_{trough} in the highest three quantiles driving the trend towards statistical significance.

Figure 1. Observed Proportion and Predicted Probability of RSV-Associated MALRI, Days 1 to 150 vs. $AUC_{0\text{-}150d}$



Source: Applicant's Modeling and Simulation Report, Figure 5-2, page 26.
Black dots: area under the concentration-time curve from Day 1 to Day 150 ($AUC_{0\text{-}150d}$) from individual participants. Closed circles (error bars) show the observed proportion of participants with an event (95% CI based on the Pearson-Klopper method) by exposure quartile and are plotted at the median exposure of each quartile of $AUC_{0\text{-}150d}$. Solid (blue line and gray area) curves are the model-predicted (logistic regression) probability of the event (95% CI).
Median (range) of $AUC_{0\text{-}150d}$ (ug*day/mL) for each quartile is 4900 [3050, 5430) for Q1, 5860 [5430, 6270) for Q2, 6680 [6270, 7240) for Q3, and 7980 [7240, 11700] for Q4.
Reviewer's note: the y axis for the percentage of participant with RSV-associated MALRI (Day 1 to 150) is capped at 10% (instead of 100%) for clarity and to better observe the relationship.
Abbreviations: $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; CI, confidence interval; RSV-associated MALRI, RSV-associated medically attended lower respiratory infection; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; RSV, respiratory syncytial virus

Figure 2. Observed Proportion and Predicted Probability of RSV-Associated MALRI, Days 1 to 150, vs. C_{trough} on Day 150



Source: FDA reviewer.
Upper panel: Closed circles (error bars) show the observed proportion of participants with an event (95% CI based on the Pearson-Klopper method) by exposure decile and are plotted at the median exposure of each decile of C_{trough} on Day 150. Solid (blue line and gray area) curves are the model-predicted (logistic regression) probability of the event (95% CI).
Lower panel: boxplot of C_{trough} on Day 150 in participants with or without RSV-associated MALRI (Days 1 to 150) event.
Abbreviations: CI, confidence interval; C_{trough}, trough concentration; n, number of participants with a given event; RSV-associated MALRI, RSV-associated medically attended lower respiratory infection; RSV, respiratory syncytial virus

An exposure-response analysis for efficacy was not conducted for Trial MK-1654-007. Trial MK-1654-007 was a smaller efficacy study without a formal sample size calculation, conducted in infants at increased risk for severe RSV disease entering their first RSV season. Based on the similarity in the pathophysiology of RSV infection between infants with and without certain medical comorbidities, as well as the drug's mechanism of action, it is reasonable to conclude that the exposure-response analysis from Trial MK-1654-004 supports the proposed dosing regimen for infants at high risk. Of note, risk factors for severe RSV such as CLD or CHD were not significant covariates for clesrovimab pharmacokinetics (see Sections 8 and 14.5).

Conclusion

A single 105-mg dose of clesrovimab, irrespective of body weight, gestational age, and comorbidities, is recommended for all neonates and infants born during or entering their first RSV season. See Section 6.3.3 for the dosage recommendation for infants undergoing CPB or ECMO.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Trials Reviewed for Efficacy

The evaluation of efficacy included two randomized trials: Trial MK-1654-004, an adequate and well-controlled clinical investigation, and Trial MK-1654-007, which provided confirmatory evidence for the marketing application.

Trial MK-1654-004 was a Phase 2b/3, multicenter, randomized, double-blind, placebo-controlled trial, where participants were randomized in a 2:1 ratio to receive clesrovimab or placebo and followed for at least 365 days. Trial MK-1654-007 was a Phase 3, multicenter, randomized, partially blinded, palivizumab-controlled trial, where participants were randomized in a 1:1 ratio to receive clesrovimab or palivizumab and followed for at least 365 days.

The key differences between Trials MK-1654-004 and MK-1654-007 included the primary endpoint, comparators used, and trial populations. Specifically, the primary efficacy endpoint in Trial MK-1654-004 was the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose, while safety was the primary endpoint for Trial MK-1654-007 and the incidence of MALRI was a secondary endpoint in Trial MK-1654-007. The trial population in Trial MK-1654-004 consisted of healthy infants ≥29 weeks gestational age from birth up to 1 year entering their first RSV season, with placebo as the comparator. In contrast, the population in Trial MK-1654-007 included infants ≤35 weeks gestational age, or infants with CLD of prematurity or hemodynamically significant CHD, from birth up to 1 year entering their first RSV season, with palivizumab as the comparator. Because Trial MK-1654-007 was not fully powered to detect an efficacy difference between clesrovimab and palivizumab, the efficacy of clesrovimab in the population in Trial MK-1654-007 was extrapolated from healthy infants in Trial MK-1654-004 based on pharmacokinetics. The efficacy of clesrovimab was also assessed in Trial MK-1654-007 via secondary endpoints comparing incidence rates of RSV-associated MALRI and RSV-associated hospitalization occurring from 1 to 150 days between the clesrovimab and palivizumab arms. Trial MK-1654-004 enrolled and randomized more than three times as many participants as Trial MK-1654-007 (3632 versus 901). No integration of efficacy data was conducted for the two trials due to the differences described above.

6.2.2. Trial MK-1654-004

6.2.2.1. Design, Trial MK-1654-004

Trial MK-1654-004 was designed as a Phase 2b/3 double-blind, placebo-controlled trial in healthy infants born at ≥29 to <35 weeks gestational age (early and moderate preterm) and at ≥35 weeks gestational age (late preterm and term) and entering their first RSV season.

Assuming the incidence of RSV-associated MALRI in the placebo group is 10% per season, and the incidence of RSV-associated MALRI in the MK-1654 group is 3% per season (efficacy =70%), a total of approximately 167 cases of RSV-associated MALRI in the Trial MK-1654 and placebo groups were expected to accrue by the end of the trial based on enrolling

approximately 3300 participants with a 2:1 randomization ratio. Based on these assumptions, the trial would provide 95% power to demonstrate that the efficacy of MK-1654 compared to placebo to prevent RSV-associated MALRI is >25%, assuming 70% efficacy, at an overall one-sided Type-1 error rate of 2.5%.

Approximately 3300 infants up to 1 year of age entering their first RSV season were planned to be randomized in a 2:1 ratio to receive either a single dose of clesrovimab or placebo. Randomization was stratified on region (Northern or Southern Hemisphere), gestational age (early and moderate preterm [≥29 to <35 weeks gestational age], or late preterm and term infants [≥35 weeks gestational age]), and chronological age at time of consent (<6 or ≥6 months of age). A minimum of 600 early and moderate preterm infants were expected to be enrolled into the trial. A minimum of 90% of enrolled infants were expected to be 0 through 8 months of age.

Two cohorts of participants were planned: 300 participants for Phase 2b (aged >2 weeks to 1-year-old), and approximately 3000 participants for Phase 3 (aged from birth to 1-year-old).

All enrolled participants were to be followed for at least 365 days after receiving study intervention. Efficacy surveillance for respiratory infection symptoms were conducted for up to 180 days postdose. All adverse events (AEs) and AESIs were collected for 42 days postdose, and SAEs were to be collected for the duration of trial participation.

A subset of participants (the first 1650 participants enrolled) continued to be followed from Days 365 through 515 postdose. No additional study intervention was administered. Weekly surveillance to monitor the incidence of RSV-associated MALRI and hospitalization was conducted between Days 365 and 515, and SAEs continued to be collected for the duration of trial participation.

The planned trial design is depicted in Section 15.1, Figure 21.

Primary Efficacy Objective and Endpoint

The primary efficacy objective of this trial was to evaluate the efficacy of clesrovimab compared to placebo as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose.

The primary efficacy endpoint was the incidence of RSV-associated MALRI (outpatient and inpatient), defined as the following seen in an outpatient or inpatient clinical setting:

- Cough or difficulty breathing
- One or more of the following: wheezing, chest wall indrawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms
- RSV-positive RT-PCR NP sample

Key Secondary Endpoints

- Incidence of RSV-associated hospitalization from Days 1 through 150 postdose
  - RSV-associated hospitalization, defined as the following:
    - Hospital admission for respiratory illness
    - RSV-positive RT-PCR NP sample

- Incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose

Prespecified Hypothesis Testing Order, Type-I Error Control, and Interim Analysis

The primary efficacy endpoint and one of the secondary endpoints, incidence of RSV-associated hospitalization from Days 1 through 150 postdose, were tested in a prespecified hierarchical order. In this scenario, the secondary hypothesis was tested only if the treatment effect on the primary efficacy endpoint was demonstrated at the significance level of one-sided alpha of 0.025.

Of note, the statistical analysis plan outlined a plan for two interim analyses. The interim analyses were conducted solely for futility assessment. No Type-1 error adjustment is needed for the futility analyses.

Analysis Populations

FAS

The protocol-defined full analysis set (FAS) population consisted of all randomized participants who received one dose of study treatment. The FAS population served as the primary population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. Participants were included in the treatment group based on the study treatment they were randomized to for the efficacy analyses. Of note, even though the FAS was defined as above, the Applicant excluded participants with protocol violations from the FAS used for their efficacy analyses and these participants were also excluded from the analyses presented in this review. However, the Prescribing Information presents the results from the protocol-defined FAS population (i.e., participants with protocol violations were not excluded from the efficacy results in the Prescribing Information). Notably, the efficacy results were not impacted by the inclusion or exclusion of these participants (see sensitivity analyses below).

PPE Population

To be eligible for inclusion in the per-protocol efficacy (PPE) population, trial participants must have satisfied the following criteria:

- Received one dose of the correct clinical material corresponding to the treatment group the participants were randomized into.
- Had at least one follow-up visit/phone call for assessment of RSV disease.
- At any time during dosing or efficacy follow-up, did not experience a protocol deviation that may have interfered with the assessment of protection against RSV infection conferred by clesrovimab.

The PPE population serves as a supportive analysis population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. Participants were included in the treatment group based on their randomization.

Safety Analysis Population

The protocol-defined safety analysis population was the all-participants as-treated (APaT) population, which consists of all randomized participants who received a dose of study treatment. Participants were included in the treatment group based on the study treatment they actually received for the analysis of safety data using the APaT population. Of note, although the safety analysis population was defined as above, the Applicant excluded participants with certain protocol violations (see Section 7.6.1) from the safety population and these participants were excluded from the safety analyses presented in this review. However, the Prescribing Information presents the results from the prespecified APaT population. Notably, the results of the safety assessment were not meaningfully impacted by Applicant's exclusion of participants with certain protocol violations.

6.2.2.2. Eligibility Criteria, Trial MK-1654-004

Inclusion Criteria for Trial MK-1654-004

A participant will be eligible for inclusion in the trial if the participant:

- Is healthy (based on medical history and physical examination results).
- Is male or female.
- Is an early or moderate preterm (born at ≥29 to 34 weeks and 6 days gestational age) or late preterm or full-term (born at ≥35 weeks gestational age) infant.
- Has a chronological age from birth up to 1 year (Phase 2b cohort: from >2 weeks of age up to 1 year; Phase 3 cohort: from birth up to 1 year) and entering their first RSV season at the time of informed consent.

For participants enrolled at sites in countries from the E.U. region or the United Kingdom, age requirements were as follows:

- Chronological age from birth up to 8 months and 29 days (Phase 2b cohort: from >2 weeks of age up to 8 months and 29 days; Phase 3 cohort: from birth up to 8 months and 29 days).
- Entering their first RSV season at the time that documented informed consent was provided.

Key Exclusion Criteria for Trial MK-1654-004

The participant must be excluded from the trial if the participant:

- Is recommended to receive palivizumab per local guidelines or professional society recommendations.
- Has known hypersensitivity to any component of MK-1654.
- Has a bleeding disorder contraindicating intramuscular administration.
- Has 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.
  - Note: If the participant meets this exclusion criterion, Visit 1 (Day 1) may be rescheduled for a time when this criterion is not met.

- Has received any vaccine or mAb for the prevention of RSV, including receipt of maternal RSV vaccination during the mother's pregnancy.

6.2.2.3. Statistical Analysis Plan, Trial MK-1654-004

The efficacy endpoint is defined as RRR,

Efficacy =1- R_t/R_p,

where R_t and R_p are the incidence rates of RSV-associated disease in the clesrovimab and placebo groups, respectively. The incidence rate is defined as the number of RSV-associated disease cases divided by the total person-time of follow-up for efficacy.

Every participant is counted a single time for each applicable endpoint. While a participant may have multiple cases, only the first occurrence of the case for each endpoint is counted for the analysis. The efficacy analyses were based on the data cutoff of 04-MAR-2024.

Analyses of the Primary Endpoint

For the primary endpoint analysis, a Poisson regression model with robust variance (Zou 2004) was used to estimate the relative risk on the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose between the two treatment groups. The model included the following covariates: treatment group (clesrovimab and placebo), hemisphere at randomization (Northern Hemisphere and Southern Hemisphere), gestational age group (early and moderate preterm infant (>=29 to <35 weeks) and late preterm and full-term infant (≥35 weeks), and age group (age ≤6 months and age >6 months) at the time of consent. To allow for differences in follow-up times among the participants, log (follow-up time) as the offset term was added in the modified Poisson regression. Estimate and 95% CI of relative risk reduction were estimated from the model. The one-sided p-value was estimated by an exact binomial method.

The statistical criterion for success required the lower limit of the 95% CI for relative risk reduction to be greater than 25%, the protocol prespecified threshold for this superiority test.

Analyses of Secondary Endpoints

Similar to the primary efficacy endpoint analysis, a Poisson regression model with robust variance was used to estimate the relative risk for two secondary efficacy endpoints. Of note, the model contained the same covariates as the model for primary endpoint analysis. The statistical criterion for success requires the lower limit of the 95% CI for relative risk reduction in RSV-associated hospitalization from Days 1 through 150 postdose to be greater than 0.

Missing Data (To Evaluate the Impact of Missing Data)

If a participant failed to return to the clinic for a required study visit and/or if the site was unable to contact the participant, they were considered a trial dropout. For the primary and secondary efficacy endpoint analyses, the missing data were not imputed.

In the analysis of primary and secondary efficacy endpoints, 108 participants did not complete the Day-150 follow-up visit. Of these, one participant experienced an event before Day 150. The remaining 107 participants were considered not to have experienced an event, and their follow-

up time calculated up to their last available study date in the primary and secondary efficacy analyses. In addition, there were 15 participants who had completed the trial but had protocol violations and were excluded from the FAS for the efficacy endpoint analyses presented in this review (though as previously noted the full FAS population is included in the Prescribing Information). Sensitivity analyses were conducted to assess the impact of the missing values and the exclusion in the primary efficacy endpoint analysis.

Subgroup Analyses

The relative risk reduction for the primary and secondary efficacy endpoints were examined among subgroups: RSV subtype (RSV A and RSV B), gestational age (early and moderate preterm infant (≥29 to <35 weeks) and late preterm and full-term infant (≥35 weeks), age (≤6 months, 6 to 9 months, and ≥9 months), baseline body weight (≤5 kg, 5 to 8 kg, and ≥8 kg), sex (male and female), race (American Indian or Alaska Native, Asian, Black or African American, Multiple, Native Hawaiian or Other Pacific Islander, White, and missing), hemisphere (Northern Hemisphere and Southern Hemisphere), and climate (temperate and tropical/subtropical).

For the analyses by RSV subtype, the RSV A and RSV B subgroups are not mutually exclusive. The efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate.

For the other subgroup analyses, the efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate, or an exact binomial method if convergence issues occurred with the Poisson approach.

6.2.2.4. Results of Analyses, Trial MK-1654-004

This section summarizes participant disposition, demographics, baseline disease characteristics, and primary efficacy results based on data submitted by the Applicant.

As shown in Table 7, a total of 3632 participants were randomized across 192 study sites in 22 countries. Among them, 3614 (99.5%) received the dose of study drug. The majority (86.8%) of participants completed the trial through either Day 365 (RSV Season 1) or Day 515 (RSV Season 2 for selected participants). A total of 6.7% participants discontinued the trial. The disposition of participants was generally comparable between the two groups.

Table 7. Participant Disposition, All Randomized Participants, RSV Season 1, Trial MK-1654-004

Participants in Population	Clesrovimab (N=2421) n (%)	Placebo (N=1211) n (%)	Total (N=3632) n (%)
Participants randomized			
Full analysis set	2411 (99.6)	1203 (99.3)	3614 (99.5)
Safety population	2409 (99.5)	1202 (99.3)	3611 (99.4)
Per protocol efficacy population	2392 (98.8)	1199 (99.0)	3591 (98.9)
Dosed at Day 1			
Clesrovimab	2411 (99.6)	1 (<1)	2412 (66.4)
Placebo	0	1202 (99.3)	1202 (33.1)
Not dosed	10 (<1)	8 (<1)	18 (<1)

Participants in Population	Clesrovimab (N=2421) n (%)	Placebo (N=1211) n (%)	Total (N=3632) n (%)
Trial disposition			
Completed	2104 (86.9)	1049 (86.6)	3153 (86.8)
Discontinued	159 (6.6)	83 (6.9)	242 (6.7)
Death	6 (<1)	3 (<1)	9 (<1)
Lost to follow-up	65 (2.7)	33 (2.7)	98 (2.7)
Physician decision	12 (<1)	4 (<1)	16 (<1)
Randomized by mistake without study treatment	0	1 (<1)	1 (<1)
Withdrawal by parent	75 (3.1)	40 (3.3)	115 (3.2)
Other	1 (<1)	2 (<1)	3 (<1)
Ongoing	158 (6.5)	79 (6.5)	237 (6.5)

Source: FDA statistical reviewer; Tool: SAS. Data source: adsl.xpt.
Abbreviations: N, number of participants in study arm; n, number of participants with given characteristic; RSV, respiratory syncytial virus

Of the 3614 participants who were randomized and dosed, 98.8% finished the Day-42 follow-up visit through which all AEs and AESIs were collected (only SAEs were collected from Day 42 to 365), and 97% of them finished the Day-150 follow-up visit (Table 8). Of note, 108 (3%) participants who were initially randomized and dosed did not complete the Day-150 follow-up visit. Of these, one participant experienced an event before Day 150, while 13 participants missed the Day-150 follow-up visit but remained in the trial beyond Day 150.

Table 8. Summary of Follow-Up Visits, All Dosed Participants, Trial MK-1654-004

Summary of Follow-Up Visits	Clesrovimab n (%)	Placebo n (%)	Total n (%)
Participants in RSV Season 1 population	2411	1203	3614
Day 1 predose	2411 (100.0)	1203 (100.0)	3614 (100.0)
Day 7	2400 (99.5)	1196 (99.4)	3596 (99.5)
Day 42	2384 (98.9)	1187 (98.7)	3571 (98.8)
Day 90	2365 (98.1)	1186 (98.6)	3551 (98.3)
Day 150	2339 (97.0)	1167 (97.0)	3506 (97.0)
Day 240	2311 (95.9)	1159 (96.3)	3470 (96.0)
Day 365	2127 (88.2)	1064 (88.4)	3191 (88.3)
Participants in RSV Season 2 population	1016	502	1518
Day 515	994 (97.8)	492 (98.0)	1486 (97.9)

Source: FDA statistical reviewer; Tool: SAS. Data source: adsl.xpt, sv.xpt.
Abbreviations: n, number of participants with given characteristic; RSV, respiratory syncytial virus

Among participants who received clesrovimab or placebo, the median age of infants was 3.1 months (range: 0 to 12 months); 80% were less than 6 months; 16% were greater than or equal to 6 to less than 9 months, 4% were greater than or equal to 9 months of age; 51% were male. Of these participants, 18% were GA greater than or equal to 29 weeks and less than 35 weeks, and 82% were GA greater than or equal to 35 weeks. The racial distribution was as follows: 45% were White; 27% were Asian; 14% were Black or African American; 12% were multiracial and 2% were American Indian or Alaska Native. Overall, the baseline characteristics were balanced between the clesrovimab group and placebo groups (Table 9).

Table 9. Baseline Demographics and Clinical Characteristics, Full Analysis Set, Trial MK-1654-004

Characteristics	Clesrovimab (N=2411) n (%)	Placebo (N=1203) n (%)	Total (N=3614) n (%)
Sex			
Male	1228 (50.9)	617 (51.3)	1845 (51.1)
Female	1183 (49.1)	586 (48.7)	1769 (48.9)
Age at randomization (months)[1]			
<6	1918 (79.6)	960 (79.8)	2878 (79.6)
≥6 to <9	388 (16.1)	196 (16.3)	584 (16.2)
≥9	105 (4.4)	47 (3.9)	152 (4.2)
Mean	3.7	3.7	3.7
SD	2.6	2.6	2.6
Median	3.0	3.1	3.1
Range	0.1 to 11.9	0.1 to 11.7	0.1 to 11.9
Race			
American Indian or Alaska Native	50 (2.1)	18 (1.5)	68 (1.9)
Asian	641 (26.6)	320 (26.6)	961 (26.6)
Black or African American	326 (13.5)	171 (14.2)	497 (13.8)
Multiple	302 (12.5)	138 (11.5)	440 (12.2)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	2 (<1)
White	1082 (44.9)	550 (45.7)	1632 (45.2)
Missing	9 (<1)	5 (<1)	14 (<1)
Gestational age			
Early and moderate preterm infant (≥29 to <35 weeks)	422 (17.5)	209 (17.4)	631 (17.5)
Late preterm and full-term infant (≥35 weeks)	1989 (82.5)	994 (82.6)	2983 (82.5)
Hemisphere at randomization			
Northern hemisphere	1650 (68.4)	814 (67.7)	2464 (68.2)
Southern hemisphere	761 (31.6)	389 (32.3)	1150 (31.8)
Climate at randomization			
Temperate	1952 (81.0)	970 (80.6)	2922 (80.9)
Tropical/subtropical	459 (19.0)	233 (19.4)	692 (19.1)
Body weight at randomization (kg)			
Mean	5.8	5.9	5.8
SD	2.0	2.0	2.0
Median	5.8	5.8	5.8
Range	1.6 to 11.9	1.6 to 11.6	1.6 to 11.9

Source: FDA statistical reviewer; Tool: SAS. Data source: adsl.xpt.
[1] For age categories, the statistical reviewer used the natural calendar to decide the age in months and then categorized participants into age groups. The primary endpoint also uses the natural calendar to convert age in months. The Applicant used the average number of days (30.4 days/month) to determine the age in months. The different ways to convert age in months can result in a small difference in the demographics table.
Abbreviations: N, number of participants in treatment arm; n, number of participants with given characteristic SD, standard deviation

Primary Endpoint Results

The Applicant's primary efficacy results were confirmed by the FDA statistical review team.

The FAS population used in the efficacy analyses contained all randomized and dosed participants but excluded those with protocol violations. A total of 3614 participants were randomized and dosed, and of these, 15 participants were excluded from the FAS due to protocol violations, with 13 participants from the clesrovimab group and 2 participants from the placebo group excluded by the Applicant and from the analyses presented in this review. The details of exclusion for these 15 patients are shown in Table 97. Thus, there were 2398 participants in the

clesrovimab group and 1201 participants in the placebo group. When including the 15 participants who had protocol violations, the sensitivity analysis results were consistent with the primary efficacy result. The efficacy results using the pre-specified FAS are presented in the Section 14 of the Prescribing Information.

Administration of clesrovimab reduced the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose compared with placebo, with a relative risk reduction of 60.4% (95% CI: 44.1%, 71.9%; $p<0.001$). The lower bound of the 95% CI was greater than the prespecified 25% threshold, thereby the trial met the statistical criterion for success.

Table 10. Relative Risk Reduction in RSV-Associated MALRI (Outpatient and Inpatient) From Days 1 Through 150 Postdose, Full Analysis Set, Trial MK-1654-004

Clesrovimab (N=2411)				Placebo (N=1203)				Relative Risk Reduction (%)	
No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Estimate (95% CI)[3]	p-Value (One-Sided)[3]
2398	60	11685.6	0.026	1201	74	5710.5	0.065	60.4 (44.1,71.9)	<0.001

Source: FDA statistical reviewer; Tool: SAS. Data source: adeff.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method. For the RSV-associated MALRI endpoint, the model included the following covariates: hemisphere at randomization, gestational age group, and age group at randomization. One-sided p-value was estimated by an exact binomial method.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus

Sensitivity Analyses for Primary Efficacy Endpoint

A series of sensitivity analyses were conducted to repeat the primary efficacy endpoint analysis based on different settings. The settings for the sensitivity analyses are as follows:

- Setting 1: Includes RT-PCR results for RSV from both the central laboratory and local laboratories. As a result, this setting may include more cases than the primary endpoint analysis, which only includes RT-PCR results for RSV from the central laboratory.
- Setting 2: Uses per-protocol efficacy population.
- Setting 3: Includes all the participants who were randomized and dosed; thus, the population includes an additional 15 participants (13 in clesrovimab group and 2 in placebo group) who were excluded from the FAS due to either improper storage of study treatment (5 in clesrovimab group and 2 in placebo group), or suspected misconduct (5 in clesrovimab group), or enrolled in the trial more than once (3 in clesrovimab group). These results are presented in the Prescribing Information.
- Setting 4: Uses a univariate Poisson regression model with the treatment group as the only covariate in the model.
- Setting 5: Imputes responses for 107 participants who were randomized and dosed but did not complete the Day-150 follow-up visit. The responses are imputed using a binomial distribution with the probability parameter set to the proportion of events observed in the placebo group.
- Setting 6: Imputes responses for 107 participants who were randomized and dosed but did not complete the Day-150 follow-up visit and replaces their follow-up time with the last visit days which were shorter than the follow-up days used in the primary efficacy analysis. The responses of these 107 participants are imputed using a binomial distribution with the probability parameter set to the proportion of events observed in the placebo group.
- Setting 7: Assumes all 107 participants who were randomized and dosed but did not complete the Day-150 follow-up visit experienced the event of RSV-Associated MALRI (outpatient and inpatient).

The sensitivity analyses, except for Setting 7, yielded results closely aligned with the primary endpoint analysis, indicating the robustness of the primary efficacy result. Setting 7, which assumed all 107 noncompleting participants experienced RSV-associated MALRI (outpatient and inpatient), represents an extreme scenario and produced divergent results; in this extreme scenario, the lower 95% confidence of 23.7% fell slightly below the prespecified 25% threshold. The results from Setting 3, which included the additional 15 participants who were excluded from the FAS by the Applicant, show that inclusion or exclusion of these 15 participants would not materially impact the efficacy assessment of this drug.

Table 11. Sensitivity Analyses on RSV-Associated MALRI (Outpatient and Inpatient) From Days 1 Through 150 Postdose, Trial MK-1654-004

	Clesrovimab (N=2411)				Placebo (N=1203)				Relative Risk Reduction (%)	
Settings	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Estimate (95% CI)[3]	p-Value (One-Sided)[3]
1	2398	62	11680.0	0.027	1201	77	5699.0	0.068	60.7 (44.8, 72.0)	<0.001
2	2392	60	11655.6	0.026	1199	74	5701.0	0.065	60.3 (44.0, 71.9)	<0.001
3	2411	60	11750.6	0.026	1203	74	5720.5	0.065	60.5 (44.2, 72.0)	<0.001
4	2398	60	11685.6	0.026	1201	74	5710.5	0.065	60.4 (44.2, 71.9)	<0.001
5	2398	66	11685.6	0.028	1201	79	5710.5	0.069	59.2 (43.2, 70.6)	<0.001
6	2398	66	11578.0	0.029	1201	79	5662.4	0.070	59.2 (43.2, 70.7)	<0.001
7	2398	132	11685.6	0.056	1201	109	5710.5	0.095	40.8 (23.7, 54.1)	0.039

Source: FDA statistical reviewer; Tool: SAS. Data source: adeff.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method. For the RSV-associated MALRI endpoint, the model included the following covariates: hemisphere at randomization, gestational age group, and age group at randomization. One-sided p-value was estimated by an exact binomial method.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus

Secondary Endpoint Results

RSV-associated hospitalization from Days 1 through 150 postdose and RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose were evaluated as secondary endpoints, with RSV-associated hospitalization from Day 1 through 150 postdose prespecified in the testing hierarchy. For RSV-associated hospitalization from Days 1 through 150 postdose the relative risk reduction of clesrovimab compared to placebo was 84.2% (95% CI: 66.6%, 92.6%, $p<0.001$). The lower bound of the 95% CI was greater than 0%, thereby meeting the statistical criterion for success. For RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose, the relative risk reduction of clesrovimab compared to placebo was 59.5% (95% CI: 43.3%, 71.1%) (note that this analysis was without Type-1 error control). The detailed results are shown in Table 12.

Table 12. Secondary Endpoint Results, Full Analysis Set, Trial MK-1654-004

	Clesrovimab (N=2411)				Placebo (N=1203)				Relative Risk Reduction (%)	
Endpoint	No. of Participants	No. of Cases	Total Follow-up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-up Time in Months[1]	Incidence Rate Over 5 Months[2]	Estimate (95% CI)[3]	p-Value (One-Sided)[3]
RSV-associated hospitalization from Days 1 through 150 postdose	2398	9	11864.8	0.004	1201	28	5859	0.024	84.2 (66.6, 92.6)	<0.001
RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose	2398	64	13970.8	0.027	1201	77	6813.6	0.068	59.5 (43.3, 71.1)	N/A

Source: FDA statistical reviewer; Tool: SAS. Data source: adeff.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method. For the RSV-associated hospitalization endpoint, the model included the following covariates: hemisphere at randomization, gestational age group, and age group at randomization. For the RSV-associated MALRI endpoint, the model included the following covariates: hemisphere at randomization, gestational age group, and age group at randomization. One-sided p-value was estimated by an exact binomial method.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; N/A, not applicable; No., number; RSV, respiratory syncytial virus

Sensitivity Analyses for Alpha-Controlled Secondary Efficacy Endpoint

A sensitivity analysis was conducted to repeat the alpha-controlled secondary efficacy endpoint analysis based on the population including all the participants who were randomized and dosed (FAS); thus, the population includes an additional 15 patients (13 in clesrovimab group and 2 in placebo group) who were excluded from the FAS population due to either improper storage of study treatment (5 in clesrovimab group and 2 in placebo group), or suspected misconduct (5 in clesrovimab group), or enrolled in the trial more than once (3 in clesrovimab group). The results from this sensitivity analysis closely aligned with the alpha-controlled secondary endpoint analysis, indicating the robustness of the alpha-controlled secondary efficacy results.

Table 13. Sensitivity Analyses on RSV-Associated Hospitalization From Days 1 Through 150 Postdose, FAS, Trial MK-1654-004

Clesrovimab (N=2411)				Placebo (N=1203)				Relative Risk Reduction (%)	
No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Estimate (95% CI)[3]	p-Value (One-Sided)[3]
2411	9	11929.8	0.004	1203	28	5869.0	0.024	84.3 (66.7, 92.6)	<0.001

Source: FDA statistical reviewer; Tool: SAS. Data source: adeff.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method. For the RSV-associated hospitalization endpoint, the model included the following covariates: hemisphere at randomization, gestational age group, and age group at randomization. For the RSV-associated MALRI endpoint, the model included the following covariates: hemisphere at randomization, gestational age group, and age group at randomization. One-sided p-value was estimated by an exact binomial method.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; N/A, not applicable; No., number; RSV, respiratory syncytial virus

Subgroup Analyses

Subgroup analyses were conducted on the primary efficacy endpoint: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose.

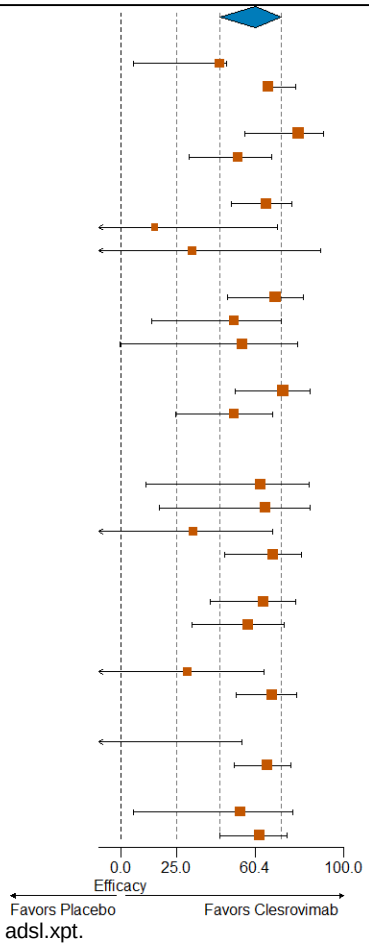
As shown in Figure 3, the relative risk reduction of clesrovimab compared to placebo across RSV subtypes appears potentially inconsistent: RSV A shows a lower relative risk reduction of 44.4% (95% CI: 5.5%, 47.2%), compared with RSV B at 66.2% (95% CI: 67.3%, 78.3%). See Section 6.3.4 for additional information regarding efficacy by RSV subtype. The relative risk reduction of clesrovimab compared to placebo in age subgroups also shows potential inconsistencies. The estimated RRR for the ≤6 months age subgroup was similar to that observed in the overall primary efficacy results, while the RRR estimates for the age subgroups of 6 to 9 months and ≥9 months were lower than what was observed in the overall primary efficacy results. Inconsistencies in the relative risk reduction across the baseline body weight subgroups were observed, as well. The ≤5 kg subgroup followed a trend similar to the overall primary efficacy results, however, in the ≥5 to <8 kg and ≥8 kg subgroups, RRR estimates were lower than observed in the overall primary efficacy results. See Section 6.3.1 for a discussion of efficacy across age and weight subgroups. Lastly, regarding efficacy by region, the sample size, and the number of cases in the United States were both small, thus, the comparisons of efficacy between the U.S. and non-U.S. subpopulations are not reliable. Another region-based subgroup analysis conducted was North America and Western Europe versus Other countries in the trial. It was postulated that North America and Western Europe region have comparable healthcare standards and could be analyzed as a single subpopulation (North America and Western Europe). This subpopulation can then be compared with other countries whose healthcare systems/standards of care may differ. The estimated efficacy in these other countries was similar to that observed in the overall primary efficacy results, while the estimated RRR was slightly lower in the combined North America and Western Europe population than observed in the overall primary efficacy results. However, it is noted that the 95% CI for the RRR observed in the other countries falls within the bounds of the 95% CI for the RRR estimated for North America and Western Europe, suggesting that the differences may not be statistically significant (see Table 96 for more details).

To further evaluate the consistency of effect across subgroups, interaction tests of the treatment by baseline factor were conducted. The p-values of post hoc interaction tests of treatment by age group (<6 months versus ⩾6 months), and by baseline body weight (<5 kg versus ⩾5 kg) are 0.084 and 0.205 respectively (Altman and Bland 2003), which shows that there were no statistically significant interactions between the treatment and these two baseline factors, which indicates a consistent effect across each of the two baseline factors.

Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. In addition, the trial was not powered to detect the difference in these subgroup analyses. Finally, numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

Figure 3. Subgroup Analyses, Full Analysis Set, Trial MK-1654-004

Variable	Incidence Rate Over 5 Months Clesrovimab	Placebo	Relative Risk Reduction (95% CI)
Overall	0.026	0.065	60.4 (44.1, 71.9)
RSV Type			
RSV A	0.012	0.022	44.4 (5.5, 47.2)
RSV B	0.014	0.041	66.2 (67.3, 78.3)
Gestational Age			
Early and Moderate Preterm	0.022	0.11	79.8 (55.5, 90.8)
Late Preterm and Full-term	0.026	0.056	52.6 (30.3, 67.8)
Age			
<6 Months	0.025	0.073	65.3 (49.6, 76.5)
≥6 to <9 Months	0.027	0.032	15.2 (-140.5, 70.3)
≥9 Months	0.03	0.044	32.2 (-446.2, 89.4)
Body Weight			
<5 Kg	0.028	0.089	69.3 (47.9, 81.8)
≥5 to <8 Kg	0.022	0.045	50.7 (13.9, 71.8)
≥8 Kg	0.032	0.07	54.5 (-0.6, 79.4)
Sex			
Female	0.016	0.057	72.7 (51.2, 84.7)
Male	0.035	0.072	50.9 (24.4, 68.1)
Race			
American Indian or Alaska Native	0	0	-
Asian	0.014	0.038	62.7 (11.1, 84.3)
Black or African American	0.029	0.083	64.8 (17.1, 85)
Multiple	0.063	0.094	32.5 (-42.1, 67.9)
White	0.023	0.071	68.1 (46.5, 81)
Hemisphere			
Northern Hemisphere	0.016	0.045	63.8 (39.8, 78.3)
Southern Hemisphere	0.047	0.109	57.1 (31.6, 73.1)
Climate			
Sub-tropical or Tropical Regions	0.048	0.068	29.8 (-37.5, 64.1)
Temperate Regions	0.021	0.064	67.9 (51.8, 78.6)
U.S. vs.Non-U.S. Region			
U.S.	0.033	0.02	-67.7 (-515, 54.3)
Non-U.S. Region	0.025	0.072	65.7 (50.7, 76.2)
North America and Western Europe vs. Other Countries			
North America and Western Europe	0.025	0.053	53.6 (5.6, 77.2)
Other Countries	0.026	0.069	62.3 (44.1, 74.5)



Source: FDA statistical reviewer; Tool: R. Data source: adeff.xpt, adsl.xpt.
The point estimate sizes are reflective of their value.
For the analyses by RSV subtype, the RSV A and RSV B are not mutually exclusive. The efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate.
For the other subgroup efficacy analyses, the efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, or an exact binomial method if convergence issues exist with the Poisson approach.
Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus; U.S., United States

6.2.3. Trial MK-1654-007

6.2.3.1. Design, Trial MK-1654-007

Trial MK-1654-007 was a Phase 3, multicenter, randomized, partially blinded, palivizumab-controlled study in infants and children at increased risk for severe RSV disease entering their first RSV season.

There was no formal sample size calculation. The chosen sample size considered various factors including difficulties in enrolling this particular population, as well as estimates of efficacy and the associated levels of precision for different sample sizes. A sample size of 500 participants per treatment group was expected to provide the desired precision in estimates of the incidence rates of RSV-associated MALRI from Days 1 to 150 postdose in each treatment group.

Approximately 1000 infants who 1) had either CLD of prematurity (gestational age ≤32 weeks) or hemodynamically significant CHD (regardless of gestational age), or were ≤35 weeks gestational age, and 2) had a chronological age from birth up to one year and were entering their first RSV season, were planned to be randomized in a 1:1 ratio to receive either clesrovimab (single dose) or palivizumab (three to five monthly doses of 15 mg/kg). Approximately 300 of these infants received clesrovimab before their second RSV season. Randomization was stratified according to region (Northern or Southern Hemisphere) and participant condition (CLD, CHD, neither CLD nor CHD <29 weeks gestational age, and neither CLD nor CHD ≥29 weeks gestational age). Infants 0 through 8 months (i.e., up to 8 months and 29 days) of age at the time of consent comprised at least 90% of the participants.

Participants' treatment assignment was unblinded at the Day-60 visit before any visit procedures. Participants in the clesrovimab group did not have any additional planned doses in RSV Season 1 and continued with safety monitoring, efficacy surveillance, and blood sample collection. Participants in the palivizumab group received at least three and up to five single doses of palivizumab, once every 28 (+4) days (inclusive of Dosing Day; minimum of 28 days between doses).

Each participant received the first dose of assigned study intervention on RSV Season 1 Day 1. All participants enrolled were administered subsequent doses as scheduled and were followed for 365 days. Participants enrolled for 2 RSV seasons received a dose of clesrovimab in RSV Season 2 and were followed for an additional 180 days postdose. Most participants took part in the trial for 365 days (one RSV season), and participants who enrolled, consented, and remained eligible for two RSV seasons participated in the trial for up to 575 days.

The planned trial design is depicted in Section 15.2, Figure 22.

The primary objective in Trial MK-1654-007 was to evaluate the safety and tolerability of clesrovimab compared to palivizumab in RSV Season 1 as assessed by the proportion of participants experiencing AEs. Efficacy was included in the secondary objectives.

Key Secondary Endpoint

Incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose, defined as the following seen in an outpatient or inpatient clinical setting:

- Cough or difficulty breathing
- One or more of the following: wheezing, chest wall indrawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms
- RSV-positive RT-PCR NP sample

Incidence of RSV-associated hospitalization from Days 1 through 150 postdose, defined as the following:

- Hospital admission for respiratory illness
- RSV-positive RT-PCR NP sample

Prespecified Hypothesis Testing Order, Type-I Error Control, and Interim Analysis

There is no formal hypothesis testing in this trial and no Type-I error control. An interim analysis (IA) was planned after the first 30 participants were randomized or after the first hemisphere enrollment (~17 weeks) was complete in the initial RSV season of the trial, whichever occurred first. Summaries of the safety, available PK data, and available incidence of RSV-associated MALRI and RSV-associated hospitalization were reviewed by the external data monitoring committee (eDMC).

Analysis Populations

FAS Population

The FAS population consisted of all randomized participants who received at least 1 dose of study treatment. The FAS population served as the primary population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. Participants were included in the treatment group based on the study treatment they were randomized to for the efficacy analyses. Of note, even though the FAS was defined as above, participants with protocol violations were excluded from the FAS used for the efficacy analyses presented in this review. However, the Prescribing Information presents the results from the prespecified FAS population.

PPE Population

To be eligible for inclusion in the PPE population, trial participants must have satisfied the following criteria:

- Received a complete regimen of the correct clinical material corresponding to the treatment group the participants were randomized into (i.e., one dose of clesrovimab for participants randomized to the clesrovimab group and three to five doses of palivizumab within the protocol-specified windows for participants randomized to the palivizumab group based on the date of enrollment and the predefined RSV season end date at each site).
- Had at least one follow-up visit/contact for assessment of RSV disease.
- Did not undergo 1) ECMO or 2) surgical intervention for CHD requiring cardiopulmonary bypass during the efficacy follow-up period (Day 150 or Day 180).
- At any time during dosing or efficacy follow-up, did not experience a protocol deviation that may have interfered with the assessment of protection against RSV infection conferred by clesrovimab.

Safety Analysis Population

Safety analyses were conducted in the APaT population, which consisted of all randomized/allocated participants who received at least one dose of study treatment. Participants were included in the treatment group based on the study treatment they actually received for the analysis of safety data using the APaT population. Of note, even though the safety analysis population was defined as above, participants with protocol violations were excluded from the population as well for the safety analyses.

6.2.3.2. Eligibility Criteria, Trial MK-1654-007

Key Inclusion Criteria

A participant will be eligible for inclusion in the trial if the participant:

- Is recommended to receive palivizumab in accordance with national or local guidelines or professional society recommendations, and meets 1 or more of the following criteria:
  - Early or moderate preterm group (excluding participants with CLD or hemodynamically significant CHD): ≤35 weeks, 0 days gestational age*.
    Note: Participants in the early or moderate preterm group who meet the additional inclusion criteria for RSV Season 2, will be consented for participation in two RSV seasons.
  - CLD/CHD group:
    - CLD participants: have CLD of prematurity (also known as bronchopulmonary dysplasia), defined by the American Academy of Pediatrics (American°Academy°of°Pediatrics 2014) as ≤32 weeks gestational age* and require medical intervention/management (i.e., supplemental oxygen, bronchodilators, or chronic systemic corticosteroids) for at least 28 days after birth, or as per other national or local guidelines or professional society recommendations.
    - CHD participants: have hemodynamically significant CHD, defined by the American Academy of Pediatrics (American°Academy°of°Pediatrics 2014) as uncorrected or palliated cyanotic or acyanotic disease associated with documented pulmonary hypertension (e.g., systolic pulmonary arterial pressure ≥40 mm Hg or ≥1/2 systolic blood pressure) or a requirement for daily medication to manage congestive heart failure, or as diagnosed by a pediatric cardiologist, or as per other national or local guidelines or professional society recommendations.
      Note: CLD and CHD participants may be eligible and consented for inclusion in two RSV seasons, as described in Section 5.1.

*Gestational age as calculated by the treating physician or qualified healthcare provider at the time of delivery or as documented in the medical record at the time of birth (e.g., acceptable methods include assessment using prenatal [obstetric and/or sonographic evaluation using biometric markers] or postnatal [Ballard or New Ballard] methods).

- Is available to complete the follow-up period:
  - Up to 575 days (180 days after RSV Season 2 dose) for participants eligible for RSV Season 2 dose of MK-1654
  - Approximately 365 days after the RSV Season 1 Dose 1 for all other participants
- Is male or female and has a chronological age from birth up to 1 year and is entering their first RSV season at the time of informed consent.

Additional Inclusion Criteria for Participation in RSV Season 2

A participant may be eligible and consented at the beginning of the trial for inclusion in RSV Season 2 (and eligibility reconfirmed at the RSV Season 1 Day 240 and RSV Season 2 Day 1 visits) if the participant meets one of the following inclusion criteria:

- Participants enrolled in the CLD/CHD group as defined in Inclusion Criteria #1b.
  - Participants with CHD are required to meet the following additional criteria:
    - Have hemodynamically significant CHD at the beginning of RSV Season 2.
    - If the participant has had surgically repaired hemodynamically significant CHD that did not include ECMO or cardiopulmonary bypass:
      - Continues to require medications to manage CHD.
      - Any additional medical intervention related to their CHD.
- Participants enrolled in the early or moderate preterm group as defined in Inclusion Criteria #1a, with the following conditions:
  - Neuromuscular disease or congenital pulmonary anomaly that impairs the ability to clear secretions from the upper airway due to ineffective cough.
  - Down syndrome (trisomy of chromosome 21).
  - Cystic fibrosis with nutritional compromise (i.e., weight <10th percentile at time of enrollment).
  - Native Americans and Alaskan Indians.

Exclusion Criteria

The participant must be excluded from the trial if the participant:

Medical Conditions

- Requires mechanical ventilation at time of enrollment.
- Has a life expectancy <6 months.
- Has known hepatic or renal dysfunction, or chronic seizure disorder.
- Is hospitalized at the time of randomization unless discharge is expected within 7 days after randomization.
- Has severe immunodeficiency or is severely immunocompromised, including but not limited to:
  - Acquired immunodeficiency syndrome (AIDS) (cluster of differentiation [CD] 4 percentage <15%, or history of AIDS-defining condition)
  - Leukemia, myeloproliferative disorder, or other malignancy and receiving or expected to receive chemotherapy during the trial
  - Status post solid-organ or bone marrow transplantation and on a systemic immunosuppressive regimen
  - Severe combined immunodeficiency

- Has known hypersensitivity to any component of MK-1654 (refer to the Investigator's Brochure for a list of components) or palivizumab (refer to the Synagis® Prescribing Information for a list of components).
- Has received other investigational agents at any time before trial entry.
- Has a prior surgical correction of CHD or anticipated cardiac surgical procedure within 60 days of randomization resulting in hemodynamically insignificant CHD.
- Requires ECMO or continuous positive airway pressure at the time of enrollment.
- Has an anticipated or planned cardiac transplantation to occur during the course of this trial.
- Has a bleeding disorder contraindicating intramuscular administration.
- Has 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.
    - Note: If the participant meets this exclusion criterion, the RSV Season 1 or RSV Season 2 Day 1 visits may be rescheduled for a time when this criterion is not met.
- Has symptoms of lower respiratory infection within 7 days predose.
    - Note: If the participant meets this exclusion criterion, the RSV Season 1 or RSV Season 2 Day 1 visits may be rescheduled for a time when this criterion is not met.

Prior/Concomitant Therapy

- Has received any vaccine or mAb for the prevention of RSV, including receipt of maternal RSV vaccination during the mother's pregnancy.

Exclusion Criteria for Participation in RSV Season 2

A participant may be eligible and consented at the beginning of the trial for inclusion in RSV Season 2 for this trial. Eligibility will be reconfirmed at the RSV Season 1 Day 240 and RSV Season 2 Day 1 visits, and the participant must be excluded from RSV Season 2 participation if they meet one of the following inclusion criteria:

- Has a life expectancy <6 months.
- Has known hepatic or renal dysfunction, or chronic seizure disorder.
- Has severe immunodeficiency or is severely immunocompromised, including but not limited to:
    - AIDS (CD4 percentage <15%, or history of AIDS-defining condition), leukemia, myeloproliferative disorder, or other malignancy and receiving or expected to receive chemotherapy during the trial
    - Status post solid-organ or bone marrow transplantation and on a systemic immunosuppressive regimen
    - Severe combined immunodeficiency
- Had 1) ECMO or 2) surgical intervention during the RSV season for CHD and required cardiopulmonary bypass during the procedure in RSV Season 1.

- Has known hypersensitivity to any component of MK-1654 (refer to the IB for a list of components).
- Has bleeding disorder contraindicating intramuscular administration.

6.2.3.3. Statistical Analysis Plan, Trial MK-1654-007

The efficacy endpoint is defined as RRR,

Efficacy =1- R_t/R_p,

where R_t and R_p are the incidence rates of RSV-associated disease in the clesrovimab and palivizumab groups, respectively. Incidence rate = number of RSV-associated disease cases/total person-time of follow-up for efficacy.

Every participant is counted a single time for each applicable endpoint. A participant may have multiple cases. For each participant, only the first occurrence of the case for each endpoint is counted for the analysis. The statistical analyses were based on the data cutoff of March 4, 2024.

Analyses of the Secondary Endpoint

The relative risk reduction of clesrovimab compared to palivizumab with respect to the RSV-associated MALRI endpoint in RSV Season 1 was estimated and the 95% CI of efficacy was obtained based on the Poisson regression model (Zou 2004) with robust variance method with only the term of treatment group (clesrovimab and palivizumab) included.

The incidence of RSV-associated hospitalization in the clesrovimab and palivizumab groups in RSV Season 1 was estimated and the exact 95% CI was provided using the exact method based on the relationship between the Poisson and Chi-square distributions (Ulm 1990).

Missing Data (To Evaluate the Impact of Missing Data)

If a participant failed to return to the clinic for a required study visit and/or if the site was unable to contact the participant, they were considered trial dropouts. For efficacy endpoints, there was no imputation for the Applicant's analyses.

Subgroup Analyses

The relative risk reduction for the primary efficacy endpoint was examined among subgroups: RSV subtype (RSV A and RSV B), hemisphere (Northern Hemisphere and Southern Hemisphere), and participant condition (CHD, CLD, neither CLD nor CHD, and ≥29 weeks gestational age, and neither CLD nor CHD, and <29 weeks gestational age). For the analyses by RSV subtype, the RSV A and RSV B subgroups are not mutually exclusive. The efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate.

For the other subgroup analyses, the efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate, or an exact binomial method if convergence issues exist with the Poisson approach.

6.2.3.4. Results of Analyses, Trial MK-1654-007

This section summarizes participant disposition, demographics, baseline disease characteristics, and key secondary efficacy results based on data submitted by the Applicant.

A total of 901 participants were randomized across 109 study sites in 27 countries. Among them, 896 (98.8%) participants received their Day-1 dose of study intervention (clesrovimab or palivizumab). 458 (50.8%) infants completed their RSV Season 1 follow-up (through Day 365 or until RSV Season 2 dose). A total of 7.3% participants discontinued from the trial. The disposition of participants was generally comparable between the two groups.

Table 14. Participant Disposition, All Randomized Participants, RSV Season 1, Trial MK-1654-007

Participant Disposition	Clesrovimab (N=450) n (%)	Palivizumab (N=451) n (%)	Total (N=901) n (%)
Participants randomized			
Full analysis set	446 (99.1)	450 (99.8)	896 (99.4)
Safety population[1]	445 (98.9)	450 (99.8)	895 (99.3)
Per protocol efficacy population	440 (97.8)	367 (81.4)	807 (89.6)
Dosed at Day 1			
Clesrovimab	446 (99.1)	0	446 (49.5)
Palivizumab	0	450 (99.8)	450 (49.9)
No dose	4 (<1)	1 (<1)	5 (<1)
Trial disposition			
Completed	228 (50.7)	230 (51.0)	458 (50.8)
Discontinued	35 (7.8)	31 (6.9)	66 (7.3)
Death	8 (1.8)	4 (<1)	12 (1.3)
Lost to follow-up	7 (1.6)	6 (1.3)	13 (1.4)
Physician decision	2 (<1)	1 (<1)	3 (<1)
Randomized by mistake without study treatment	1 (<1)	1 (<1)	2 (<1)
Ongoing	187 (41.6)	190 (42.1)	377 (41.8)
Dosed with			
Dose 1 (Day 1)	446 (99.1)	450 (99.8)	896 (99.4)
Dose 2 (Day 28)	432 (96.0)	445 (98.7)	877 (97.3)
Dose 3 (Day 60)	0	429 (95.1)	429 (47.6)
Dose 4 (Day 90)	0	326 (72.3)	326 (36.2)
Dose 5 (Day 120)	0	240 (53.2)	240 (26.6)
Unscheduled	3 (<1)	2 (<1)	5 (<1)

Source: FDA statistical reviewer; Tool: SAS. Data source: adsl.xpt.
[1] One participant was excluded due to administration of the incorrect study intervention.
Abbreviations: MK-1654, clesrovimab; N, number of randomized participants; n, number of participants with given characteristic; RSV, respiratory syncytial virus

Among participants who received clesrovimab or palivizumab, the median age of infants was 2.5 months (range: 0 to 12 months); 89% were less than 6 months; 9% were greater than or equal to 6 to less than 9 months, 2% were greater than or equal to 9 months of age; and 50% were male. Of these participants, 28% had CLD, 11% had CHD, 6% were GA less than 29 weeks with neither CLD nor CHD and 55% were GA greater than or equal to 29 weeks with neither CLD nor CHD. The racial distribution was as follows: 52% were White; 18% were Asian; 15% were Black or African American; 12% were multiracial, and 1% were American Indian or Alaska Native; 32% were of Hispanic or Latino ethnicity. Overall, the baseline characteristics were balanced between the clesrovimab and palivizumab groups (Table 15).

Table 15. Baseline Demographics and Clinical Characteristics, Full Analysis Set, Trial MK-1654-007

Baseline Demographics and Clinical Characteristics	Clesrovimab (N=446) n (%)	Palivizumab (N=450) n (%)	Total (N=896) n (%)
Sex			
Male	225 (50.4)	221 (49.1)	446 (49.8)
Female	221 (49.6)	229 (50.9)	450 (50.2)
Age at randomization (months)[1]			
<6	409 (91.7)	390 (86.7)	799 (89.2)
≥6 to <9	33 (7.4)	51 (11.3)	84 (9.4)
≥9	4 (<1)	9 (2.0)	13 (1.5)
Mean	3.0	3.0	3.0
SD	1.94	2.30	2.13
Median	2.7	2.3	2.5
Min, max	0.2, 11.4	0.0, 12.0	0.0, 12.0
Race			
American Indian or Alaska Native	5 (1.1)	7 (1.6)	12 (1.3)
Asian	82 (18.4)	80 (17.8)	162 (18.1)
Black or African American	67 (15.0)	71 (15.8)	138 (15.4)
Multiple	56 (12.6)	53 (11.8)	109 (12.2)
Native Hawaiian or Other Pacific Islander	5 (1.1)	2 (<1)	7 (<1)
White	231 (51.8)	237 (52.7)	468 (52.2)
Gestational age			
≥29 to <35 weeks	299 (67.0)	290 (64.4)	589 (65.7)
≥35 weeks	49 (11.0)	52 (11.6)	101 (11.3)
<29 weeks	98 (22.0)	108 (24.0)	206 (23.0)
Participants condition			
CHD	52 (11.7)	49 (10.9)	101 (11.3)
CLD	124 (27.8)	126 (28.0)	250 (27.9)
Neither CLD nor CHD, and ≥29 weeks gestational age	244 (54.7)	251 (55.8)	495 (55.2)
Neither CLD nor CHD, and <29 weeks gestational age	26 (5.8)	24 (5.3)	50 (5.6)
Region at randomization			
Northern hemisphere	318 (71.3)	323 (71.8)	641 (71.5)
Southern hemisphere	128 (28.7)	127 (28.2)	255 (28.5)
Climate at randomization			
Temperate	367 (82.3)	369 (82.0)	736 (82.1)
Tropical/subtropical	79 (17.7)	81 (18.0)	160 (17.9)
Body weight at randomization (kg)			
Mean	3.8	3.6	3.7
SD	1.5	1.5	1.5
Median	3.5	3.2	3.3
Range	1.1 to 9.6	1.5 to 9.1	1.1 to 9.6

Source: FDA statistical reviewer; Tool: SAS. Data source: adsl.xpt.
[1] For age categories, the statistical reviewer used the natural calendar to decide the age in months and then categorized participants into age groups. The primary endpoint also uses the natural calendar to convert age in months. The Applicant used the average number of days (30.4 days/month) to determine the age in months. The different ways to convert age in months can result in a small difference in the demographics table.
Abbreviations: CHD, congenital heart disease; CLD, chronic lung disease; N, number of participants in treatment arm; n, number of participants with given characteristic SD, standard deviation

Secondary Endpoint Results

The Applicant's efficacy results were confirmed by the FDA statistical review team.

The FAS population contained all randomized and dosed participants but excluded participants with protocol violations. A total of 896 participants were randomized and dosed, and of these, 16

participants were excluded from the FAS due to protocol violations, with 3 participants from the clesrovimab group and 13 participants from the palivizumab group excluded. The details of exclusion for these 16 patients are shown in Table 98. Consequently, there were 443 in the clesrovimab group and 437 in the palivizumab group. For additional information on the impact of these exclusions, please refer to the sensitivity analyses section below. The Prescribing Information presents the results from the protocol-defined FAS population. Notably, the results of the efficacy assessment were not meaningfully impacted by Applicant's exclusion of participants with protocol violations.

For RSV-associated MALRI (outpatient and inpatient) from Days 1 to 150 postdose, the relative risk reduction of clesrovimab compared to palivizumab was -18.0% (95% CI: -155.5%, 45.5%). The incidence rates of RSV-associated MALRI were generally comparable between clesrovimab arm (incidence rate =3.6%, 95% CI: 2.0%, 6.0%) and palivizumab arm (incidence rate =3.0%, 95% CI: 1.6%, 5.3%) from Days 1 through 150 in RSV Season 1.

For RSV-associated hospitalization from Days 1 to 150 postdose, the relative risk reduction of clesrovimab compared to palivizumab was 15.9% (95% CI: -176.0%, 74.4%). The incidence rates of RSV-associated hospitalization were generally comparable between clesrovimab arm (incidence rate =1.3%, 95% CI: 0.4%, 3.0%) and palivizumab arm (incidence rate =1.5%, 95% CI: 0.6%, 3.3%) from Days 1 through 150 in RSV Season 1.

Neither of the two analyses were statistically powered. The detailed results are shown in Table 16.

Table 16. Secondary Endpoint Results, Full Analysis Set, Trial MK-1654-007

	Clesrovimab (N=446)				Palivizumab (N=450)				Relative Risk Reduction (%) Estimate (95% CI)[3]
Endpoints	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	
RSV-associated outpatient and inpatient MALRI Days from 1 to 150 RSV Season 1	443	14	1946.9	0.036 (0.020, 0.060)	437	12	1969.5	0.030 (0.016, 0.053)	-18.0 (-155.5, 45.5)
RSV-associated hospitalization Days from 1 to 150 RSV Season 1	443	5	1968.9	0.013 (0.004, 0.030)	437	6	1987.3	0.015 (0.006, 0.033)	15.9 (-176.0, 74.4)

Source: FDA statistical reviewer; Tool: SAS. Data source: adeff.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method. The statistical models for both RSV-associated MALRI and RSV-associated hospitalization endpoints incorporated treatment group as the only covariate.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus

Sensitivity Analyses

A series of sensitivity analyses were conducted to repeat the secondary efficacy endpoint analyses based on the population including all the participants who were randomized and dosed (consistent with the FAS as defined in the protocol); thus, the population includes an additional 16 patients (3 in the MK-1654 group and 13 in the palivizumab group) who were excluded from the FAS population due

to either improper storage of study intervention (3 in the MK-1654 group and 12 in the palivizumab group) or no consent (1 in the palivizumab group). The results including all randomized and dosed participants are presented in the Prescribing Information.

The results from sensitivity analyses closely aligned with the secondary endpoint analyses, indicating the robustness of the secondary efficacy results.

Table 17. Sensitivity Analyses on Secondary Endpoints, Full Analysis Set, Trial MK-1654-007

	Clesrovimab (N=446)				Placebo (N=450)				
Endpoints	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Relative Risk Reduction (%) Estimate (95% CI)[3]
RSV-associated outpatient and inpatient MALRI Days from 1 to 150 RSV Season 1	446	14	1960.7	0.036 (0.020, 0.060)	450	12	2034.5	0.029 (0.015, 0.052)	-21.1 (-162.1, 44.1)
RSV-associated hospitalization Days from 1 to 150 RSV Season 1	446	5	1982.7	0.013 (0.004, 0.029)	450	6	2052.3	0.015 (0.005, 0.032)	13.7 (-183.0, 73.7)

Source: FDA statistical reviewer; Tool: SAS. Data source: adeff.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method. The statistical models for both RSV-associated MALRI and RSV-associated hospitalization endpoints incorporated treatment group as the only covariate.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus

6.3. Key Efficacy Review Issues

6.3.1. Efficacy of a Single Clesrovimab 105-mg Dose for All Participants, Regardless of Chronological Age and Weight

Issue

The Applicant proposed an indication for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. The results of Trial MK-1654-004 provide compelling evidence that clesrovimab reduces the risk of MALRI in the first year of life overall. However, whether the same 105-mg clesrovimab dose is appropriate for all chronological age groups and weight bands within the first year of life warrants careful assessment.

Background

Trial MK-1654-004 enrolled healthy preterm and term infants at least 29 weeks gestational age. All participants received a single, 105-mg clesrovimab dose during their first RSV season. Body weight is known to be a significant covariate for clesrovimab pharmacokinetics, and age and weight are generally correlated among infants. However, the Applicant purports that differences in exposure by age and body weight among infants in their first RSV season are not clinically meaningful and efficacy is comparable across age and weight bands. Therefore, the Applicant recommends the same dose for all infants born during or entering their first RSV season.

Assessment

Given that Trial MK-1654-004 was designed as an adequate and well-controlled clinical investigation, while Trial MK-1654-007 focused on pharmacokinetics and safety, Trial MK-1654-004 was used to assess efficacy across age and baseline body weight subgroups. The efficacy of clesrovimab in healthy infants up to 1 year of age was demonstrated in Trial MK-1654-004. In this trial, the overall incidence rate of RSV-associated MALRI (outpatient or inpatient) over 5 months was 0.026 in the clesrovimab group and 0.065 in the placebo group, resulting in a relative risk reduction of 60.4% (95% CI: 44.1%, 71.9%) (see Section 6.2.2.4).

Efficacy by Baseline Body Weight

The efficacy by weight subgroups was evaluated and is presented in Table 18 (shown in the columns of 'Incidence Rate Over 5 Months' and 'Relative Risk Reduction (%) Estimate (95% CI)'). The incidence rates of RSV-associated MALRI were lower in the clesrovimab group compared to the placebo group across all-weight subgroups. The relative risk reduction in the lowest-weight subgroup (<5 kg) was the greatest, which was slightly higher than the overall primary efficacy outcome. In the middle-weight subgroup (≥5 to <8 kg), slightly lower efficacy in terms of RRR and its lower bound 95% CI was observed. The analysis results of the highest-weight subgroup (≥8 kg) suggested a trend that clesrovimab was less effective than observed in the overall analysis, in terms of point estimates of RRR and its lower bounds of 95% CIs.

Table 18. Subgroup Analyses by Weight, Full Analysis Set, Trial MK-1654-004

	Clesrovimab (N=2411)				Placebo (N=1203)				
Weight Subgroups	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Relative Risk Reduction (%) Estimate (95% CI)[3]
<5 kg	860	23	4181.4	0.028	428	36	2012.1	0.089	69.3 (47.9, 81.8)
≥5 to <8 kg	1150	25	5622.5	0.022	577	25	2770.6	0.045	50.7 (13.9, 71.8)
≥8 kg	388	12	1881.7	0.032	196	13	927.9	0.070	54.5 (-0.6, 79.4)

Source: FDA statistical reviewer; Tool: R. Data source: adeff.xpt, adsl.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method with the treatment group as the only one covariate.
Abbreviations: CI, confidence interval; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus

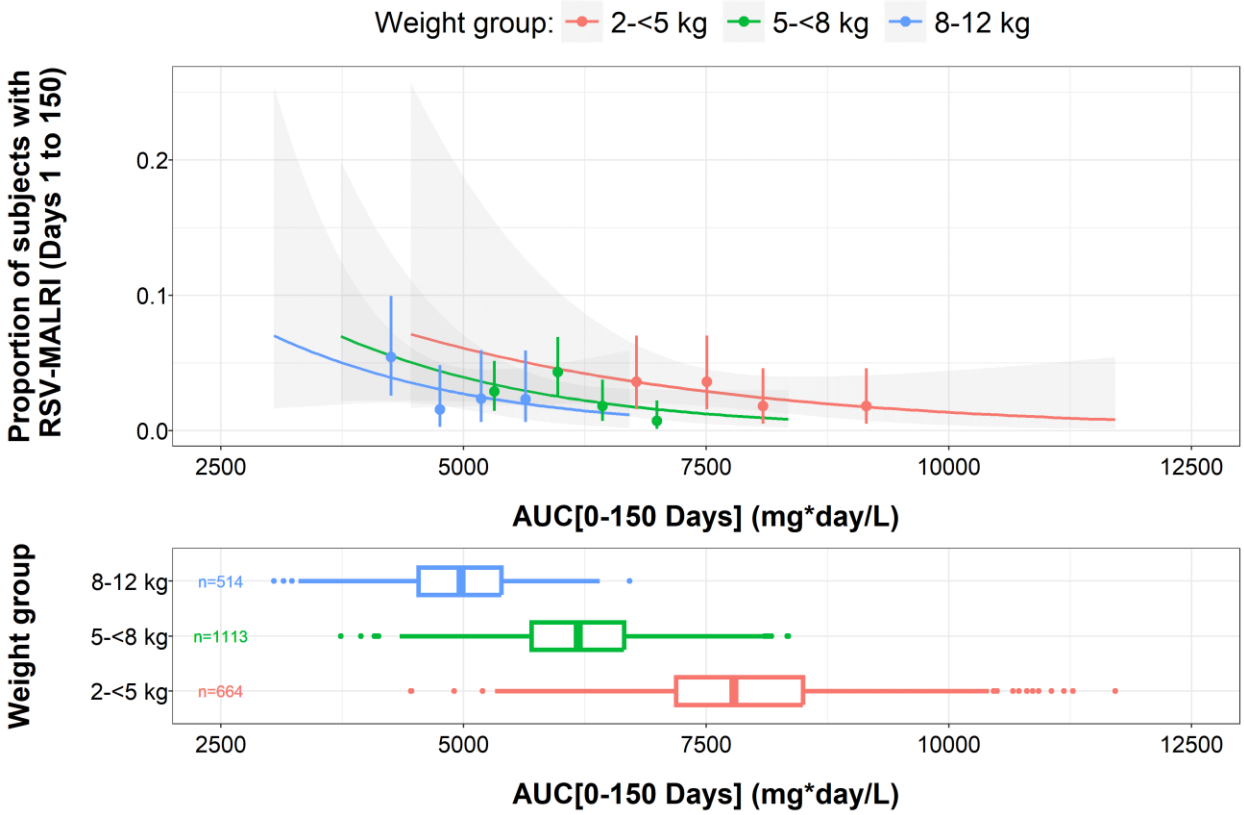
The p-value of a post hoc interaction test of treatment effect by baseline body weight (<5 kg versus ≥5 kg) is 0.205. Given the lack of a statistically significant interaction between the treatment effect and baseline body weight, there is no evidence of heterogeneity in treatment effect across baseline body weight subgroups.

Although efficacy trends varied across baseline body weight subgroups, the small sample sizes and limited number of events in these subgroups mean that the results should be viewed as descriptive and exploratory in nature. Of note, the incidence rates in the placebo group varied across these three baseline body weight subgroups and the placebo incidence rate in the middle-weight subgroup (≥5 to <8 kg) was much lower than that observed in the lowest-weight subgroup (<5 kg). This observation in the placebo group contributed to the observed RRR variability in the baseline body weight subgroup analyses. Consequently, no definitive conclusions can be drawn from the weight subgroup analyses in Trial MK-1654-004.

Exposure-Response Analysis by Weight

An exploratory assessment of the relationship between RSV-associated MALRI from Days 1 to 150 and clesrovimab exposure ($AUC_{0\text{-}150d}$), using a logistic regression analysis adjusted by weight subgroups, did not find baseline weight subgroups as significant predictors of the exposure-response relationship. Figure 4 shows an inverse relationship with weight subgroups, with heavier subgroups having a lower or comparable proportion of events compared to participants in the <5-kg weight subgroup. In addition, participants in the ≥8-kg weight subgroup have lower or comparable proportion and probability of RSV-associated MALRI across the entire lower range of exposure compared to the other weight groups. No difference was observed between RSV-associated MALRI and C_{trough} at Day 150, stratified by baseline weight subgroups.

Figure 4. Observed Proportion and Predicted Probability of RSV-Associated MALRI, Days 1 to 150, vs. $AUC_{0\text{-}150d}$, Adjusted by Baseline Weight Group



Source: FDA reviewer
Upper panel: Closed circles (error bars) show the observed proportion of participants with an event (95% CI based on the Pearson-Klopper method) in each exposure quartile, stratified by baseline weight group and plotted at the median exposure of each quartile of clesrovimab area under the concentration-time curve from time 0 to Day 150 ($AUC_{0\text{-}150d}$). Solid (blue line and gray area) curves are the model-predicted (logistic regression) probability of the event (95% CI).
Lower panel: boxplot of $AUC_{0\text{-}150d}$ in participants with different baseline weight group.
Abbreviations: $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; CI, confidence interval; MALRI, medically attended lower respiratory infection; RSV, respiratory syncytial virus

Efficacy by Age

In general, there is a strong correlation between age and body weight in infants. In addition to exploring efficacy by baseline body weight, subgroup analyses of efficacy by age were also conducted. The efficacy in various age subgroups was assessed and is shown in Table 19 (in the columns of 'Incidence Rate Over 5 Months' and 'Relative Risk Reduction (%) Estimate (95% CI))'). The incidence rates of RSV-associated outpatient or inpatient MALRI, from Days 1 through 150 postdose, were lower in the clesrovimab group than in the placebo group across all age subgroups. The relative risk reduction in the youngest age subgroup (<6 months) was similar to the overall primary efficacy results. However, in older age subgroups (≥6 to <9 months and ≥9 months), much smaller efficacy in terms of RRRs and their lower bounds of 95% CIs were observed compared to the overall primary efficacy results. Of note, the incidence rates in the placebo group for older age subgroups (≥6 to <9 months and ≥9 months) were much smaller than that in the younger age subgroup (<6 months). The efficacy trends observed here were potentially inconsistent across age subgroups.

The p-value of a post hoc interaction test of treatment by age group (<6 months versus ≥6 months) is 0.084. Given the lack of a statistically significant interaction between the treatment effect and age group, there is no evidence of heterogeneity in treatment effect across age groups.

Table 19. Subgroup Analyses by Age, Full Analysis Set, Trial MK-1654-004

	Clesrovimab (N=2411)				Placebo (N=1203)				
Age Subgroups	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Relative Risk Reduction (%) Estimate (95% CI)[3]
<6 months	1910	47	9323.9	0.025	959	66	4537.4	0.073	65.3 (49.6, 76.5)
≥6 to <9 months	384	10	1856.1	0.027	195	6	944.6	0.032	15.2 (-140.5, 70.3)
≥9 months	104	3	505.6	0.03	47	2	228.6	0.044	32.2 (-446.2, 89.4)

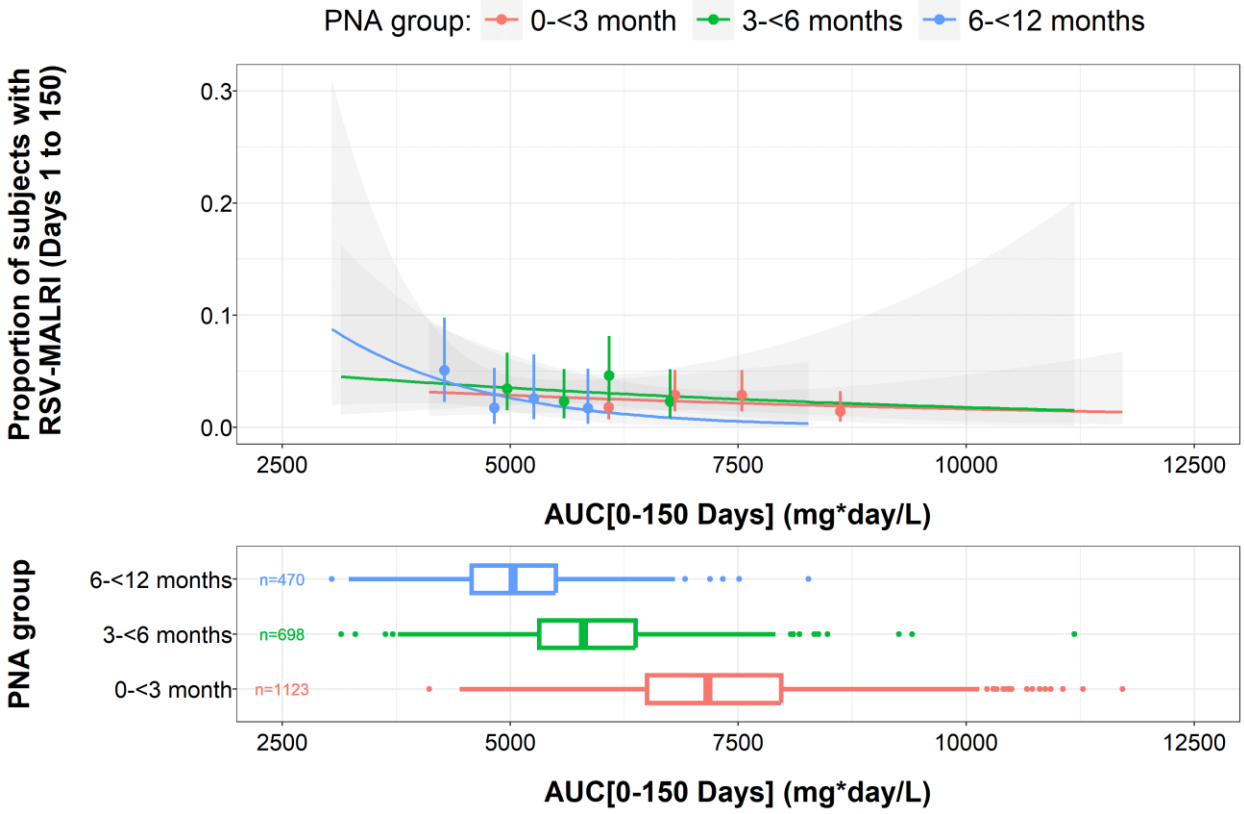
Source: FDA statistical reviewer; Tool: R. Data source: adeff.xpt, adsl.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method with the treatment group as the only one covariate.
Abbreviations: CI, confidence interval; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus

The small sample sizes and limited number of events in these subgroups mean that the efficacy by age results are descriptive and exploratory in nature. As such, no definitive conclusions can be drawn from the age subgroup analyses in Trial MK-1654-004.

Exposure-Response Analysis by Age

An exploratory assessment of the relationship between RSV-associated MALRI from Days 1 to 150 and clesrovimab exposure ($AUC_{0\text{-}150d}$), using a logistic regression analysis adjusted by baseline postnatal age subgroups, did not find baseline postnatal age subgroups as significant predictors of the exposure-response relationship. Age cutoffs of 3 and 6 months were used to group participants for the exposure-response analysis, to have at least 10 participants with exposure measures per subgroup. Figure 5 shows no significant difference in the proportion and probability of RSV-associated MALRI (Day 1 to 150) across the clesrovimab exposure ranges in the different baseline postnatal age subgroups. No difference was observed between RSV-associated MALRI and C_{trough} at Day 150, stratified by baseline postnatal age subgroups.

Figure 5. Observed Proportion and Predicted Probability of RSV-Associated MALRI, Days 1 to 150, vs. $AUC_{0\text{-}150d}$, Adjusted by Baseline Postnatal Age Group



Source: FDA reviewer
Upper panel: Closed circles (error bars) show the observed proportion of participants with an event (95% CI based on the Pearson-Klopper method) in each exposure quartile, stratified by baseline postnatal age (PNA) group and plotted at the median exposure of each quartile of clesrovimab area under the concentration-time curve from time 0 to Day 150 ($AUC_{0\text{-}150d}$). Solid (blue line and gray area) curves are the model-predicted (logistic regression) probability of the event (95% CI).
Lower panel: boxplot of $AUC_{0\text{-}150d}$ in participants with different baseline PNA group.
Abbreviations: $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; CI, confidence interval; MALRI, medically attended lower respiratory infection; RSV, respiratory syncytial virus

Conclusion

Although lower efficacy (in terms of RRRs and their lower bounds of 95% CIs) was observed in the older and heavier participants compared to the overall population, clesrovimab use was associated with decreased MALRI compared to placebo in all age and weight subgroups. Importantly, the age and weight subgroups had small sample sizes and a limited number of events, therefore these comparisons are descriptive and exploratory in nature. Further, the lower RRR in older and heavier infants appears to have been driven at least in part by lower rates of MALRI among older and heavier placebo participants, which is to be expected as infants grow and are better able to prevent and respond to RSV infection without any preventative intervention. It was also noted that there was no significant difference in the proportion of RSV-associated MALRI (Day 1 to 150) across the clesrovimab exposure ranges in the different age and weight subgroups. Therefore, the totality of the data supports a 105-mg clesrovimab dose for all infants entering their first RSV season, regardless of chronological age or weight.

6.3.2. Duration of Protection Following a Single Dose of Clesrovimab

Issue

Efficacy was assessed through Day 150 postdose as the primary endpoint and through Day 180 postdose as a secondary endpoint. Kaplan-Meier curves for the overall population as well as for key subgroups were analyzed to determine if efficacy was maintained through the entire 150-day period and to assess what, if any, conclusions could be drawn regarding efficacy beyond Day 150.

Background

Efficacy was assessed through 150 days (approximately 5 months) postdose as the primary endpoint and through 180 days (approximately 6 months) postdose as a secondary endpoint. One hundred and fifty days is considered a reasonable duration for a typical RSV season.

Assessment

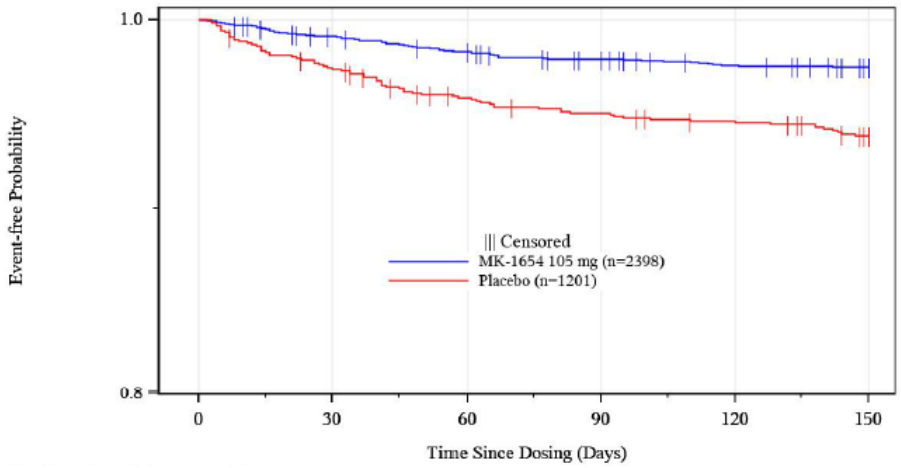
The Kaplan-Meier curves for the time from dosing to the first RSV-associated outpatient or inpatient MALRI, from Days 1 through 150 postdose, overall and for the subgroups of participants weighing <5 kg, ≥5 to <8 kg, and ≥8 kg are shown in Figure 6.

The Kaplan-Meier curves for overall population do not cross and the difference between clesrovimab and placebo groups is relatively constant, indicating that the treatment effect is maintained through Day 150.

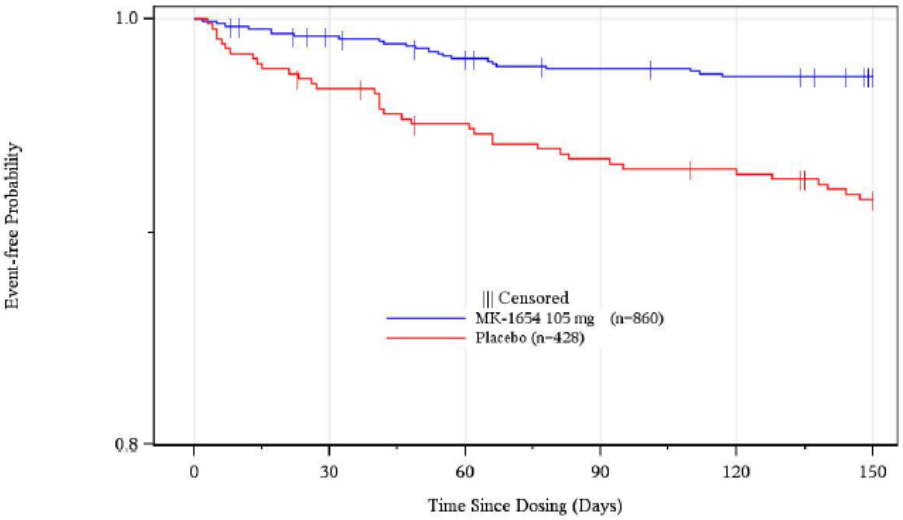
Across all the weight subgroups, the Kaplan-Meier plots show that the curves for the clesrovimab and placebo arms do not cross as was seen in the overall analysis, indicating that the treatment effects of clesrovimab over placebo remained over time for all three weight subgroups even though the differences in subgroups of ≥5 to <8 kg, and ≥8 kg of weight were smaller than in the <5 kg subgroup.

Figure 6. Kaplan-Meier Plot of Time From Dosing to First RSV-Associated Outpatient or Inpatient MALRI for Weight Subgroups, Full Analysis Set, Trial MK-1654-004

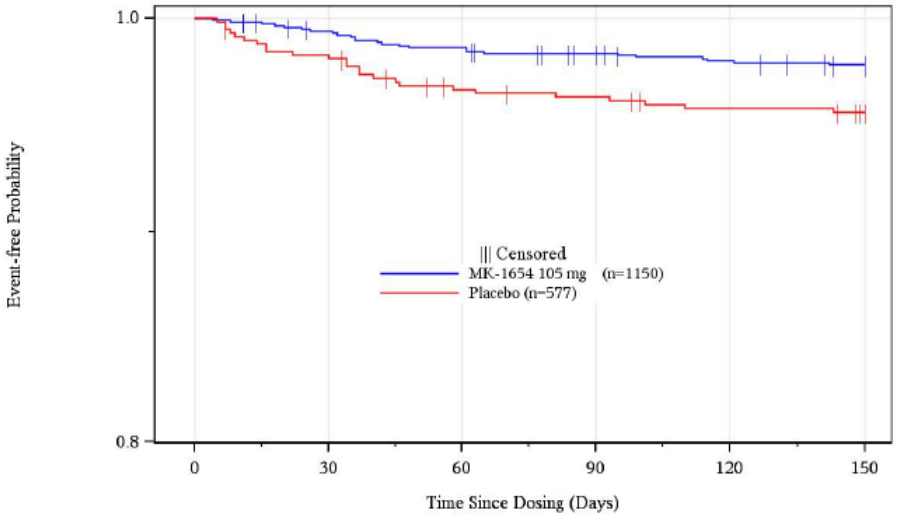
Overall



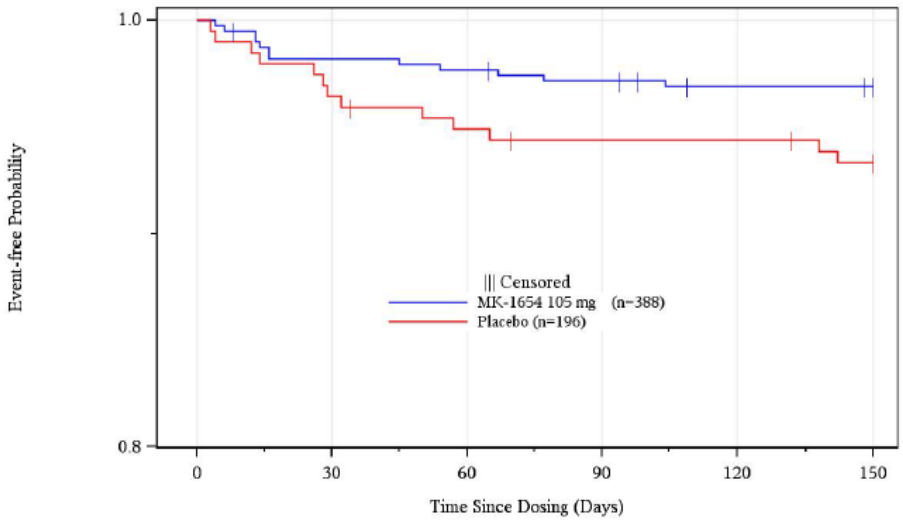
<5 kg



≥5 to <8 kg



≥8 kg

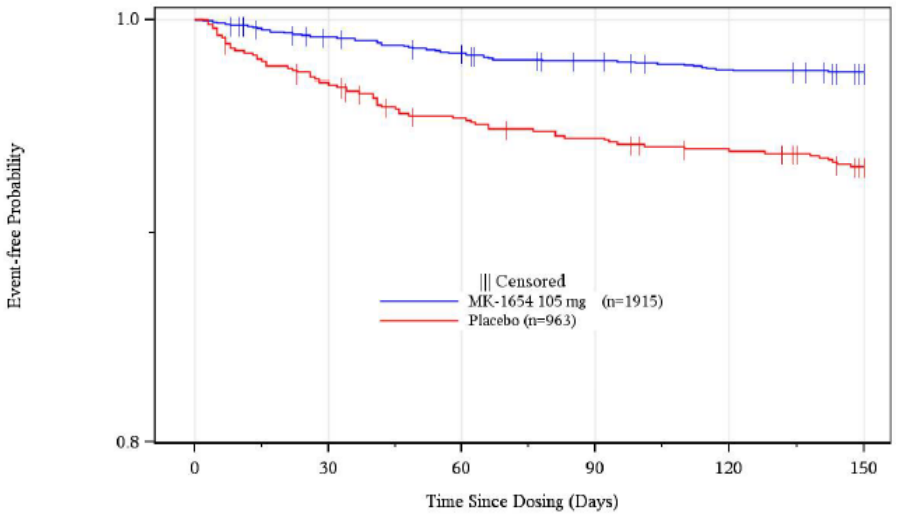


Source: Response to FDA IR Received on February 28, 2025, Biostatistics and Clinical Information, Figure 4 - Figure 6. Data source: adeff.xpt, adsl.xpt.
Abbreviations: IR, Information Request; MALRI, medically attended lower respiratory infection; MK-1654, clesrovimab; n, number of participants in treatment arm; RSV, respiratory syncytial virus

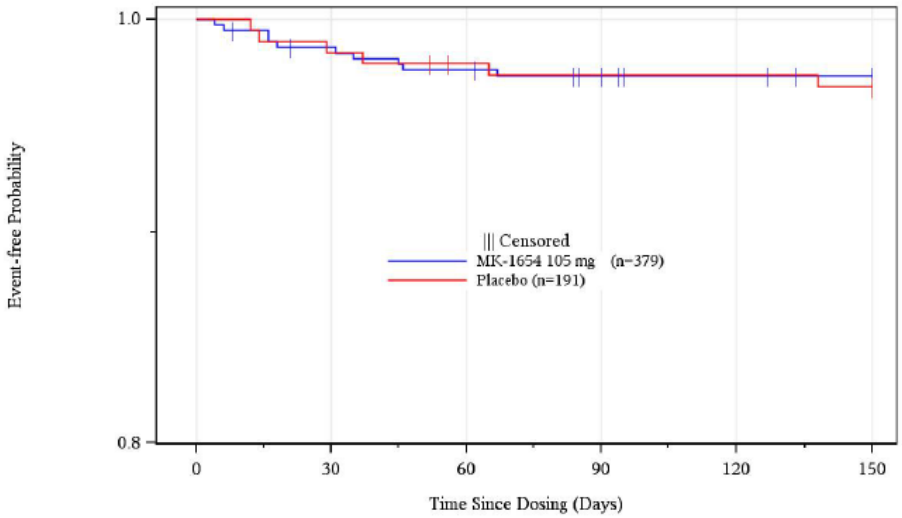
Similar analyses were conducted for chronological age subgroups. The Kaplan-Meier curves for the time from dosing to first RSV-associated outpatient or inpatient MALRI, from Days 1 through 150 postdose, for the subgroups of participants <6 months, ≥6 to <9 months, and ≥9 months of age are shown in Figure 7. In the <6-months subgroup, the Kaplan-Meier plot demonstrates that the curves for the clesrovimab and placebo arms do not cross, indicating that the difference between the two groups remained consistent over time, i.e., the efficacy of clesrovimab over the placebo maintained through Day 150. In contrast, the curves for the ≥6 to <9 months and ≥9-months subgroups almost overlapped, mainly due to much lower incidence rates in the placebo group observed in these older age subgroups (≥6 to <9 months and ≥9 months). These are post hoc subgroup analyses with small sample sizes and limited number of events in these subgroups, especially for the older age subgroups, and the trial was not powered to detect these subgroup differences, which means that these subgroup results should be viewed as descriptive and exploratory in nature. As such, no definitive conclusions can be drawn from these subgroup analyses in Trial MK-1654-004.

Figure 7. Kaplan-Meier Plot of Time From Dosing to First RSV-Associated Outpatient or Inpatient MALRI for Age Subgroups, Full Analysis Set, Trial MK-1654-004

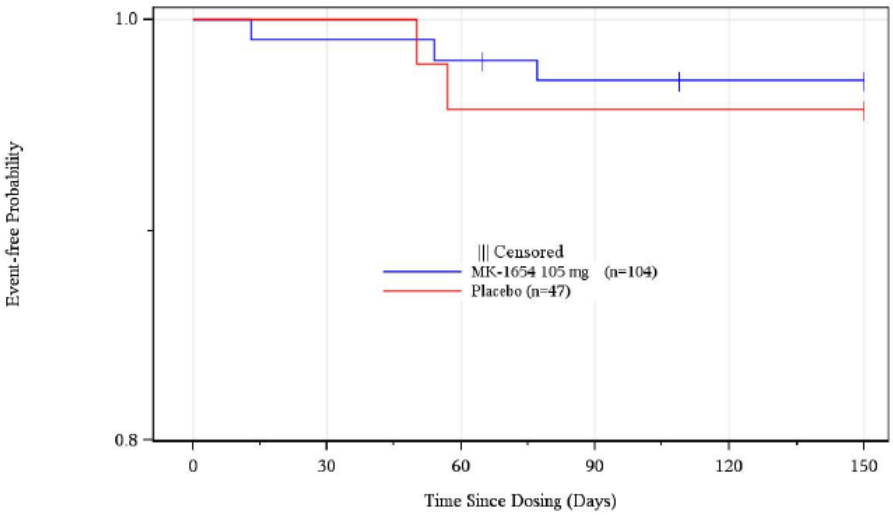
<6 months



≥6 to <9 months



≥9 months

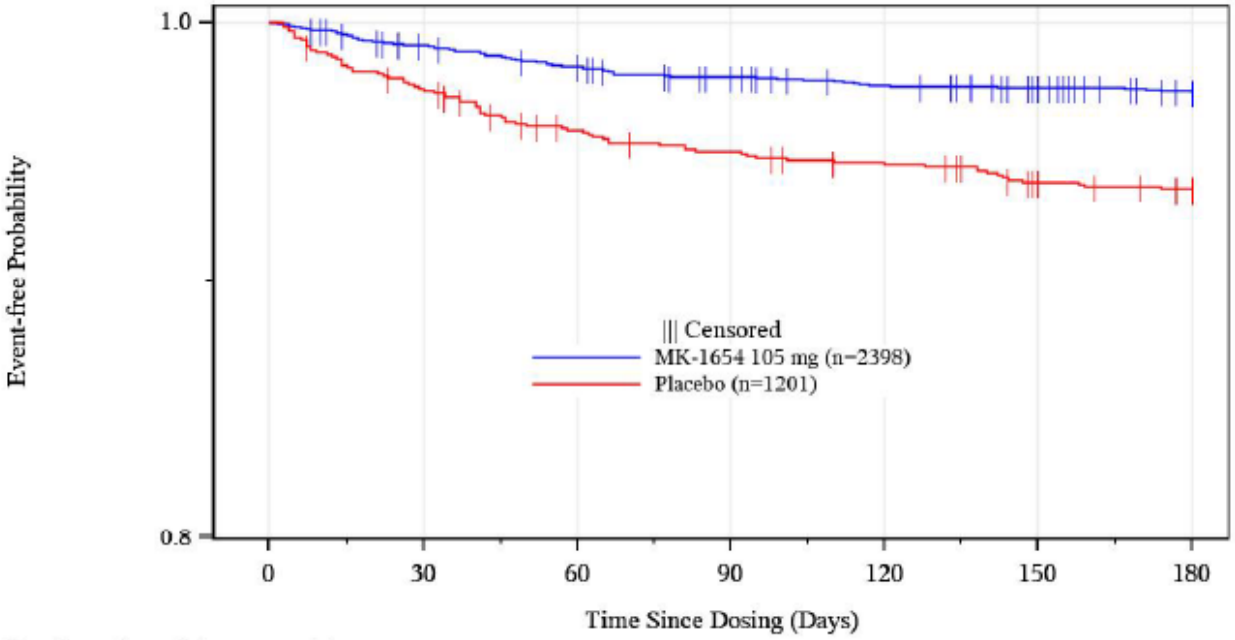


Source: Response to FDA IR Received on February 28, 2025, Biostatistics and Clinical Information, Figure 1 - Figure 3. Data source: adeff.xpt, adsl.xpt.
Abbreviations: MALRI, medically attended lower respiratory infection; MK-1654, clesrovimab; n, number of participants in treatment arm; RSV, respiratory syncytial virus

The duration of protection was also assessed with RSV-associated MALRI (outpatient and inpatient) from Days 1 to 180 postdose. The Kaplan-Meier curves for the time from dosing to the first RSV-associated MALRI (outpatient and inpatient) from Days 1 to 180 postdose, are shown in Figure 8.

The Kaplan-Meier curves for the overall population did not cross and the difference between clesrovimab and placebo groups is relatively constant, indicating that the treatment effect is maintained through Day 180. Although evaluation of this secondary endpoint suggested potential efficacy from 150 days to 180 days, this endpoint did not have Type-1 error control and few cases of RSV-associated MALRI occurred between Days 150 and 180 (four cases in clesrovimab group versus three cases in placebo group). This suggests no difference in terms of RSV-associated MALRI (outpatient and inpatient) between the two groups from Day 150 to Day 180.

Figure 8. Kaplan-Meier Plot of Time From Dosing to First RSV-Associated MALRI, Outpatient or Inpatient, Days From 1 to 180 Postdose, Full Analysis Set, Trial MK-1654-004



Number of participants at risk

MK-1654 105 mg (n=2398)	2398	2366	2344	2324	2309	2294	2278
Placebo (n=1201)	1201	1168	1142	1130	1122	1107	1098

Number of events inside period

MK-1654 105 mg (n=2398)	21	20	9	8	2	3	1
Placebo (n=1201)	31	19	10	5	9	3	0

Source: Clinical Study Report P004V01MK1654 (Merck 2024b)
Abbreviations: MALRI, medically attended lower respiratory infection; MK-1654, clesrovimab; n, number of participants in treatment arm; RSV, respiratory syncytial virus

Conclusion

The efficacy of clesrovimab is maintained through the full 150-day primary endpoint assessment window. The durability of effect through Day 150 was also observed in all the body weight subgroups and in the <6 months chronological age subgroup, which included most participants in the trial. It was difficult to assess the durability of effect for the older chronological age subgroups because of small sample sizes and a limited number of events. Although evaluation of the secondary endpoint of efficacy of clesrovimab against RSV-associated MALRI from Days 1 through 180 postdose also showed a decreased incidence of RSV-associated MALRI from Days 1 through 180 postdose in the clesrovimab group as compared with the placebo group, with efficacy of 59.5% (95% CI: 43.3%, 71.1%), this secondary endpoint did not have Type-1 error control. Additionally, very few new cases of RSV-associated MALRI occurred between Days 150 through 180, with only four cases in the clesrovimab group and three cases in the placebo

group between Days 150 through 180. Therefore, while the efficacy of a single dose of clesrovimab is maintained through Day 150, limited conclusions can be drawn regarding potential efficacy beyond 5 months (Day 150).

6.3.3. The Need for a Second Clesrovimab Dose for Infants Undergoing ECMO or CPB

Issue

For infants undergoing ECMO or cardiac surgery requiring CPB during or entering their first RSV season, the Applicant proposed an additional 105-mg dose, regardless of time of ECMO or CPB relative to the Season-1 dose as soon as the infant is stable after surgery to ensure adequate clesrovimab serum levels. The necessity and appropriateness of the proposed recommended dosage was evaluated.

Background

Effect of ECMO or CPB on Pharmacokinetics of Other Monoclonal Antibodies With the Same or Similar Indications

Palivizumab and nirsevimab concentrations are decreased in children undergoing ECMO or CPB. A mean decrease of 58% in palivizumab serum concentration was observed in children after CPB (American°Academy°of°Pediatrics 2014). CPB reduced nirsevimab concentration by 29.3% when performed within 90 days postinitial dose and by 52.4% when performed after 90 days postinitial dose (FDA 2023). Both palivizumab and nirsevimab United States Prescribing Information (USPI) recommend an additional postsurgery dose in children undergoing CPB to ensure adequate serum concentrations.

Potential Mechanism

The Applicant stated that the mechanism by which therapeutic mAb concentrations are reduced after ECMO or CPB is likely mediated by nonspecific protein adsorption to ECMO or CPB circuit surfaces (Doyle and Hunt 2018).

Assessment

A total of nine participants who received clesrovimab in Trial MK-1654-007 underwent ECMO or CPB, with eight in RSV Season 1 and one in RSV Season 2. Of the nine participants, four received an additional dose of clesrovimab (three in Season 1 and one in Season 2). The Applicant stated that the determinations regarding the need for additional dosing following ECMO or CPB were made based on the RSV seasonality and the medical needs. No participant underwent surgery requiring ECMO or CPB in Trial MK-1654-004. Table 20 provides redosing and PK information for the nine participants that received ECMO or CPB, with selected baseline demographic data.

Table 20. Overview of Participants Undergoing CPB or ECMO, Trial MK-1654-007

Participant ID	Season	Type of Procedure	Age at Baseline (Month)	Weight at Baseline (Kg)	GA (Week)	Time Between Surgery and Seasonal Dose (Day)	Time Between Redosing (Postsurgery Pharmacokinetics[a]) and Seasonal Dose (Day)	Concentrations (mcg/mL)			
								C_{7d}	C_{150d}	C_{240d}	Postsurgery Pharmacokinetics[a]
Participants with an additional dose											
(b) (6)	1	CPB	2.8	4.4	33.3	136	157	123	9.04	.	.
	1	CPB	0.6	2.06	34.3	289	337	227	17.5	3.79	0.568 (Day 337)
	1	CPB	0.4	4.19	39.1	211	269	141	11.9	1.25	.
	2	CPB	12.4	3.2	35.7	30	55	195	35.1	.	41.9 (Day 55)
Participants without an additional dose											
(b) (6)	1	ECMO	1.0	3.6	38.1	168	N/A	139	9.51[c]	1.55	N/A
	1	CPB	2.3	3.8	36.0	205	N/A	143	16.9	2.55	N/A
	1	CPB	3.6	4.67	38.3	209	N/A	111	10.8	1.25	N/A
	1	CPB	1.3	4.015	41.0	86	N/A	155	11.8[c]	.	N/A
	1	ECMO	4.0	5.4	38.3	125	N/A	106	1.32	0.25	N/A

Source: Reviewer generated table, based on datasets ADPC and ADPP, and Response to Clinical Pharmacology IR dated November 25, 2024.
Postsurgery PK samples were only collected in participants who received an additional dose.
Concentration value was missing per Applicant's dataset
[a] Postsurgery PK samples were collected immediately prior to redosing.
[b] This participant received a dose of 210 mg in Season 2 and then a postsurgery dose of clesrovimab 210 mg.
[c] PopPK-estimated C_{150d} values were reported for two participants (ID (b) (6) as observed C_{150d} were missing. The surgery status (ECMO/CPB or not) were not evaluated as a covariate during model development, likely due to limited number of cases. As a result, the model predicted concentrations might be overestimated.
Abbreviations: C_{7d}, serum concentration on Day 7; C_{150d}, serum concentration on Day 150; C_{240d}, serum concentration on Day 240; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; GA, gestational age; N/A, not applicable; PK, pharmacokinetic; PopPK, population pharmacokinetic(s)

PK Assessment

Per the Applicant, blood PK samples were collected immediately prior to the postsurgery redosing, but not immediately prior to the surgery or after redosing. Therefore, it is not possible to estimate the effect of ECMO or CPB on the pharmacokinetics for individual participants. As such, to estimate the impact of ECMO or CPB on clesrovimab pharmacokinetics, the observed mean concentration values of Day 150 and Day 240 in Trial MK-1654-007 served as the reference for comparison with the observed concentrations (i.e., protocol-scheduled pharmacokinetics on Day 150 and Day 240) in participants who received ECMO or CPB.

Effect of ECMO/CPB on Clesrovimab Pharmacokinetics

Four participants underwent surgery before Day 150; of which three participants ([redacted] (b) (6)) did not receive an additional dose. The mean Day-150 concentration from these three participants was approximately 54% lower than the reference Day-150 concentration in Trial MK-1654-007 Season 1 (see Table 21).

Table 21. Serum Concentrations on Day 150 for Participants Who Underwent Surgery Before Day 150

Geomean Concentrations (mcg/mL)	With Additional Dose	Without Additional Dose	Reference C_{150d} in Trial MK-1654-007	% Difference
Season 1	N/A (n=0)	5.2 (n=3)[a]	11.4*	↓ 54.4%

Source: Reviewer-generated table.
[a] Data source: Refer to Table 20.
* Data source: MK-1654-007 Study Report, Table 14.2-38
Abbreviations: C_{150d}, serum concentration on Day 150; n, number of participants with given characteristic; N/A, not applicable

Eight participants underwent surgery before Day 240; of which five participants ([redacted] (b) (6)) had clesrovimab Day-240 serum concentration available and none of them received the additional dose by Day 240. The mean Day-240 concentration from the five participants who did not receive an additional dose by Day 240 was approximately 61% lower than the reference Day-240 concentration in Trial MK-1654-007 Season 1 (see Table 22).

Table 22. Serum Concentrations on Day 240 for Participants Who Underwent Surgery Before Day 240

Geomean Concentrations (Number of Participants)	With Additional Dose	Without Additional Dose	Reference C_{240d} in Trial MK-1654-007*	% Difference
Season 1	N/A (n=0)	1.1 (n=5)[a]	2.8	↓ 60.7%

Source: Reviewer-generated table.
[a] Data source: Refer to Table 20.
* Data source: Trial MK-1654-007 Study Report, Table 14.2-38
Abbreviations: C_{240d}, serum concentration on Day 240; n, number of participants with given characteristic; N/A, not applicable

PK Postadditional Dose

Out of four participants who received an additional dose, only one participant provided PK data after the additional dose. Participant [redacted] (b) (6) received an additional dose on Day 50 post-Season-2 dose. Clesrovimab serum concentration on Day 150 (i.e., postadditional dose) from this participant was approximately 2.1-fold compared to the reference Day-150 concentration in Trial MK-1654-007 Season 2 (see Table 23).

Table 23. Serum Concentration for Participants With an Additional Dose

Geomean Concentrations (mcg/mL)	With Additional Dose	Without Additional Dose	Reference C_{150d} in Trial MK-1654-007	% Difference
Season 2	35.1 (n=1)	N/A (n=0)	16.7	↑ 110.2%

Source: Trial MK-1654-007 Study Report, Table 14.2-39
Abbreviations: C_{150d}, serum concentration on Day 150; n, number of participants with given characteristic; N/A, not applicable

It is not feasible to precisely estimate the impact of ECMO or CPB on the pharmacokinetics of clesrovimab due to the limited data available, the proposed mechanism of effect (i.e., nonspecific adsorption), and varying timing of ECMO or CPB relative to RSV season/clesrovimab dosing. Based on the limited PK data, the effect of ECMO or CPB on the pharmacokinetics of clesrovimab in Trial MK-1654-007 is consistent with the postsurgery PK reductions observed with palivizumab and nirsevimab. The magnitude of the effects of ECMO or CPB suggests that, in some cases, an additional dose may result in exposures nearly 2-fold higher than those observed in Trials MK-1654-004 or MK-1654-007.

Safety Assessment

Of the four participants in the clesrovimab group who received an additional dose of clesrovimab postprocedure in Trial MK-1654-007 in either RSV season, two participants experienced AEs after the additional dose. In RSV Season 1, one participant experienced an AE after the postprocedure dose (105 mg) of Grade 2 upper respiratory tract infection, which occurred 12 days after redosing, was nonserious, and was assessed as not related to study intervention by the Investigator. The single participant in RSV Season 2 who received a postprocedure dose of clesrovimab (210 mg) reported two nonserious AEs after the additional dose: somnolence on Day 3 (Toxicity Grade 1, duration 23 hours) and pharyngitis on Day 37 (Toxicity Grade 1, duration 21 days) postredosing, which were both assessed as not related to study intervention by the Investigator. No AEs were reported after redosing in the other two participants who received an additional dose of clesrovimab.

Based on the available data, there were no major safety concerns for the participants who received an additional dose of clesrovimab after undergoing ECMO or CPB procedures. While the safety data for participants who received the additional dose are limited, overall, the safety profile of clesrovimab in neonates and infants, additional safety data from adults (including 12 adults who received a single dose administration of 3000 mg IV which provided exposures greater than double that of a 105 mg dose in an infant), and a sufficient nonclinical safety margin all support the proposed additional 105-mg dose in infants after undergoing ECMO or CPB procedures.

Conclusion

The impact of ECMO or CPB on the pharmacokinetics of clesrovimab was not fully characterized due to the lack of paired concentrations collected before and after surgery from the same participants and the limited number of participants. Based on the limited data submitted and the observed impact from similar monoclonal antibodies (i.e., nirsevimab and palivizumab), the potential mechanism of removal of monoclonal antibodies, and the safety profiles from nonclinical and clinical studies, the proposed additional 105-mg dose in infants after ECMO or CPB in Season 1, regardless of time relative to the Season-1 dose, is reasonable and is recommended by the review team.

6.3.4. Efficacy by RSV Subtype

Issue

While the primary efficacy endpoint of relative risk reduction of RSV-associated MALRI Days 1 through 150 was met in Trial MK-1654-004, we noted potential inconsistencies between the RRR estimates for the RSV A and RSV B subtypes. In particular, we note that subgroup analysis of efficacy by RSV subtype suggested potential decreased efficacy against RSV A compared to that observed for RSV B, though a favorable trend toward a decreased incidence rate of MALRI through Day 150 was still observed for RSV A among participants receiving clesrovimab (0.012) compared to placebo (0.022), with an RRR and 95% CI of 44.4% and (5.5%, 67.3%), respectively.

Background

RSV can be divided into two major subtypes, RSV A and RSV B. Both subtypes cocirculate annually, and the dominant circulating strain fluctuates over time. Nonclinical data suggest that clesrovimab is active against both RSV A and RSV B.

Assessment

Summary of Nonclinical Virology Data Regarding Activity by RSV Subtype

The neutralization activity of clesrovimab against laboratory strains and clinical isolates of RSV A and RSV B was evaluated in cell culture (summarized in Section 5.1 and detailed in Section 20).

Against a panel of 47 historical clinical isolates, collected from 1987 to 2016, clesrovimab neutralized RSV A isolates with a median EC_{50} value of 25pM (3.71 ng/mL) (n=24; range of 1.2 to 74pM [0.18 to 11.11 ng/mL]), and each of the RSV B isolates with a comparable median EC_{50} value of 30pM (4.48 ng/mL) (n=23; range of 4 to 198pM [0.59 to 29.65 ng/mL]). Against a panel of 12 contemporary clinical isolates, collected from 2016 to 2021, clesrovimab neutralized each of the six RSV A isolates with a median EC_{50} value of 121pM (18.02 ng/mL) (n=6; range of 59 to 186pM [8.79 to 27.74 ng/mL]), and each of the six RSV B isolates with a median EC_{50} value of 130pM (19.41 ng/mL) (n=6; range of 95 to 153pM [14.22 to 22.92 ng/mL]). The increase in EC_{50} values for contemporary compared with historical isolates is thought related to assay differences.

Efficacy by RSV Subtype in Clinical Trials

For the analyses by RSV subtype, RSV subtype A and RSV subtype B are not mutually exclusive subgroups. In the full analysis set, two participants in the clesrovimab group were infected with both RSV A and RSV B, while no participants in the placebo group were infected with both subtypes. The incidence rate of RSV-associated MALRI (outpatient and inpatient) from Days 1 to 150 postdose was lower in the clesrovimab group compared to the placebo group for both RSV subtypes (Table 24). The relative risk reduction for RSV B was similar to the overall primary efficacy result and was higher than that for RSV A. The subgroup analysis by RSV subtypes suggests a potentially decreased efficacy against RSV A. However, reassuringly, we observed that the relative risk reductions in RSV-associated hospitalization from Days 1 to 150 postdose for RSV A and RSV B are comparable (Table 25).

Since the analyses by RSV subtype were not powered and were without multiplicity adjustment of multiple tests, no definitive conclusions can be drawn from these results in Trial MK-1654-004.

Table 24. Subgroup Analyses by RSV Subtype in RSV-Associated MALRI (Outpatient and Inpatient) From Days 1 Through 150 Postdose, Full Analysis Set, Trial MK-1654-004

	Clesrovimab (N=2411)				Placebo (N=1203)				Relative Risk Reduction (%)	
Endpoint	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Estimate (95% CI)[3]	p-Value (One-Sided)[3]
RSV-associated outpatient and inpatient MALRI	2398	60	11685.6	0.026	1201	74	5710.5	0.065	60.4 (44.1, 71.9)	<0.001
By RSV subtype										
RSV A	2398	29	11780.2	0.012	1201	26	5868.9	0.022	44.4 (5.5, 67.3)	N/A
RSV B	2398	33	11786.1	0.014	1201	48	5797.4	0.041	66.2 (47.2, 78.3)	N/A

Source: FDA statistical reviewer; Tool: R. Data source: adeff.xpt, adsl.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method with the treatment group as the only one covariate.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; N/A, not applicable; No., number; RSV, respiratory syncytial virus

Table 25. Subgroup Analyses by RSV Subtype in RSV-Associated Hospitalization Days From 1 to 150 Postdose, Full Analysis Set, Trial MK-1654-004

	Clesrovimab (N=2411)				Placebo (N=1203)				Relative Risk Reduction (%)	
Endpoint	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Estimate (95% CI)[3]	p-Value (One-Sided)[3]
RSV-associated hospitalization	2398	9	11864.8	0.004	1201	28	5859.0	0.024	84.2 (66.6, 92.6)	<0.001
By RSV subtype										
RSV A	2398	4	11879.9	0.002	1201	12	5916.0	0.010	83.4 (48.5, 94.6)	N/A
RSV B	2398	5	11874.2	0.002	1201	16	5898.7	0.014	84.5 (57.6, 94.3)	N/A

Source: FDA statistical reviewer; Tool: R. Data source: adeff.xpt, adsl.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the Poisson regression model with robust variance method with the treatment group as the only one covariate.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; N/A, not applicable; No., number; RSV, respiratory syncytial virus

Conclusion

While we note that subgroup analysis of efficacy by RSV subtype shows potentially decreased efficacy against RSV A compared to that observed for RSV B, the totality of the clinical and nonclinical data suggests that clesrovimab is effective for the prevention of both RSV A and RSV B.

6.3.5. Impact of the Presence of Antidrug Antibodies on Clesrovimab Efficacy

Issue

There was a trend of lower efficacy in ADA-positive participants compared to ADA-negative participants in Trials MK-1654-004 and MK-1654-007.

Background

The incidence rate of ADA and the impact of ADA on pharmacokinetics, SNA, and efficacy of clesrovimab have been evaluated. While ADA did not have a significant impact on pharmacokinetics and SNA (see Section 14.4), the incidence rates of RSV-associated MALRI in the ADA-positive subgroup were numerically higher relative to participants who did not develop ADAs in Trials MK-1654-004 and MK-1654-007.

Assessment

A subgroup analysis was conducted for the primary efficacy endpoint for Trial MK-1654-004 (i.e., RSV-associated MALRI outpatient and inpatient from Days 1 through 150 postdose), to estimate the risk ratio with 95% CI by ADA status. The results are shown in Table 26.

Table 26. RSV-Associated Outpatient and Inpatient MALRI (Days 1 to 150 Postdose) by ADA Status at Day 150 in Participants Treated With Clesrovimab, Full Analysis Set Population, Trial MK-1654-004

	ADA+				ADA-				
Endpoint	n	No. of Cases	Total Follow-Up Time (Months)	Incidence Rate Over 5 Months (95% CI)	n	No. of Cases	Total Follow-Up Time (Months)	Incidence Rate Over 5 Months (95% CI)	Risk Ratio Estimate (95% CI) p-Value
RSV-associated MALRI by ADA Status at Day 150	120	14	560.7	0.125 (0.068, 0.209)	1898	41	9340.0	0.022 (0.016, 0.030)	5.688 (3.010,10.471) p<0.0001

Source: Reviewer analysis with Poisson regression model (risk ratio = ratio of incidence rates). Data source: Table 14.2-55, page 459, CSR MK-1654-004
Abbreviations: ADA, antidrug antibody; CI, confidence interval; CSR, clinical study report; MALRI, medically attended lower respiratory infection; n, number of participants; No., number; RSV, respiratory syncytial virus

The subgroup analysis results suggest that the incidence rate of MALRI at Day 150 in the ADA-positive group is 5.7 times higher than that in the ADA-negative group. The results from Fisher's exact test (risk ratio 5.401; 95% CI: 3.030, 9.627; p<0.0001) demonstrated that the percentage of participants with MALRI at Day 150 in the ADA-positive group is approximately 5.4 times higher than that in the ADA-negative group. In addition, the trend of low efficacy in the ADA-positive group was consistently observed for all primary, secondary, and exploratory endpoints (see Section 14.4). However, a definite conclusion on statistical significance cannot be drawn as this is an exploratory, post hoc analysis and the overall event rate (MALRI) is low.

The review team acknowledges the following observations that preclude the review team from reaching a definitive conclusion on the effects of ADA on efficacy. First, the incidence of ADA at Day 150 is low (5.7% in Trial MK-1654-004 and 4.5% in Trial MK-1654-007). Furthermore, temporal association between the emergence of ADA and MALRI events could not be evaluated as ADA was first measured at Day 150, while most MALRI cases were observed by Day 90. Lack of apparent impact of ADA on pharmacokinetics and pharmacodynamics (i.e., RSV SNA titers) and low ADA titers (<1000) in all participants who were ADA-positive and had MALRI also limit the interpretation of the observed trend of lower efficacy in the ADA-positive group. With these limitations in mind, the Applicant claimed that ADA did not affect the efficacy of clesrovimab. However, given the significant imbalance in RSV-associated MALRI in the ADA-positive group compared to the ADA-negative group, the review team is unable to conclude that there is no impact of ADA on efficacy at this time.

Along with the above limitations, the review team recognizes that the clinical implications of a potential impact of ADA on efficacy are also unclear, as clesrovimab is intended to be administered as a single dose. Future data from Season 2 of the ongoing trial, Trial MK-1654-007, may provide further information on the impact of ADA on clesrovimab efficacy upon repeat dosing.

Conclusion

While there was a trend of lower efficacy in ADA-positive participants compared to ADA-negative participants in Trials MK-1654-004 and MK-1654-007, a definitive conclusion cannot be drawn at this time. Given the low rate of ADA positivity, overall efficacy regardless of ADA status, and the proposed single-dose administration, the efficacy results by ADA status do not alter the review team's overall assessment of the benefit-risk of clesrovimab.

6.3.6. Potential for Reduced Susceptibility to Clesrovimab Through Natural Variability/Polymorphisms

Issue

The clinical efficacy of clesrovimab against RSV could be impacted by naturally occurring variants which harbor F protein polymorphisms associated with reduced susceptibility to clesrovimab.

Background

Like other viruses, RSV is continually evolving, particularly in genomic regions expressing envelope and fusion proteins which are exposed on the virion surface and key targets of immune surveillance. Amino acid substitutions in the F protein may alter specific epitopes, or the overall structure of the protein, potentially impacting the binding and neutralization by clesrovimab.

Assessment

The evaluation of whether clesrovimab is likely to retain activity against the range of RSV variants circulating in the past or present relied on supporting data from nonclinical studies (detailed in Section 20), and surveillance studies (see Section 18.1). Cell culture studies included the evaluation of clesrovimab cell culture neutralization activity against panels of historical and contemporary RSV isolates. Surveillance studies included evaluation of polymorphisms seen in public-sequence databases, and of RSV variants in clinical samples from RSV-infected individuals.

Nonclinical Supporting Data

As summarized in Section 5.1, and detailed in Section 20.4, clesrovimab was tested against historical and contemporary clinical RSV isolates in a cell culture neutralization assay. Clesrovimab neutralized 47 RSV clinical isolates collected from North America locations between 1987 and 2016 with median EC_{50} values for RSV A isolates of 25pM (3.71 ng/mL) (n=24; range of 1.2 to 74pM [0.18 to 11.11 ng/mL]), and for RSV B isolates of 30pM (4.48 ng/mL) (n=23; range of 4 to 198pM [0.59 to 29.65 ng/mL]). Clesrovimab also neutralized 12 contemporary isolates from Texas, United States, between 2016 and 2021, with a median EC_{50} value for RSV A isolates of 121pM (18.02 ng/mL) (n=6; range of 59 to 186pM [8.79 to 27.74 ng/mL]), and for RSV B isolates of 130pM (19.41 ng/mL) (n=6; range of 95 to 153pM [14.22 to 22.92 ng/mL]). The relatively high EC_{50} values for contemporary isolates compared with historical isolates is thought to be related to assay differences rather than possible differences in the RSV F protein because the values for the control viruses were also increased.

The sequence diversity of the historical isolates was representative of the diversity of sequences downloaded from GenBank®, but there was little diversity for the contemporary isolates, with three of the six RSV A isolates (i.e., four distinct isolates) and four of the six RSV B isolates (i.e., three distinct isolates) having identical F protein sequences.

RSV Surveillance Programs

To determine whether clesrovimab maintains activity from one season to the next, contemporary and circulating clinical RSV variants were monitored by accessing public RSV sequence databases and through sequencing of the F protein from clinical isolates.

To this end, the Applicant conducted an analysis of F protein sequences downloaded from GenBank®, and a global surveillance study of RSV clinical isolates collected between 2019 and 2023 in eight countries across the Northern and Southern hemispheres.

Polymorphic substitutions in the clesrovimab binding region were identified from an analysis of 15,257 complete F protein sequences downloaded from GenBank® (accessed April 15, 2024). The clesrovimab binding site (nonlinear, amino acids 426 to 429, 432, 433, 440, 441, 443, 445 to 447) was 99.8% conserved by identity in 15,495 of the 15,527 sequences, and a total of 13

variants were identified from sequences which were not conserved. The most common polymorphism, I432T (0.04% of sequences), conferred reduced susceptibility to clesrovimab in a cell culture neutralization assay of 4-fold (RSV A) or 1.6-fold (RSV B). One polymorphism seen in three RSV A sequences, G446E, is a resistance-associated substitution selected in cell culture and confers >3,800-fold loss of susceptibility to clesrovimab. For the other polymorphisms identified (N426T, N428D, I432V, K433Q/R, D440N, S443T, K445R, G446V, V447L/M; none of these changes would lead to loss or addition of an asparagine-linked glycosylation site), cell culture neutralization data were reported only for RSV B I432V (3-fold loss of susceptibility to clesrovimab), and K445R polymorphism (no impact on susceptibility to clesrovimab [<5-fold change]). Note that S443P substitution was identified in variants selected in cell culture passage of RSV A and RSV B which had >3,800-fold and >360-fold reduced susceptibility to clesrovimab, respectively, so other changes at position 443 may also impact susceptibility to clesrovimab.

An assessment was also conducted of F protein amino acid residues located ≤5Å from the clesrovimab epitope (positions E161, S182, N183, G184, G430, I431, V442, G464, K465, Y468, and K470), and polymorphisms seen at these positions in the GenBank® database. Polymorphisms at these positions that were seen in ≥2 sequences included S182A, V442M, K465R, and K470R (most common variant was K465R, seen in six sequences [0.04%]). Phenotypic data for these polymorphisms were not reported. Only RSV A K470R and RSV B K470E polymorphisms were observed in an analysis of breakthrough infections in clinical studies (see Section 18.4).

In the global surveillance program, clinical isolates were collected from individuals who were not enrolled in clinical trials and of various ages (<1 year to >60 years of age). The RSV F protein region was successfully sequenced for 555 of these isolates, showing that the clesrovimab binding site was highly conserved (>99%) in 300 (54%) RSV A and 255 (46%) RSV B sequences. Two binding-site polymorphisms were identified at low variant allele frequency (VAF): RSV A: R429H (6% VAF) and RSV B: R429C (13% VAF), and one was seen at high VAF: RSV B K445R (70% VAF); phenotypic data are not available for the R429 polymorphisms, but RSV B K445R polymorphism had no impact on susceptibility to clesrovimab (<5-fold change).

Conclusion

In cell culture, clesrovimab was able to neutralize historical and contemporary RSV A and RSV B clinical isolates with similar activities as compared with laboratory reference strains. While there was an increase in EC_{50} values for the contemporary compared with historical isolates, this was thought to result from the assays for each panel being conducted several years apart, with possible changes in reagents and assay conditions, and not from possible differences in the RSV F protein. The sequence diversity of the historical isolates was representative of the diversity of sequences downloaded from GenBank®, but there was little diversity for the contemporary isolates, with three of the 6 RSV isolates and four of the 6 RSV B isolates having identical F protein sequences.

In sequences downloaded from GenBank® (n=15,527) and a surveillance program in which the RSV F gene was sequenced for 555 clinical isolates collected from global locations, there were few instances of F protein polymorphisms which occurred within or near the clesrovimab binding site.

Given the limited cell culture neutralization data for contemporary RSV isolates, and the potential for the emergence of new polymorphisms impacting the activity of clesrovimab, it will be important as a postmarketing requirement for the Applicant to continue to monitor the F protein sequences of circulating RSV variants, and to evaluate novel variants phenotypically.

6.3.7. Potential for Treatment-Emergent Resistance to Clesrovimab

Issue

Prophylaxis with clesrovimab could theoretically select for variants with amino acid substitutions which reduce susceptibility and result in a breakthrough infection. Breakthrough infections could potentially result in worse disease outcomes and transmission of resistant virus. The assessment of resistance emergence following prophylaxis with clesrovimab is critical to understanding the overall risk-benefit profile of clesrovimab.

Background

Cell-culture passage experiments were conducted to determine the likelihood that resistant virus could be selected following exposure to clesrovimab, and to identify and characterize substitutions that may be associated with clesrovimab resistance. In addition, RSV sequence data from clinical trials of clesrovimab were analyzed to determine whether particular variants were associated with breakthrough infection or with more severe disease in clesrovimab-treated participants (see Section 18.4).

Assessment

Nonclinical Supporting Data

To determine the potential for selection of RSV resistance to clesrovimab, and to identify amino acid residues associated with resistance, cell culture serial passage of RSV A and RSV B in the presence of clesrovimab was conducted (see Section 20.6). For RSV A, four variants were generated after six rounds of serial infection, and for RSV B, one variant was generated after nine rounds of serial infection. None of the four RSV A or 1 RSV B variants which were selected were susceptible to neutralization in cell culture by clesrovimab up to the highest concentration tested, with reduced susceptibility to clesrovimab of >3,800-fold (RSV A) or >360-fold (RSV B). The four RSV A variants harbored the following clesrovimab binding-site substitutions: G446E, S443P + K445N, S443P + G446E, or S443P, respectively, and the RSV B variant harbored S443P substitution.

While four of the five resistant variants appeared to have reduced replication ability in human epidermoid carcinoma #2 (HEp-2) cells, it is not clear whether this is predictive of reduced fitness in humans. Even with reduced replication, there is a potential for such variants to pick up compensatory substitutions with continued drug exposure. Also, three RSV F sequences expressing G446E substitution were identified in GenBank® (see Section 18.1), indicating that this substitution may be present in circulating variants, and therefore does not prevent replication or potential transmission of the variant.

Clinical Supporting Data

Genotypic analysis was conducted of the RSV F gene from nasopharyngeal samples collected in clinical trials of clesrovimab, MK-1654-004 and MK-1654-007. (see Section 18.4). The main objectives of FDA analyses of the sequence data were to determine if there was a correlation of clesrovimab treatment with increased incidence of substitutions in antigenic Site IV/clesrovimab-binding site, which may be resistance-associated, or if there was a correlation of these substitutions with increased incidence of RSV-associated MALRI or RSV-associated hospitalization.

Trial MK-1654-004

In the sequencing dataset for Trial MK-1654-004, after removing nonqualifying samples, there were a total of 568 samples (319 from the clesrovimab arm, 249 from the placebo arm) from 523 participants (303 in the clesrovimab arm, 220 in the placebo arm). For clinical events meeting the primary endpoint of RSV-associated MALRI, sequence data were available for 58/62 (94%) of qualifying infections in the clesrovimab arm, and 67/74 (91%) of qualifying infections in the placebo arm.

There were generally more cases of RSV B compared with RSV A infections within each trial arm. For infections meeting the primary endpoint (including those with mixed RSV A/B), there were 29/60 (48%) clesrovimab and 26/74 (35%) placebo participants with RSV A, and 33/60 (55%) clesrovimab and 48/74 (65%) placebo participants with RSV B.

An analysis was conducted of all amino acid substitutions occurring in or near the clesrovimab binding site, using all available sequence data from Days 1 through 180 postdose, and a VAF threshold of ≥3%. The threshold was based on the validation report for the sequencing assay, where a 3% cutoff eliminated most sequencing errors. The amino acid positions evaluated included Site IV (426-447) and/or those within 5Å of the clesrovimab binding site (161, 182 to 184, 430, 431, 442, 464, 465, 468, 470), and residues directly adjacent to these positions (Table 27).

More substitutions in or near the clesrovimab binding site were observed in RSV infections of clesrovimab-treated participants (21/156 [13.5%]) compared with placebo (5/150 [3%]), with similar numbers for RSV A and RSV B. For the clesrovimab binding site only (amino acid positions 426 to 447), there were 15/156 (9.6%) RSV infections with substitutions in clesrovimab-treated participants, compared with 2/150 (1.3%) placebo participants.

Most of the binding-site substitutions affected residue G446 (RSV A: G446E, G446R or G446W; RSV B: G446E or G446R) and were seen at ≥50% VAF in at least one participant each. Other substitutions seen in clesrovimab-treated participants at <10% VAF were RSV B: F435S, S443L, G446V, and V447I, and substitutions occurring within 5Å of the clesrovimab binding site included RSV A: S466N and K470R (both >99% VAF), and RSV B: V452E and N454T (both <10% VAF). Of all these substitutions, G446E, G446R, and G446W are resistance-associated (G446E and G446W cause a reduction in susceptibility to clesrovimab of >2,941-fold [RSV A] or >1,299-fold [RSV B], and G446R causes a reduction of >1,563-fold [RSV A] [see Section 20.6]), and the others do not have cell culture neutralization data.

There was no clear association of the occurrence of binding-site substitutions and RSV-associated MALRI, with 5/60 (8.3%) clesrovimab-treated participants who met the primary

endpoint of RSV-associated MALRI from Days 1 through 150 having a binding-site substitution identified, and for each of these instances the substitution was seen at <5% VAF.

There was also no correlation with RSV-associated hospitalization, although for substitutions seen at ≥50% VAF, one participant with RSV-associated hospitalization had RSV A with G446W substitution.

Table 27. Substitutions in or Near Clesrovimab Binding Site[a], Seen at ≥3% VAF in ≥1 Participant, Days 1 to 180 Postdose, Trial MK-1654-004

Position	Substitution	Clesrovimab	Placebo	Participant ID	VAF (%)	Day of Swabbing[c]	Clinical Endpoint
RSV A		*(n=76)*	*(n=59)*				
426	N426H	1	0	(b) (6)	3.8	22	MALRI
433	K433T	0	1		21.5	21	-
446	G446E	3	0		93.4	16	-
					6.3	8	-
					4.3	29	MALRI
	G446R	3	0		3.3	9	MALRI
					22.7	8	-
					51.4	42	
	G446W	1	0		96.9	70	HOSP
457	Y457H	0	1		4.0	146	-
466	S466N	2	0		99.9	79	-
					99.8	79	-
470	K470R	1	0		99.7	28	-
RSV B		*(n=80[e])*	*(n=91[e])*				
435	F435S	1	0		7.1	28	HOSP
443	S443L	1	0		3.5	6	-
		0	1		3.2	6	MALRI HOSP
446	G446E	3	0		99.8	42	-
					5.1	36	-
					99.8	23	-
	G446R	1	0		63.9	43	-
	G446V	2	0		4.1	51	MALRI
					5.8	7	-
447	V447I	1	0		3.9	22	MALRI
452	V452E	0	1		3.5	28	-
		2	0		3.4	43	-
					3.3	39	-
454	N454T	1	0		3.7	118	MALRI
470	K470E	0	1		8.7	43	-

Position	Substitution	Clesrovimab	Placebo	Participant ID	VAF (%)	Day of Swabbing[c]	Clinical Endpoint
Total RSV A[f]		*10 (13%)*	*2 (3%)*				
Total RSV B[f]		*11 (14%)*	*3 (3%)*				

Source: FDA analysis; Table 117
[a] Includes Site IV amino acids at F protein positions 426-447 and/or within 5Å of clesrovimab binding site (161, 182-184, 430, 431, 442, 464, 465, 468, 470), and adjacent residues
[b] Two participants had RSV with two binding-site substitutions each
[c] Relative to dosing day, for each instance
[e] For RSV B, there were 80 and 91 qualifying infections in 79 and 89 clesrovimab and placebo participants, respectively.
[f] Sequences with more than one binding-site substitution were counted once
Abbreviations: HOSP, RSV hospitalization; ID, identifier; MALRI, medically attended lower respiratory infection; n, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

For other postdose time-periods which were assessed, which included Days 181 through 364 postdose, and 365 through 515, while there were instances of substitutions in or near the clesrovimab binding site, they were less prevalent relative to the Days 1 through 180 period, and similar numbers overall were seen in RSV infections of clesrovimab-treated and placebo participants. There was no clear association of substitutions in these later time-periods with RSV-associated MALRI or RSV-associated hospitalization, although in general there were too few instances to draw firm conclusions.

Analyses of F protein amino acids outside of the clesrovimab binding site and nearby residues, for each postdose time-period, did not identify RSV variants, or individual and concurrent substitutions, which were clearly associated with clesrovimab treatment, or with increased rates of RSV-associated MALRI or RSV-associated hospitalization.

Trial MK-1654-007

In ongoing Trial MK-1654-007, there were a total of 60 samples (30 from the clesrovimab arm, 30 from the palivizumab arm) from 56 participants (29 in the clesrovimab arm, 27 in the palivizumab arm) in the sequencing dataset, after removing nonqualifying samples. For the secondary endpoint of RSV-associated MALRI in Season 1 from Day 1 through 150, sequence data were available for 12/14 (86%) of qualifying infections in the clesrovimab arm, and 11/12 (92%) in the palivizumab arm. Overall, there were similar numbers of participants infected with RSV A and RSV B.

Individual amino acid substitutions occurring in or near the clesrovimab binding site were identified, using all available sequence data from Days 1 through 180 postdose, and a VAF threshold of ≥3%. In addition, substitutions occurring in the palivizumab binding site (amino acids 262 to 275) were identified (Table 28).

In general, and given the small numbers of participants, there were too few instances of binding-site substitutions to draw conclusions with respect to association with treatment, RSV-associated MALRI, or RSV-associated hospitalization. However, clesrovimab binding-site substitutions (at positions 426 to 447) were seen only in RSV infections of clesrovimab-treated participants (n=4), and palivizumab binding-site substitutions (positions 262 to 275) were only seen in palivizumab-treated participants (n=3). The RSV infections with binding-site substitutions at ≥50% VAF included RSV A: G446W, and RSV B: G446E and G446R, seen in one clesrovimab-treated participant each. One other binding-site substitution was seen in a clesrovimab-treated participant at <10% VAF, RSV A: F435L (no phenotypic data).

For clesrovimab-treated participants, there were 2/14 (14%) participants who met the primary endpoint of RSV-associated MALRI from Days 1 through 150 and had a binding-site substitution identified, and for one of these participants ((b) (6)), the substitution was seen at >99% VAF.

Table 28. Substitutions in Clesrovimab Binding Site IV and/or Positions Within Five Angstroms of Clesrovimab Binding Site[a], or Palivizumab Binding Site[b], Seen at ≥3% VAF in ≥1 Participant, Days 1 to 180 Postdose, Trial MK-1654-007

Position	Substitution	Clesrovimab	Palivizumab	Participant ID	VAF (%)	Day of Swabbing[d]	Clinical Endpoint
RSV A		*(n=12)*	*(n=17)*				
185	V185A	0	1	(b) (6)	5.4	85	MALRI
275	S275F [f]	0	2		99.3	102	- [g]
					78.1	102	-
	S275Y	0	1		16.3	102	-
435	F435L	1	0		6.14	44	-
446	G446R				13.3		
	G446W				54.5		
470	K470R	0	1		3.2	85	MALRI
RSV B		*(n=9)*	*(n=9)*				
275	S275L[f]	0	1		86.0	124	-
446	G446E	2	0		3.4	9	MALRI HOSP
					99.9	28	-
446	G446R	1	0		99.7	13	MALRI HOSP
455	T455A	1	0		10.9	13	
Total RSV A[h]		*1 (8%)*	*2 (12%)*				
Total RSV B[h]		*3 (33%)*	*1 (11%)*				

Source: FDA analysis; Table 126
[a] Includes Site IV amino acids at F protein positions 426-447 and/or within 5Å of clesrovimab binding site (161, 182-184, 430, 431, 442, 464, 465, 468, 470), and adjacent residues
[b] Palivizumab binding site: amino acids 262-275
[c] Four participants had RSV with ≥2 binding-site substitutions each
[d] Relative to dosing day, for each instance
[f] Substitutions S275F and S275L confer >25,000-fold reduced susceptibility to palivizumab (MedImmune 1998)
[g] Participant (b) (6) had two cases of RSV infection within 30 days, with different consensus sequences. The first case met the endpoint of RSV-associated MALRI, and the second case where S275F substitution was seen did not meet any endpoint.
[h] Sequences with more than one binding-site substitution were counted once, and totals are for substitutions in the binding site of the respective antibody.
Abbreviations: Å, Angstroms; HOSP, RSV hospitalization; ID, identifier; MALRI, medically attended lower respiratory infection; n, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

For the other postdose time-period that was assessed (Season 2, Days 1 through 180 postdose), there were only two instances of substitutions in or near the clesrovimab binding site (both G446R). However, there were few participants with sequence data from Season 2, so it was not possible to draw conclusions with respect to clesrovimab treatment or clinical outcomes.

Analyses of F protein amino acids outside of the clesrovimab binding site and nearby residues, for each postdose time-period, did not identify RSV variants, or individual and concurrent substitutions, which were clearly associated with clesrovimab treatment, or with increased rates of RSV-associated MALRI or RSV-associated hospitalization.

Conclusion

In pivotal Trial MK-1654-004, there was an increased frequency of clesrovimab binding-site substitutions in the clesrovimab arm compared with placebo arm, indicating that they may have been selected by exposure to clesrovimab and be resistance-associated. Similar binding-site substitutions were identified in Trial MK-1654-007. Of the substitutions identified, phenotypic data were available only for G446E, G446R, and G446W substitutions, and each caused loss of susceptibility to clesrovimab (G446E and G448W: >2,941-fold change for RSV A, >1,299-fold change for RSV B; G446R: >1,563-fold for RSV A [RSV B not tested]). G446E substitution was also selected in cell culture passage in the presence of clesrovimab.

There was no clear association of the emergence of binding-site substitutions with RSV-associated MALRI or RSV-associated hospitalization. However, it is likely that for participants with these clinical outcomes, the more relevant RSV population resides in the lung, which may differ genotypically from the population sampled in the nasopharyngeal compartment. Hence, it is possible that the lack of clesrovimab binding-site substitutions in clesrovimab-treated participants with RSV-associated MALRI or RSV-associated hospitalization is because they were less likely to be selected in the upper respiratory tract.

There were limited cell culture neutralization data for substitutions identified more frequently in clesrovimab-treated participants compared with placebo participants, which were largely confined to the clesrovimab epitope and proximal residues. It will be important as a postmarketing requirement for the Applicant to assess these substitutions phenotypically, particularly because if they are resistance-associated and become prevalent in circulating variants, the data will be needed to determine optimal prophylaxis options.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

MK-1654 (clesrovimab) nonclinical safety studies included a good laboratory practice (GLP) 2-week IV/IM repeat-dose toxicology study in Wistar Han rats with a 4-week recovery period, a GLP tissue cross-reactivity (TCR) study in normal adult, neonatal, and juvenile human tissues, and a local tolerability/single-dose IM study in Wistar Han rats. All pertinent studies and findings are summarized below. Full reviews for all studies are in Section 13.1.

No adverse, product-related findings were observed in the GLP 2-week toxicology study in Wistar Han rats up to the highest doses tested (no-observed-adverse-effect level [NOAEL] =300 mg/kg [IV] and 25 mg/kg [IM]). Minor, nonadverse effects were observed in the IV groups including: decreased neutrophils (~40%) and increased eosinophils (50%) in high-dose females only at Day 42, and increased alanine aminotransferase (ALT) (33%) in mid-dose females at Day 42 with slight liver weight decrease (13 to 16%) in the mid- and high-dose females. Further, no-adverse-injection-site findings were observed following IV or IM dosing. Lastly, no off-target binding was observed with MK-1654 in a TCR study in normal adult, neonatal, and juvenile human tissues.

Genotoxicity, carcinogenicity, and developmental and reproductive toxicology (DART) studies were not conducted since they are not needed, as MK-1654 is a monoclonal antibody to an exogenous virus-specific target and will be administered as a single dose in infants (refer to Sections 13.1.2.2 to 13.1.2.4 for more information). This is also consistent with recommendations in the International Council for Harmonization (ICH) S6(R1) guidance.

Overall, the nonclinical safety assessment was considered acceptable to support licensing of MK-1654 from a pharmacology/toxicology perspective. The exposure multiples at the NOAEL for IV administration in the GLP 2-week toxicology study in Wistar Han rats are presented in Table 29 and are acceptable.

Table 29. Exposure Multiples of MK-1654

Study	NOAEL (mg/kg/dose)	Adverse Findings	Nonclinical $AUC_{0\text{-}72h}$ (µg*Day/mL)[c]	Exposure Multiple Year 1[a]	Exposure Multiple Year 2[b]
2-week rat IV	300	None	9,890	44	41

Source: Applicant table; Toxicology Written Summary; page 14
[a] Infants ≥25 weeks gestational age and postnatal age 0 to 8 months after administration of 105 mg (IM, $AUC_{0\text{-}72h}$ =226 day*µg/mL according to the Applicant)
[b] Infants ≥25 weeks gestational age and postnatal age 9 to 20 months after administration of 210 mg (IM, $AUC_{0\text{-}72h}$ =242 day*µg/mL according to the Applicant)
[C] On Day 13.
Abbreviations: $AUC_{0\text{-}72h}$, area under the concentration-time curve from 0 to 72 hours; IV, intravenous; IM, intramuscular; MK-1654, clesrovimab; NOAEL, no-observed-adverse-effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

7.2.1. Drug Class Considerations

Potential safety concerns for clesrovimab were identified based on clinical experience with other approved RSV monoclonal antibody products, nirsevimab and palivizumab.

Clesrovimab is a fully human immunoglobulin G1 monoclonal antibody directed against the fusion (F) protein of RSV, with three YTE amino acid substitutions in the Fc region. It is related to nirsevimab and palivizumab, which are monoclonal antibodies targeting the F protein of RSV. Nirsevimab was approved by the FDA in 2023 for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Palivizumab was approved by the FDA in 1998 for the prevention of serious RSV lower respiratory tract disease in high-risk infants, infants born ≤35 weeks gestational age, and infants with bronchopulmonary dysplasia (chronic lung disease of prematurity) or hemodynamically unstable congenital heart disease. Clesrovimab and nirsevimab have a triple amino acid substitution (YTE mutation) to extend the serum half-life, allowing for a single intramuscular dose prior to or during the RSV season, while palivizumab is administered as monthly IM injections during the RSV season (with a maximum of five doses in a single season).

Clesrovimab, nirsevimab, and palivizumab are all recombinant, humanized IgG1 monoclonal antibodies that target the F protein of RSV and block RSV entry into the cell. The safety findings

observed with use of palivizumab and nirsevimab are relevant to clesrovimab due to similarities between these three monoclonal antibodies.

Palivizumab was approved by the FDA in 1998; there have been more than 25 years of experience with this monoclonal antibody since its approval. The following safety findings are included in the palivizumab package insert:

- Anaphylaxis and anaphylactic shock, including fatal cases, and hypersensitivity reactions have been reported following both the initial exposure and re-exposure to palivizumab. Clinical presentations have included urticaria, angioedema, dyspnea, cyanosis, hypotonia, hypotension, cyanosis, and unresponsiveness.
- In clinical trials of palivizumab, fever was reported more frequently with palivizumab (27%) than with the placebo control (25%). Rash was reported in 12% of participants who received palivizumab and in 10% who received placebo. Of note, the differences between the palivizumab arm and placebo control arm were slight.
- Adverse reactions reported postmarketing are severe thrombocytopenia and injection site reactions.

Nirsevimab was approved by the FDA in 2023. The following safety findings are included in the current nirsevimab Prescribing Information:

- The following warning is included in Section 5.1:
    - **Hypersensitivity Reactions Including Anaphylaxis**
    - Serious hypersensitivity reactions have been reported postmarketing following administration of nirsevimab. These reactions included urticaria, dyspnea, cyanosis, and/or hypotonia. Anaphylaxis has been observed with human IgG1 monoclonal antibodies. If signs and symptoms of anaphylaxis or other clinically significant hypersensitivity reactions occur, initiate appropriate treatment.
- Section 6 notes that in clinical trials of nirsevimab, rash, and injection site reactions were reported more frequently in the nirsevimab arm than in the placebo/comparator arm. Across the pivotal trials 03 and 04, rash occurring within 14 days postdose was reported in 0.9% of nirsevimab recipients and 0.6% of placebo recipients. Injection site reactions occurring within 7 days postdose were reported in 0.3% of nirsevimab recipients and 0 in placebo recipients.
- Hypersensitivity reactions are included in the Postmarketing Experience section.

In summary, experience with palivizumab and nirsevimab provides a useful reference for potential safety concerns that may be observed with wider use of clesrovimab.

7.2.2. Other Drug-Specific Factors

Clesrovimab has the potential to interfere with rapid antigen RSV assays, particularly with assays that use an antibody targeting the same or overlapping epitope as the immunoprophylaxis mAb, which may lead to false negative or equivocal results. The Applicant assessed commonly used rapid antigen tests for interference by clesrovimab; these data were reviewed by the Division of Antiviral's Clinical Virology team and a Center for Devices and Radiological Health (CDRH) consult was requested. CDRH agreed with the Applicant's conclusion that "for rapid antigen diagnostic kit results, which are negative when clinical observations are consistent with

RSV infection, it is recommended to confirm using an RT-PCR-based assay." In individuals who have received clesrovimab prophylaxis, a negative RSV rapid antigen assay result should be confirmed with an RT-PCR-based assay. This recommendation will be conveyed in the Prescribing Information. Use of a rapid antigen test which targets a different viral protein may also be considered. Refer to Section 7.7.2 and Section 18 for further discussion regarding the potential for interference between rapid antigen assay tests and clesrovimab in individuals who receive clesrovimab.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Clesrovimab (MK-1654) is not approved in the U.S. market or in any foreign market; therefore, no postmarketing experience is available for clesrovimab.

7.3.1. Adverse Events Identified in Postmarket Experiences

There are no postmarketing data available for review as clesrovimab has not been approved in the U.S. market or in any foreign market and is currently not in use at this time.

7.3.2. Expectations on Safety

Expectations of safety in the postmarketing setting are based on safety data from the Phase 2b/3 and Phase 3 clinical trials of clesrovimab and the safety profiles of nirsevimab and palivizumab.

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 2 and 3 trial populations. There were no safety concerns observed that necessitate issuing a Risk Evaluation and Mitigation Strategy for nirsevimab. Emergence of new events can be managed by the planned pharmacovigilance activities. Refer to Section 7.7.3 for pharmacovigilance discussion, and Section 24 for description of postmarketing requirements and commitments.

There are no specific safety concerns that are expected from unapproved uses of clesrovimab.

7.3.3. Additional Safety Issues From Other Disciplines

Not applicable.

7.4. FDA Approach to the Safety Review

Data from six clinical trials were submitted to support licensure of clesrovimab, also known as MK-1654, for the proposed indication: three Phase 1 trials (MK-1654-001 and MK-1654-003 in healthy adults, MK-1654-008 in healthy adults, children, and infants), one Phase 1b/2a trial (MK-1654-002 in healthy preterm and term infants), one Phase 2b/3 trial (MK-1654-004 in

healthy preterm and term infants), and one Phase 3 trial (MK-1654-007 in infants and children at increased risk for severe RSV disease).

Note that an additional trial, MK-1654-005, was not initially planned for submission by the Applicant to the BLA. Trial MK-1654-005 was a human challenge study in adults (b) (4) Only 16 adult participants received a relevant dose of 900 mg IV (the closest dose based on allometric scaling to the 105 mg IM dose for infants)."

During a pre-BLA meeting with the Applicant, the Applicant proposed not to include Trial MK-1654-005 in the BLA. The FDA requested an overall safety summary of Trial MK-1654-005 to confirm that the trial results revealed no safety concerns (including hypersensitivity, anaphylaxis, and rash). The Applicant confirmed that no genotypic data were collected for this trial. The Applicant agreed to provide a brief Clinical Study Report for Trial MK-1654-005 including an overall safety summary of Trial MK-1654-005.

Data from two pivotal trials, MK-1654-004 and MK-1654-007, were analyzed to provide the primary source of support for the safety of clesrovimab for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. FDA analyses of the safety datasets from Trials MK-1654-004 and MK-1654-007 were conducted by the Clinical Data Scientists. Results from the Phase 1 trials and the Safety Update Report (SUR) for the two pivotal trials contributed to the benefit-risk assessment of clesrovimab.

Trial MK-1654-004 enrolled infants born at ≥29 to <35 weeks gestational age (early and moderate preterm) and at ≥35 weeks gestational age (late preterm and term infants). Two cohorts of participants were planned: aged >2 weeks to 1-year-old (Phase 2b, planned 300 participants) and aged from birth to 1-year-old (Phase 3, approximately 3000 participants). All participants were to receive a single 105-mg IM dose of clesrovimab or placebo (0.9% sodium chloride, sterile saline), regardless of weight. Clinical safety assessments included evaluation of adverse events, including adverse events of special interest, and of vital signs. Legally acceptable representatives used an eDiary from Days 1 through 42 postdose to record the following information:

- Solicited daily body temperature to identify fever* Days 1 through 5 postdose

*Note: Fever is defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C).

- Solicited injection site AEs (redness/erythema, swelling, and tenderness/pain) on Days 1 through 5 postdose

Note: Injection site AEs of redness/erythema and swelling were measured by the legally acceptable representative using a trial-supplied ruler.

- Solicited systemic AEs (irritability, drowsiness, and appetite loss) on Days 1 through 5 postdose
- Anaphylaxis/hypersensitivity AESI on Days 1 through 42 postdose
- Rash AESI on Days 1 through 42 postdose

- Any other AEs on Days 1 through 42 postdose
- Concomitant medications and nonstudy vaccinations on Days 1 through 42 postdose

In Trial MK-1654-004, approximately 1500 participants (N=1518, with 1017 participants in the clesrovimab group and 501 participants in the placebo group) of the total 3614 participants were followed from Days 365 through 515 postdose (Season 2) without additional study intervention administration. Weekly surveillance to monitor the incidence of RSV-associated MALRI and hospitalization was conducted between Days 365 and 515, and SAEs continued to be collected for the duration of trial participation. The interim Clinical Study Report included in this BLA submission includes complete efficacy data and safety follow-up through at least 240 days postdose for all participants up to the data cutoff date of March 4, 2024.

Trial MK-1654-007 is an ongoing, partially blinded, randomized, active-controlled study to evaluate the safety and efficacy of clesrovimab versus palivizumab and the pharmacokinetics of clesrovimab in approximately 1000 infant participants at increased risk for severe RSV disease, from birth up to 1 year of age entering their first RSV season, who were randomized 1:1 to receive clesrovimab (105 mg IM) or palivizumab (three to five monthly doses of 15 mg/kg). Infants with the following risk factors for severe RSV disease were enrolled: early-moderate preterm (≤35 weeks gestational age), CLD of prematurity, or hemodynamically significant CHD.

Clinical safety assessments included evaluation of adverse events, including adverse events of special interest, and of vital signs. Legally acceptable representatives use the eDiary to record the following information in RSV Season 1:

- Solicited daily body temperature to identify fever for 5 days after each dose.

Note: Fever is defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C).

- Solicited injection site AEs (redness/erythema, swelling, and tenderness/pain) are collected for 5 days after each dose.

Note: Injection site AEs of redness/erythema and swelling will be measured by the legally acceptable representative using a trial-supplied ruler.

- Solicited systemic AEs (irritability, drowsiness, and appetite lost) for 5 days after each dose.
- Anaphylaxis/hypersensitivity AESI on:
  - Day 1 through 14 days Postdose 2
- Rash AESI on:
  - Day 1 through 14 days Postdose 2
- Any other AEs:
  - Day 1 through 14 days Postdose 2
  - For 14 days after each dose of palivizumab
- Concomitant medications and nonstudy vaccinations:
  - Day 1 through 14 days Postdose 2

Note: Participants undergoing cardiopulmonary bypass may have received an additional postsurgery dose of clesrovimab and AESIs and other AEs were followed for 42 days after this additional dose.

In Trial MK-1654-007, the safety, efficacy and pharmacokinetics are being evaluated in a subset of infants/children who continue to be at increased risk for severe RSV disease due to certain risk factors (i.e., CLD of prematurity, ongoing hemodynamically significant CHD or other protocol-specified conditions as described in Section 6.2.3.2) will receive clesrovimab 210 mg open-label in RSV Season 2. The Applicant is not currently seeking a Season 2 indication.

Refer to Section 17 for discussion of safety data for Trials MK-1654-001, MK-1654-002, MK-1654-003, MK-1654-005, and MK-1654-008.

The results from Trial MK-1654-004 and Trial MK-1654-007 were not pooled because they enrolled different populations. Trial MK-1654-004 enrolled healthy infants, whereas Trial MK-1654-007 enrolled high-risk (palivizumab-eligible) infants. During the pre-BLA meeting, the Applicant communicated that based on prior agreements, there were no plans to pool or integrate safety data across trials for an Integrated Summary of Safety given that the trials were conducted at different times and AEs were mapped using different dictionary versions. The FDA communicated that an Integrated Summary of Safety is recommended for BLAs and noted that it would be informative to analyze certain AEs of interest from pooled adult and pediatric populations. The Applicant stated that it would not be feasible to integrate safety data for this BLA submission but agreed to provide separately pooled infant and adult datasets without dictionary leveling to evaluate key safety events (i.e., injection site reaction, hypersensitivity AEs, rash AEs, SAEs/intervention-related SAEs, and deaths).

No major data quality or integrity issues were identified that would preclude performing an adequate safety review for this BLA. There were no major issues identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in Trials MK-1654-004 and MK-1654-007 were reviewed and found to be acceptable.

Adverse events in the pivotal trials (Trial MK-1654-004 and Trial MK-1654-007) were graded based on the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 severity scale.

Note that the risk differences shown in the safety tables throughout this review used descriptive statistics only (there is no alpha control) and should be interpreted with caution. In addition, the incidence rates presented in the safety tables throughout this review are rounded to one decimal place, which in some instances resulted in a reported incidence rate of 0.0%, even though events occurred.

Additional safety data from Trial MK-1654-004 and Trial MK-1654-007 included in the SUR (submitted to the BLA on January 7, 2025) were also reviewed. For Trial MK-1654-004, between the BLA cutoff date and the SUR cutoff date (March 5, 2024, through August 5, 2024), the trial was completed. No additional participants were randomized or dosed, but additional SAE data was included in the SUR. For Trial MK-1654-007, from the BLA cutoff date through the SUR cutoff date (February 6, 2024, through September 26, 2024), 101 additional participants were randomized and received clesrovimab or palivizumab for RSV Season 1 (52 participants in

the clesrovimab group, 49 in the palivizumab group). At the time of the SUR, approximately 20% of MK-1654-007 participants were ongoing in the trial.

7.5. Adequacy of the Clinical Safety Database

The safety database for the to-be-marketed dose of clesrovimab consists of 2947 pediatric participants (2412-participants from Trial MK-1654-004, 446 participants from Trial MK-1654-007, Season 1, 64 participants from Trial MK-1654-002, and 25 participants from Trial MK-1654-008) with follow-up through 240 days after the first dose of study drug was administered. This is considered adequate to assess the safety of clesrovimab for the proposed indication of prevention of RSV lower respiratory tract disease in neonates and infants (healthy infants and infants at increased risk for severe RSV disease) who are born during or entering their first RSV season. A total of 3051 infants/children received clesrovimab at any dose. A total of 172 adults (excluding Trial MK-1654-005) received clesrovimab at any dose.

In Trial MK-1654-004, the safety database included 2412 healthy preterm or term infants who received clesrovimab, of which 422 were early or moderate preterm (≥29 to <35 weeks gestational age) and 1990 were late preterm or term infants (≥35 weeks gestational age).

In Trial MK-1654-007, the safety database included 446 high-risk infants who received clesrovimab in Season 1, of which 27.8% had CLD, 11.7% had CHD, 5.8% were <29 weeks gestational age without CLD of prematurity or CHD, and 54.7% were ≥29 to <35 weeks gestational age without CLD of prematurity or CHD.

During the clinical development of clesrovimab, the Agency recommended a safety database of at least 2500 to 3000 infants exposed to clesrovimab at the to-be-marketed dose. This size allows for estimations regarding the frequency of rare adverse events. The size of this safety database is considered sufficient to identify anticipated safety issues and to predict that clesrovimab-associated adverse reactions not observed in the clinical trials are unlikely to be common in the real-world setting. In addition, extensive experience with palivizumab and recent experience with nirsevimab (both closely related products) provide additional support for the safety of clesrovimab.

7.6. Safety Results

7.6.1. Safety Results, Trial MK-1654-004

Analysis Populations

Safety analyses were conducted with the APaT population (safety population), which consisted of all randomized participants who received a single dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they received for the analyses of safety data using the APaT population.

Of note, although the safety analysis population was defined as above, participants with certain protocol violations were excluded from the safety population as well as from the safety analyses presented in this review (and are described below). However, the Prescribing Information presents the results from the prespecified APaT population.

In Trial MK-1654-004, three participants were excluded from the APaT population due to enrollment at two different sites and receiving two doses of study intervention (one participant received clesrovimab twice; the other two participants received one dose each of clesrovimab and placebo). Safety data for these participants were included in a separate listing. Of the three participants who were dosed twice, two participants experienced AEs of drug-related injection site erythema and somnolence following receipt of clesrovimab. None of these participants experienced an SAE or death.

One participant in placebo group was dosed with clesrovimab and was included in the MK-1654 group for the safety analyses.

Key Safety Assessments

Key safety assessments presented below include serious adverse events including death, adverse events leading to discontinuation, common treatment-emergent adverse events and adverse reactions, and adverse events of special interest (e.g., anaphylaxis/hypersensitivity, rash).

The safety monitoring occurred for solicited AEs (eDiary) through Day 5 postdose, AESI (anaphylaxis/hypersensitivity, rash) and nonserious AEs through Day 42 postdose, and SAEs throughout trial participation (at least 365 days).

Safety Analyses, Trial MK-1654-004

Table 30 provides an overview of the rates of AEs reported in participants in the clesrovimab (MK-1654) group compared to the placebo group during the trial period.

7.6.1.1. Overview of Treatment-Emergent Adverse Events, Trial MK-1654-004

Table 30. Overview of Adverse Events, Safety Population, Trial MK-1654-004

Event Category	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
SAE	278 (11.5)	149 (12.4)	-0.9 (-3.2, 1.3)
SAEs with fatal outcome	7 (0.3)	3 (0.2)	0.0 (-0.5, 0.4)
Life-threatening SAEs	18 (0.7)	15 (1.2)	-0.5 (-1.3, 0.1)
SAEs requiring hospitalization	270 (11.2)	146 (12.1)	-0.9 (-3.2, 1.2)
SAEs resulting in substantial disruption of normal life functions	22 (0.9)	15 (1.2)	-0.3 (-1.2, 0.3)
Other	2 (0.1)	2 (0.2)	-0.1 (-0.5, 0.2)
Any AE	1816 (75.4)	918 (76.4)	-1.0 (-3.9, 2.0)
Severe and worse	219 (9.1)	115 (9.6)	-0.5 (-2.6, 1.5)
Moderate	615 (25.5)	328 (27.3)	-1.8 (-4.9, 1.3)
Mild	982 (40.8)	475 (39.5)	1.2 (-2.2, 4.6)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as nonserious adverse events that occurred from Days 1 through 42 postdose and serious adverse events that occurred from visits Day 1 through Day 365 postdose.
Duration is single dose followed by 365 days safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the Investigator.
Abbreviations: AE, adverse event; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event

Overall, the incidences of adverse events reported postdose were balanced (or slightly lower for the clesrovimab group), with any AE reported in 75.4% (1816/2409) of participants in the clesrovimab group and 76.4% (918/1202) of participants in placebo group. SAEs were reported in 11.5% (278/2409) of participants in the clesrovimab group and 12.4% (149/1202) in the placebo group.

7.6.1.2. Injection Site Reactions, Trial MK-1654-004

Solicited Injection Site Reaction, Days 1 Through 5 Postdose

All injection site AEs were determined by the Investigator to be related to study intervention. Injection site reactions were reported in 9.3% (223/2409) of clesrovimab recipients versus 9.7% (117/1202) of placebo recipients. Most were Grade 1 or 2 in severity, with maximum size of ≤1 inch (injection site swelling, erythema) in either group. The proportions of participants who experienced solicited injection site reaction AEs of Grade 3 were 0.1% (2/2409) in the clesrovimab group and 0.2% (2/1202) in placebo group. No Grade 4 solicited AEs were reported.

The most commonly reported injection site reaction was injection site pain (5.1% [122/2409] in the clesrovimab group versus 6.4% [77/1202] in placebo group). Injection site erythema and injection site swelling were reported at slightly higher frequencies in the clesrovimab group versus the placebo group, with erythema reported in 3.7% (90/2409) versus 3.3% (40/1202) and injection site swelling reported in 2.7% (65/2409) versus 2.6% (31/1202) of participants in the clesrovimab versus placebo groups, respectively.

Table 31. Adverse Events Assessment of Local Administration Reaction OND Custom Medical Query (Narrow), Within 5 Days Postdose, Safety Population, Trial MK-1654-004

OCMQ (Narrow) Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Local administration reaction (OCMQ)	232 (9.6)	120 (10.0)	-0.4 (-2.5, 1.7)
Injection site bruising	4 (0.2)	2 (0.2)	-0.0 (-0.4, 0.3)
Injection site erythema	90 (3.7)	40 (3.3)	0.4 (-0.9, 1.6)
Injection site hematoma	1 (0.0)	0	0.0 (-0.3, 0.2)
Injection site hemorrhage	1 (0.0)	1 (0.1)	-0.0 (-0.4, 0.2)
Injection site induration	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)
Injection site macule	1 (0.0)	0	0.0 (-0.3, 0.2)
Injection site mass	1 (0.0)	0	0.0 (-0.3, 0.2)
Injection site pain	122 (5.1)	77 (6.4)	-1.3 (-3.1, 0.2)
Injection site rash	0	1 (0.1)	-0.1 (-0.5, 0.1)
Injection site reaction	1 (0.0)	0	0.0 (-0.3, 0.2)
Injection site swelling	65 (2.7)	31 (2.6)	0.1 (-1.1, 1.2)
Injection site warmth	1 (0.0)	0	0.0 (-0.3, 0.2)
Vessel puncture site pain	1 (0.0)	0	0.0 (-0.3, 0.2)
Maximum severity			
Death	0	0	0.0 (-0.3, 0.2)
Life-threatening	0	0	0.0 (-0.3, 0.2)
Severe	2 (0.1)	2 (0.2)	-0.1 (-0.5, 0.2)
Moderate	42 (1.7)	22 (1.8)	-0.1 (-1.1, 0.8)
Mild	188 (7.8)	96 (8.0)	-0.2 (-2.1, 1.6)

OCMQ (Narrow) Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Serious	0	0	0.0 (-0.3, 0.2)
Deaths	0	0	0.0 (-0.3, 0.2)
Resulting in discontinuation	0	0	0.0 (-0.3, 0.2)
Relatedness	231 (9.6)	120 (10.0)	-0.4 (-2.5, 1.6)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 5 postdose.
Duration is a single dose.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the Investigator.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Solicited Systemic AEs, Days 1 Through 5 Postdose

Solicited systemic AEs (decreased appetite, irritability, and somnolence) were reported in 26.2% (631/2409) of clesrovimab recipients and 28.0% (337/1202) of placebo recipients; most were Grade 1 or 2 in severity. The proportions of participants with solicited AEs of Grade 3 were ≤0.2% in either intervention group; 0% (1/2409) in clesrovimab group and 0.1% (1/1202) in placebo group experienced a solicited systemic AE of Grade 3. No Grade 4 solicited AEs were reported.

The most commonly reported solicited systemic AEs were irritability (18.7% [450/2409] in the clesrovimab group, 19.7% [237/1202] in placebo group) and somnolence (12.6% [303/2409] in clesrovimab group, 14.2% [171/1202] in placebo group).

Fever, Pyrexia, Body Temperature Increased

Fever was defined per the protocol as any rectal temperature ≥102.2°F or axillary temperature ≥101.7°F. According to the Applicant, "elevated body temperature measurements that met the protocol-specified definition of fever were to be reported as pyrexia," and "elevated body temperature measurements that did not meet the protocol-specified definition of fever but met AE criteria were to be reported as body temperature increased."

The FDA conducted analyses to evaluate protocol-defined fever (pyrexia) within various cut points: within 2, 5, and 7 days postdose. Additionally, the FDA assessed fever using cutoffs as defined by the AAP (AAP 2020). Overall, no imbalances or concerning trends in fever were observed within 2, 5, or 7 days postdose using either the protocol definition or the AAP definition of fever.

Fever: Protocol-Defined

Table 32. Participants With One or More Elevated Temperature Values Defined by the Protocol as Rectal Temperature ≥102.2°F or Axillary Temperature ≥101.7°F, Safety Population, Trial MK-1654-004

Number of Days After Dose	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
2 days	7 (0.3)	5 (0.4)	-0.1 (-0.7, 0.3)
5 days	16 (0.7)	15 (1.2)	-0.6 (-1.4, 0.1)
7 days	18 (0.7)	15 (1.2)	-0.5 (-1.4, 0.1)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with given characteristic

Fever: AAP-Defined

Table 33. Participants With One or More Elevated Temperature Values Defined by the AAP as Rectal Temperature ≥100.4°F or Axillary Temperature ≥98.4°F, Safety Population, Trial MK-1654-004

Number of Days After Dose	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
2 days	538 (22.3)	280 (23.3)	-1.0 (-3.9, 1.9)
5 days	741 (30.8)	384 (31.9)	-1.2 (-4.4, 2.0)
7 days	760 (31.5)	389 (32.4)	-0.8 (-4.1, 2.4)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AAP, American Academy of Pediatrics; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with given characteristic

Pyrexia

In Trial MK-1654-004, within 5 days postdose, no notable imbalance was seen in the AE of pyrexia, with 0.3% of participants in the clesrovimab group and 0.6% of participants in the placebo group reporting pyrexia.

Table 34. Adverse Events Assessment of Pyrexia Preferred Term, Within 5 Days Postdose, Safety Population, Trial MK-1654-004

Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Pyrexia	8 (0.3)	7 (0.6)	-0.3 (-0.9, 0.2)
Maximum severity			
Death	0	0	0.0 (-0.3, 0.2)
Life-threatening	1 (0.0)	0	0.0 (-0.3, 0.2)
Severe	2 (0.1)	0	0.1 (-0.2, 0.3)
Moderate	3 (0.1)	3 (0.2)	-0.1 (-0.6, 0.2)
Mild	2 (0.1)	4 (0.3)	-0.2 (-0.8, 0.0)

Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Serious	0	0	0.0 (-0.3, 0.2)
Deaths	0	0	0.0 (-0.3, 0.2)
Resulting in discontinuation	0	0	0.0 (-0.3, 0.2)
Relatedness	5 (0.2)	4 (0.3)	-0.1 (-0.7, 0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 5 postdose.
Duration is a single dose.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the Investigator.
Abbreviations: AE, adverse event; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event

Body Temperature Increased

Within 5 days postdose, a slightly higher incidence of the AE of body temperature increased was observed in the clesrovimab group versus the placebo group (2.1% [51/2409] versus 1.7% [20/1202]). Most events were mild in severity; only one event was assessed as serious; this was reported in the clesrovimab group. Per the narrative, the SAE of body temperature increased was assessed as a study-related SAE, Toxicity Grade 1. The participant was admitted to the hospital for observation on Study Day 4 due to drowsiness and Grade 1 increased body temperature (rectal temperature of 38 degrees Celsius). The participant also presented with mucous stools and regurgitation, without rash or signs/symptoms of hypersensitivity. The increased body temperature resolved the same day, and the participant was discharged home. On Day 5, the participant experienced upper abdominal pain. The participant had ongoing loose stools, and a PCR from a stool sample on Day 8 was positive for adenovirus. Upper abdominal pain and mucous stools resolved on Days 29 and 37, respectively. The participant experienced decreased appetite (resolved the following day) and a recurrence of increased body temperature (temperature was not recorded) on Day 40, treated with paracetamol. Regurgitation resolved on Day 41 and increased body temperature resolved on Day 42. The Investigator assessed the increased body temperature on Day 4 as related to the study intervention.

While the FDA acknowledges that the possibility of the increased body temperature being related to the study intervention cannot be definitively ruled out, the participant's initial concomitant gastrointestinal symptoms (i.e., mucous stools and regurgitation) around the time of the increased body temperature on Day 4 and the subsequent diagnosis of adenovirus infection suggest that the increased body temperature may have been due to underlying infection rather than due to study drug administration. It is also possible that the increased body temperature may have been multifactorial due to these underlying factors.

Table 35. Adverse Events Assessment of Body Temperature Increased Preferred Term, Within 5 Days Postdose, Safety Population, Trial MK-1654-004

Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference% (95% CI)
Body temperature increased	51 (2.1)	20 (1.7)	0.5 (-0.6, 1.3)
Maximum severity			
Death	0	0	0.0 (-0.3, 0.2)
Life-threatening	0	0	0.0 (-0.3, 0.2)
Severe	0	1 (0.1)	-0.1 (-0.5, 0.1)
Moderate	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)
Mild	48 (2.0)	18 (1.5)	0.5 (-0.5, 1.3)
Serious	1 (0.0)	0	0.0 (-0.3, 0.2)
Deaths	0	0	0.0 (-0.3, 0.2)
Resulting in discontinuation	0	0	0.0 (-0.3, 0.2)
Relatedness	25 (1.0)	11 (0.9)	0.1 (-0.7, 0.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 5 postdose.
Duration is a single dose.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the Investigator.
Abbreviations: CI, confidence interval; max; maximum; min, minimum; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event

A similar imbalance was noted when assessing the AE of body temperature increased within 7 days postdose.

Commonly Reported AEs, Days 1 Through 365 Days Postdose

Table 36 shows the proportions of participants with AEs occurring in at least ≥2% frequency in the safety population for Trial MK-1654-004.

Overall, AEs were balanced between the two study groups. Slight numerical imbalances were observed in various AEs in the clesrovimab versus placebo groups, such as in preferred terms (PTs) of cough, rhinorrhea, bronchitis, respiratory tract infection, teething, and vomiting (Table 36) and are thought to be unlikely to be of clinical significance. Other observed imbalances (i.e., rash, injection site reaction events) have been discussed elsewhere in the review (see Section 7.6.1.2).

Table 36. Participants With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Trial MK-1654-004

Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Any AE	1816 (75.4)	918 (76.4)	-1.0 (-3.9, 2.0)
Rhinorrhoea	170 (7.1)	72 (6.0)	1.1 (-0.7, 2.7)
Rash	59 (2.4)	19 (1.6)	0.9 (-0.2, 1.8)
Teething	74 (3.1)	27 (2.2)	0.8 (-0.3, 1.9)
Eczema	50 (2.1)	17 (1.4)	0.7 (-0.3, 1.5)
Cough	201 (8.3)	93 (7.7)	0.6 (-1.3, 2.4)
Bronchitis	81 (3.4)	34 (2.8)	0.5 (-0.7, 1.7)
Injection site erythema	90 (3.7)	40 (3.3)	0.4 (-0.9, 1.6)
Nasal congestion	205 (8.5)	98 (8.2)	0.4 (-1.6, 2.2)
Respiratory tract infection	59 (2.4)	26 (2.2)	0.3 (-0.8, 1.3)
Vomiting	65 (2.7)	29 (2.4)	0.3 (-0.9, 1.3)

Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Rhinitis	52 (2.2)	23 (1.9)	0.2 (-0.8, 1.2)
Injection site swelling	65 (2.7)	31 (2.6)	0.1 (-1.1, 1.2)
Conjunctivitis	52 (2.2)	25 (2.1)	0.1 (-1.0, 1.0)
COVID-19	68 (2.8)	33 (2.7)	0.1 (-1.2, 1.2)
Bronchiolitis	75 (3.1)	38 (3.2)	-0.0 (-1.4, 1.1)
Bacterial infection	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Furuncle	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Haemangioma of skin	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Hypotonia	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Laryngitis viral	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Metabolic acidosis	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Neutropenia	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Seborrhoea	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Suspected COVID-19	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Systemic viral infection	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Tracheobronchitis	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Tympanic membrane hyperaemia	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Vessel puncture site bruise	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Constipation	52 (2.2)	28 (2.3)	-0.2 (-1.3, 0.8)
Body temperature increased	215 (8.9)	110 (9.2)	-0.2 (-2.3, 1.7)
Weight decreased	0	3 (0.2)	-0.2 (-0.7, -0.1)*
Skin candida	0	4 (0.3)	-0.3 (-0.9, -0.1)*
Varicella	0	4 (0.3)	-0.3 (-0.9, -0.1)*
Rales	3 (0.1)	6 (0.5)	-0.4 (-1.0, -0.0)*
Dermatitis diaper	63 (2.6)	36 (3.0)	-0.4 (-1.6, 0.7)
Pneumonia respiratory syncytial viral	2 (0.1)	8 (0.7)	-0.6 (-1.2, -0.2)*
Diarrhoea	140 (5.8)	77 (6.4)	-0.6 (-2.3, 1.0)
Nasopharyngitis	138 (5.7)	77 (6.4)	-0.7 (-2.4, 0.9)
Upper respiratory tract infection	357 (14.8)	189 (15.7)	-0.9 (-3.5, 1.5)
Pneumonia	50 (2.1)	36 (3.0)	-0.9 (-2.1, 0.1)
Respiratory syncytial virus bronchiolitis	6 (0.2)	15 (1.2)	-1.0 (-1.8, -0.4)*
Decreased appetite	136 (5.6)	81 (6.7)	-1.1 (-2.9, 0.5)
Injection site pain	122 (5.1)	77 (6.4)	-1.3 (-3.1, 0.2)
Irritability	517 (21.5)	278 (23.1)	-1.7 (-4.6, 1.2)
Somnolence	316 (13.1)	178 (14.8)	-1.7 (-4.2, 0.7)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as nonserious adverse events that occurred from Days 1 through 42 postdose and serious adverse events that occurred from visits Day 1 through Day 365 postdose.
Duration is single dose followed by 365 days safety follow-up.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event

Nonserious AEs, Days 1 Through 42 Postdose

One or more nonserious AEs were reported in 72.8% (1753/2409) of participants in the MK-1654 group and 74.2% (892/1202) in the placebo group. The most frequently reported (>10%) AEs from Days 1 through 42 postdose were irritability (21.5% in clesrovimab group, 23.1% in placebo group), somnolence (13.1% in clesrovimab group, 14.8% in placebo group), and upper respiratory tract infection (14.6% in clesrovimab group versus 15.7% in placebo group).

Treatment-Related AEs

Table 37 shows the percentage of participants who experienced an AE through Day 42 or an SAE through Day 365 that was assessed as related to study intervention by the Investigator.

One or more AEs assessed as related to study treatment were reported in 24.4% (587/2409) of participants in the MK-1654 group and 24.6% (296/1202) in the placebo group. The most frequently reported (>5%) AEs assessed as related to study intervention by the Investigator from Days 1 through 365 postdose in either intervention group were solicited AEs: injection site pain, somnolence, and irritability (5.1% versus 6.4%, 9.1% versus 9.3%, and 13.1% versus 12.6% in the clesrovimab versus placebo groups, respectively).

Table 37. Adverse Events Assessed by Investigator as Treatment-Related, Occurring in >1 Participant in Either Arm, Safety Population, Trial MK-1654-004

Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Any treatment-related AE	587 (24.4)	296 (24.6)	-0.3 (-3.3, 2.7)
Irritability	315 (13.1)	152 (12.6)	0.4 (-1.9, 2.7)
Injection site erythema	90 (3.7)	40 (3.3)	0.4 (-0.9, 1.6)
Flatulence	9 (0.4)	1 (0.1)	0.3 (-0.1, 0.6)
Vomiting	7 (0.3)	1 (0.1)	0.2 (-0.2, 0.5)
Restlessness	4 (0.2)	0	0.2 (-0.2, 0.4)
Nasal congestion	3 (0.1)	0	0.1 (-0.2, 0.4)
Body temperature increased	25 (1.0)	11 (0.9)	0.1 (-0.7, 0.8)
Injection site swelling	65 (2.7)	31 (2.6)	0.1 (-1.1, 1.2)
Cough	2 (0.1)	0	0.1 (-0.2, 0.3)
Discomfort	2 (0.1)	0	0.1 (-0.2, 0.3)
Urticaria	2 (0.1)	0	0.1 (-0.2, 0.3)
Rash	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)
Injection site bruising	4 (0.2)	2 (0.2)	-0.0 (-0.4, 0.3)
Rhinorrhoea	3 (0.1)	2 (0.2)	-0.0 (-0.5, 0.2)
Constipation	2 (0.1)	2 (0.2)	-0.1 (-0.5, 0.2)
Drug eruption	2 (0.1)	2 (0.2)	-0.1 (-0.5, 0.2)
Eczema	2 (0.1)	2 (0.2)	-0.1 (-0.5, 0.2)
Erythema	2 (0.1)	2 (0.2)	-0.1 (-0.5, 0.2)
Fatigue	6 (0.2)	4 (0.3)	-0.1 (-0.6, 0.3)
Pyrexia	6 (0.2)	4 (0.3)	-0.1 (-0.6, 0.3)
Crying	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)
Injection site induration	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)
Regurgitation	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)
Somnolence	220 (9.1)	112 (9.3)	-0.2 (-2.3, 1.8)
Diarrhoea	11 (0.5)	11 (0.9)	-0.5 (-1.2, 0.1)
Decreased appetite	63 (2.6)	45 (3.7)	-1.1 (-2.5, 0.0)
Injection site pain	122 (5.1)	77 (6.4)	-1.3 (-3.1, 0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as nonserious adverse events that occurred from Days 1 through 42 postdose and serious adverse events that occurred from visits Day 1 through Day 365.
Duration is single dose followed by 365 days safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event

7.6.1.3. Deaths, Trial MK-1654-004

Table 38 summarizes the AEs leading to death in Trial MK-1654-004. A total of 10 deaths (7 [0.3%] in the clesrovimab group and 3 [0.2%] in the placebo group) occurred in Trial MK-1654-004. None of the deaths were considered by the Investigator to be related to study intervention. No pattern was observed in the AEs leading to death or the timing of death relative to study intervention, and the AE PTs varied across multiple system organ classes (SOCs). Nine deaths occurred between Days 1 through 365 postdose, one death (MK-1654 group) occurred on Day 487 postdose in a participant who had dropped out of the trial on Day 85.

Table 38. AEs Leading to Death, Safety Population, Trial MK-1654-004

Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Any AE leading to death	7 (0.3)	3 (0.2)	0.0 (-0.5, 0.4)
Aspiration	1 (0.0)	0	0.0 (-0.3, 0.2)
Pneumonitis	1 (0.0)	0	0.0 (-0.3, 0.2)
Staphylococcal sepsis	1 (0.0)	0	0.0 (-0.3, 0.2)
Sudden infant death syndrome	1 (0.0)	0	0.0 (-0.3, 0.2)
Death	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)
Acute kidney injury	0	1 (0.1)	-0.1 (-0.5, 0.1)
Acute respiratory failure	0	1 (0.1)	-0.1 (-0.5, 0.1)
Coagulopathy	0	1 (0.1)	-0.1 (-0.5, 0.1)
COVID-19	0	1 (0.1)	-0.1 (-0.5, 0.1)
COVID-19 pneumonia	0	1 (0.1)	-0.1 (-0.5, 0.1)
Mitral valve disease	0	1 (0.1)	-0.1 (-0.5, 0.1)
Thermal burn	0	1 (0.1)	-0.1 (-0.5, 0.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as serious adverse events that occurred from visits Day 1 through Day 365 postdose.
One death occurred on Day 487 postdose outside of the trial, in a participant who discontinued from the trial on Day 85.
Duration is single dose followed by 365 days safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For patient-level data, see the table “List of Adverse Events Leading to Death…”
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event

Table 39 shows a listing of causes of death by preferred term for all individual participant deaths in Trial MK-1654-004. Note that several preferred terms in the placebo group were AEs that occurred in a single participant.

Table 39. Listing of All Individual Participant Deaths, Safety Population, Trial MK-1654-004

Study Arm	Participant ID	Age (Days)	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death: Preferred Term	Cause of Death: Verbatim Term
MK-1654 105 mg	(b) (6)	74	M	MK-1654 105 mg	1	487	Death	Unknown cause of death
MK-1654 105 mg		61	F	MK-1654 105 mg	1	33	Pneumonitis	Pneumonitis
MK-1654 105 mg		35	M	MK-1654 105 mg	1	281	Staphylococcal sepsis	*S. aureus* sepsis
MK-1654 105 mg		15	M	MK-1654 105 mg	1	60	Sudden infant death syndrome	Suspected sudden infant death syndrome
MK-1654 105 mg		17	M	MK-1654 105 mg	1	260	Death	Death from natural causes[1]
MK-1654 105 mg		61	M	MK-1654 105 mg	1	25	Death	Unknown cause of death
MK-1654 105 mg		29	F	MK-1654 105 mg	1	22	Aspiration	Aspiration suspected
Placebo		66	M	N/A	1	135	Coagulopathy	Other specified coagulation disorders
		66	M	N/A	1	135	Mitral valve disease	Other nonrheumatic disorders of mitral valve function
		66	M	N/A	1	135	COVID-19	COVID-19 infection
		66	M	N/A	1	135	COVID-19 pneumonia	Interstitial pneumonia (COVID-19)
		66	M	N/A	1	135	Acute kidney injury	Acute renal failure
		66	M	N/A	1	135	Acute respiratory failure	Acute pulmonary failure
Placebo		30	M	N/A	1	271	Thermal burn	Fatal burns

Study Arm	Participant ID	Age (Days)	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death: Preferred Term	Cause of Death: Verbatim Term
Placebo	(b) (6)	21	M	N/A	1	134	Death	Unknown cause of death

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as serious adverse events that occurred from visits Day 1 through Day 365 postdose.
Duration is single dose followed by 365 days safety follow-up.
[1.] "Death from natural causes" was reported on autopsy following a history of persistent vomiting and diarrhea (onset Day 256) with dehydration.
Abbreviations: COVID-19, coronavirus disease 2019; F, female; ID, identifier; M, male; MK-1654, clesrovimab; N/A, not applicable

Per review of the case narratives, a variety of AEs were associated with death. The FDA agrees with the Applicant's assessment that the deaths do not raise clinical concerns for relatedness to study drug administration. No clustering of AEs or predominance of a specific AE that was associated with death was observed. None of the deaths appeared to be study-drug-related.

Update on Deaths From the SUR

There were no additional deaths in Trial MK-1654-004. In the cumulative dataset, the proportion of participants who died between Days 1 through 365 postdose was 0.3% (7/2409) in the MK-1654 group and 0.2% (3/1202) in the placebo group, which is unchanged from the BLA dataset.

7.6.1.4. Serious Treatment-Emergent Adverse Events, Trial MK-1654-004

SAEs occurring in at least 0.5% of participants in either arm are displayed in the table below. For SAEs reported in Trial MK-1654-004, it was noted that while no nervous system SAE PTs occurred in at least 0.5% of participants, at the SOC level, there was a small imbalance between the arms (1% [24/2409] versus 0.3% [4/1202] of participants in the clesrovimab and placebo arms, respectively), in the proportion of participants that reported an SAE in the nervous system disorders SOC. Based on this slight imbalance in SAEs noted at the level of the SOC of nervous system disorders, the FDA conducted an expanded analysis of SAEs of nervous system disorders, regardless of the frequency of events reported (see Table 40 and Table 41).

Table 40. Participants With Serious Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.5% of Participants in Any Arm, Safety Population, Trial MK-1654-004

System Organ Class Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Any SAE	278 (11.5)	149 (12.4)	-0.9 (-3.2, 1.3)
Infections and infestations (SOC)	220 (9.1)	122 (10.1)	-1.0 (-3.2, 1.0)
Gastroenteritis	20 (0.8)	7 (0.6)	0.2 (-0.4, 0.8)
Lower respiratory tract infection	13 (0.5)	4 (0.3)	0.2 (-0.4, 0.6)
Bronchitis	15 (0.6)	7 (0.6)	0.0 (-0.6, 0.5)
Laryngitis viral	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Bronchiolitis	31 (1.3)	19 (1.6)	-0.3 (-1.2, 0.5)
COVID-19	6 (0.2)	7 (0.6)	-0.3 (-1.0, 0.1)
Pneumonia respiratory syncytial viral	2 (0.1)	8 (0.7)	-0.6 (-1.2, -0.2)*
Pneumonia	42 (1.7)	29 (2.4)	-0.7 (-1.8, 0.3)
Respiratory syncytial virus bronchiolitis	5 (0.2)	13 (1.1)	-0.9 (-1.6, -0.4)*
Investigations (SOC)	1 (0.0)	4 (0.3)	-0.3 (-0.8, -0.0)*
Weight decreased	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Nervous system disorders (SOC)	24 (1.0)	4 (0.3)	0.7 (0.1, 1.2)*

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as serious adverse events that occurred from visits Day 1 through Day 365 postdose.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is single dose followed by 365 days safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SOC, system organ class

Table 41 shows the frequency of participants who experienced SAEs in the SOC of nervous system disorders, by PT.

Table 41. Expanded SOC of Nervous System Disorders, Participants With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial MK-1654-004

System Organ Class Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	MK-1654 vs. Placebo Risk Difference % (95% CI)
Nervous system disorders (SOC)	24 (1.0)	4 (0.3)	0.7 (0.1, 1.2)*
Febrile convulsion	10 (0.4)	3 (0.2)	0.2 (-0.3, 0.6)
Facial paralysis	2 (0.1)	0	0.1 (-0.2, 0.3)
Brain injury	1 (0.0)	0	0.0 (-0.3, 0.2)
Dyskinesia	1 (0.0)	0	0.0 (-0.3, 0.2)
Epilepsy	1 (0.0)	0	0.0 (-0.3, 0.2)
Hydrocephalus	1 (0.0)	0	0.0 (-0.3, 0.2)
Motor developmental delay	1 (0.0)	0	0.0 (-0.3, 0.2)
Partial seizures	1 (0.0)	0	0.0 (-0.3, 0.2)
Status epilepticus	1 (0.0)	0	0.0 (-0.3, 0.2)
Subarachnoid haemorrhage	1 (0.0)	0	0.0 (-0.3, 0.2)
Subdural effusion	1 (0.0)	0	0.0 (-0.3, 0.2)
Seizure	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as serious adverse events in the SOC of Nervous System Disorders that occurred from visits Day 1 through Day 365 postdose.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is single dose followed by 365 days safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; SOC, system organ class

A slight numerical imbalance was observed in participants who experienced seizure events, which appeared to be mainly driven by a numerical imbalance in febrile seizures, with 0.4% (10/2409) of participants in the clesrovimab group and 0.2% (3/1202) of participants in the placebo group experiencing a febrile convulsion.

Of the 20 participants (16 participants in the clesrovimab arm, 4 in the placebo arm) who experienced an SAE of seizure, one participant in each study group (one febrile seizure in the clesrovimab group and one seizure in the placebo group) occurred within 42 days after dosing. Most seizure events occurred more than 100 days postdose.

The small imbalance in the SOC of nervous system disorders appeared to be driven by a slight imbalance in febrile convulsions with a variety of other neurological conditions occurring infrequently among clesrovimab participants. Overall, the imbalance and numbers of events were small; therefore, conclusions cannot be drawn regarding the potential of causality. Additionally, it is reassuring that most seizure AEs occurred more than 100 days postdose.

Update on SAEs From the SUR

In the cumulative dataset as of the SUR data lock, the proportions of participants who experienced ≥1 SAEs were similar between the clesrovimab group and the placebo group from Days 1 through 365 postdose and consistent with data from the original BLA submission.

From the BLA data cutoff date through the end of the trial, there were five participants in the clesrovimab group and two in the placebo group who experienced ≥1 SAE. SAEs were reported cumulatively in 11.7% of participants in the clesrovimab group and 12.6% of participants in the palivizumab group (as compared with 11.5% and 12.4% in the BLA in the clesrovimab versus placebo groups, respectively). The SAEs were reported across multiple SOCs; the most frequently reported SOC was Infections and infestations in both study groups. None were considered related to study intervention.

One additional participant in the clesrovimab group experienced an SAE of asthma on Day 649 postdose after completion of the trial and postdatabase lock; this event was assessed as not related to study intervention by the Investigator.

7.6.1.5. Adverse Events of Special Interest, Trial MK-1654-004

AESIs assessed by the Applicant included anaphylaxis/hypersensitivity events (which included the following terms: anaphylaxis, angioedema, bronchospasm, drug hypersensitivity, drug-related allergic reaction, dyspnea/difficulty breathing, hypersensitivity, dysphonia, urticaria, wheezing) and rash events (which included the following terms: acute generalized exanthematous pustulosis, drug eruption, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, generalized rash of exfoliative nature [including dermatitis exfoliative and exfoliative rash], Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria). All AESIs were reported up to Day 42 postdose; after Day 42, any AESI that met serious criteria was reported to the Applicant.

Anaphylaxis/Hypersensitivity

One participant in the clesrovimab group in Trial MK-1654-004 experienced an anaphylaxis/hypersensitivity AESI of bronchospasm (Grade 2) on Day 3 postdose. This event was not serious and was considered not related to study intervention by the Investigator. No participants in the placebo group in Trial MK-1654-004 experienced an anaphylaxis/hypersensitivity AESI.

Per the narrative of the Grade 2 bronchospasm (hypersensitivity) case, the event occurred in a 246-day old female Peruvian infant in the clesrovimab group with past medical history of bronchitis and history of prior medical treatment with prednisolone and salbutamol. The participant received the study drug on April 18, 2022. Onset of the bronchospasm event was 3 days after dosing: Toxicity Grade 2. The Investigator assessed the event as not related to study drug. The participant's oxygen saturation readings were within normal limits on the date of dosing (oxygen saturation 98%, respiratory rate 38 breaths/min.) and on the date of AESI bronchospasm onset (oxygen saturation 96%, respiratory rate 40 breaths/min.).

Based on the FDA's review of the limited narrative available, it is unclear if this event was a true hypersensitivity AESI or if the bronchospasm event could have potentially been triggered by administration of the study drug. However, the FDA agrees with the assessment of the Investigator/Applicant that the hypersensitivity/bronchospasm event was unlikely to be related to study drug administration based on the following: 1) the presence of confounders, such as the participant's medical history, which is suggestive of the possibility of preexisting reactive airway disease, and 2) the timing of onset of the AE relative to study drug administration, which is less

suggestive of a Type-1 (immunoglobulin E-mediated) event. Although this participant met the protocol definition of the AESI of "anaphylaxis/hypersensitivity," this did not appear to be a true case of anaphylaxis.

A post hoc analysis conducted by the FDA for hypersensitivity AEs using Office of New Drugs (OND) Custom Medical Queries (OCMQs) showed a few additional cases of possible hypersensitivity under the PT of drug eruption; however, these events were balanced between the two study groups. Events under the hypersensitivity OCMQ were reported in 0.2% (4/2409) in the clesrovimab group and 0.2% (3/1202) in the placebo group, with drug eruptions reported in 0.2% (4/2409) and 0.2% (2/1202) in the clesrovimab versus placebo groups, respectively.

Table 42. Adverse Events Assessment of Hypersensitivity, OCMQ (Narrow), Within 42 Days Postdose, Safety Population, Trial MK-1654-004

OCMQ (Narrow) Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Hypersensitivity (OCMQ)	4 (0.2)	3 (0.2)	-0.1 (-0.6, 0.2)
Allergic gastroenteritis	0	1 (0.1)	-0.1 (-0.5, 0.1)
Drug eruption	4 (0.2)	2 (0.2)	-0.0 (-0.4, 0.3)
Maximum severity			
Death	0	0	0.0 (-0.3, 0.2)
Life-threatening	0	0	0.0 (-0.3, 0.2)
Severe	0	0	0.0 (-0.3, 0.2)
Moderate	0	0	0.0 (-0.3, 0.2)
Mild	4 (0.2)	3 (0.2)	-0.1 (-0.6, 0.2)
Serious	0	0	0.0 (-0.3, 0.2)
Deaths	0	0	0.0 (-0.3, 0.2)
Resulting in discontinuation	0	0	0.0 (-0.3, 0.2)
Relatedness	2 (0.1)	2 (0.2)	-0.1 (-0.5, 0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Days 1 through 42 postdose.
Duration is a single dose. Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the Investigator.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Rash

Primary Analysis of Rash AESIs

Rash AESIs from Days 1 through 42 postdose were reported in 0.5% (11/2409) of participants in the clesrovimab group and 0.3% (4/1202) in the placebo group, with urticaria being the most frequently reported AE by PT (0.3% [8/2409] in MK-1654 group, 0.1% [1/1202] in the placebo group). All rash AESIs were assessed as having a maximum toxicity grade of Grade 1, except for one Grade 3 event of urticaria in the clesrovimab group. The single Grade 3 event of urticaria occurred on Day 9 postdose in a participant who had a concurrent respiratory infection on Day 7 postdose; the AE resolved after 4 days (Day 12) and was assessed as not related to study intervention. All other rash AESI were Grade 1, occurred on Day 2 to 5 postdose, resolved within 2 to 21 days. No rash AESI were reported as SAEs, and most were considered not related to study intervention by the Investigator.

Expanded Analysis of Rash AEs

An expanded analysis of rash AEs that occurred within 14 days of study intervention was conducted using the following rash PTs: rash, rash macular, rash papular, rash maculo-papular, rash erythematous, rash vesicular, exfoliative rash, drug eruption, toxic skin eruption, and dermatitis allergic. According to this analysis, the proportions of participants who experienced one or more specific rash AEs were slightly higher in the clesrovimab group versus the placebo group, 2.3% rash AESI reported in the MK-1654 group and 1.9% in the placebo group. All events were nonserious and Grade 1 to 2 toxicity in both intervention groups. Most of these events were not considered to be related to study intervention per the Investigator's assessment.

An analysis of rash events within 14 days postdose using the narrow OCMQ revealed a similar imbalance between study groups, with 3.5% of clesrovimab recipients and 3.0% of placebo recipients experiencing a PT under the rash OCMQ. A variety of PTs contributed to these overall rates, as shown in the table below.

Table 43. Adverse Events Assessment of Rash, OND Custom Medical Query (Narrow), Within 14 Days Postdose, Safety Population, Trial MK-1654-004

OCMQ (Narrow) Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Rash (OCMQ)	84 (3.5)	36 (3.0)	0.5 (-0.8, 1.7)
Acne	4 (0.2)	0	0.2 (-0.2, 0.4)
Acne infantile	6 (0.2)	2 (0.2)	0.1 (-0.4, 0.4)
Candida nappy rash	0	1 (0.1)	-0.1 (-0.5, 0.1)
Dermatitis	9 (0.4)	5 (0.4)	-0.0 (-0.6, 0.4)
Dermatitis allergic	2 (0.1)	4 (0.3)	-0.2 (-0.8, 0.0)
Dermatitis contact	2 (0.1)	3 (0.2)	-0.2 (-0.7, 0.1)
Erythema multiforme	0	1 (0.1)	-0.1 (-0.5, 0.1)
Exfoliative rash	0	1 (0.1)	-0.1 (-0.5, 0.1)
Injection site rash	0	1 (0.1)	-0.1 (-0.5, 0.1)
Rash	41 (1.7)	11 (0.9)	0.8 (-0.0, 1.5)
Rash erythematous	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.2)
Rash macular	0	2 (0.2)	-0.2 (-0.6, -0.0)*
Rash maculo-papular	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.2)
Rash papular	6 (0.2)	2 (0.2)	0.1 (-0.4, 0.4)
Rash pustular	2 (0.1)	0	0.1 (-0.2, 0.3)
Rash vesicular	1 (0.0)	0	0.0 (-0.3, 0.2)
Skin exfoliation	1 (0.0)	0	0.0 (-0.3, 0.2)
Toxic skin eruption	0	1 (0.1)	-0.1 (-0.5, 0.1)
Urticaria	4 (0.2)	1 (0.1)	0.1 (-0.3, 0.4)
Viral rash	4 (0.2)	2 (0.2)	-0.0 (-0.4, 0.3)
Maximum severity			
Death	0	0	0.0 (-0.3, 0.2)
Life-threatening	0	0	0.0 (-0.3, 0.2)
Severe	1 (0.0)	0	0.0 (-0.3, 0.2)
Moderate	5 (0.2)	6 (0.5)	-0.3 (-0.9, 0.1)
Mild	78 (3.2)	30 (2.5)	0.7 (-0.5, 1.8)

OCMQ (Narrow) Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Serious	0	0	0.0 (-0.3, 0.2)
Deaths	0	0	0.0 (-0.3, 0.2)
Resulting in discontinuation	0	0	0.0 (-0.3, 0.2)
Relatedness	7 (0.3)	3 (0.2)	0.0 (-0.5, 0.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Days 1 through 14 postdose.
Duration is a single dose.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the Investigator.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Following review of the narrow (above) and broad (not shown) OCMQs related to rash, the FDA noted a potential imbalance in cases of urticaria events in Trial MK-1654-004. This prompted additional analyses of urticaria, focusing on a narrower time frame of events within 14 days postdose, consistent with the approach to rash evaluation. An imbalance in urticaria events was observed in this analysis (also using broad OCMQs), with urticaria reported in 2.4% of clesrovimab recipients and 1.5% of placebo recipients. However, this imbalance appeared to be mainly driven by the imbalance in "rash" PTs, as shown in Table 44, and there is no clear imbalance in urticaria specifically. Most of the events were mild in severity.

Table 44. Adverse Events Assessment of Urticaria, OND Custom Medical Query (Broad), Within 14 Days Postdose, Safety Population, Trial MK-1654-004

OCMQ (Broad) Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Urticaria (OCMQ)	58 (2.4)	18 (1.5)	0.9 (-0.1, 1.8)
Drug eruption	3 (0.1)	2 (0.2)	-0.0 (-0.5, 0.2)
Rash	41 (1.7)	11 (0.9)	0.8 (-0.0, 1.5)
Rash erythematous	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.2)
Rash maculo-papular	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.2)
Rash papular	6 (0.2)	2 (0.2)	0.1 (-0.4, 0.4)
Urticaria	4 (0.2)	1 (0.1)	0.1 (-0.3, 0.4)
Urticaria papular	1 (0.0)	1 (0.1)	-0.0 (-0.4, 0.2)
Maximum severity			
Death	0	0	0.0 (-0.3, 0.2)
Life-threatening	0	0	0.0 (-0.3, 0.2)
Severe	1 (0.0)	0	0.0 (-0.3, 0.2)
Moderate	3 (0.1)	3 (0.2)	-0.1 (-0.6, 0.2)
Mild	54 (2.2)	15 (1.2)	1.0 (0.1, 1.8)*
Serious	0	0	0.0 (-0.3, 0.2)
Deaths	0	0	0.0 (-0.3, 0.2)
Resulting in discontinuation	0	0	0.0 (-0.3, 0.2)
Relatedness	9 (0.4)	3 (0.2)	0.1 (-0.4, 0.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Days 1 through 14 postdose.
Duration is a single dose.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the Investigator.
Abbreviations: CI, confidence interval; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

While most urticaria events were Grade 1 or 2 in severity, one participant, in the clesrovimab group, experienced a Grade 3 event of urticaria that occurred on Day 9 postdose. This event was assessed by the Investigator as not related to study intervention. Per review of the narrative for this case, the participant had an upper respiratory infection (URI) on Day 7; onset of urticaria/rash was on Day 9. "The Investigator did not refer the participant to the dermatologist as per protocol requirement for Grade 3 rash AESI." The rash was noted to be diffuse, confluent, with wheals located on the head, face, chest, and region, back.

Per the FDA's assessment, though the severe urticaria event was assessed as "not related" by the Investigator and the participant was reported to have a URI concurrently during the time of the urticaria event, there is insufficient information to definitively rule out the possibility that the urticaria/rash event could have been related to the study drug.

Update on AESIs From the SUR

There were no additional AESI reported in the SUR. All AESI from Days 1 through 42 postdose were reported in the original BLA (Summary of Clinical Safety).

7.6.1.6. Adverse Events Leading to Treatment Discontinuation, Trial MK-1654-004

No participants discontinued treatment due to an AE, since clesrovimab is administered as a single dose.

A single participant (in the placebo group) in Trial MK-1654-004 withdrew from the trial due to an SAE of B precursor type acute leukemia, with onset 3 days postdose, and was assessed by the Investigator as intervention-related. FDA's assessment is that the SAE of acute leukemia was not related to study intervention, given that the participant had received placebo and injection of saline does not have a plausible mechanism to result in acute leukemia. Per the Applicant, no participants were withdrawn due to an AE across any of the other trials submitted to this BLA.

Table 45. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial MK-1654-004

System Organ Class Preferred Term	MK-1654 (N=2409) n (%)	Placebo (N=1202) n (%)	Risk Difference % (95% CI)
Any AE leading to discontinuation	0	0	0.0 (-0.3, 0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as nonserious adverse events that occurred from Days 1 through 42 postdose and serious adverse events that occurred from visits Day 1 through Day 365 postdose.
Duration is single dose followed by 365 days safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event

7.6.2. Safety Results, Trial MK-1654-007

7.6.2.1. Overview of Treatment-Emergent Adverse Events, Trial MK-1654-007

Analysis Populations

The proposed safety population was the APaT population, which consists of all randomized participants who received at least one dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they received for the analyses of safety data using the APaT population. Of note, although the safety analysis population was defined as above, the Applicant excluded a participant from the safety population due to a protocol violation (described below) and this participant was excluded from the safety analyses presented in this review. However, the Prescribing Information presents the results from the prespecified APaT population.

One participant in the clesrovimab group was excluded from the safety analysis due to the participant receiving the incorrect study intervention for Dose 2 (received a dose of palivizumab instead of placebo). Two AEs were reported for this participant, they were not serious or considered related to study intervention by the investigator.

Key Safety Assessments

Key safety assessments presented below include serious adverse events including death, adverse events leading to discontinuation, common treatment-emergent adverse events and adverse reactions, and adverse events of special interest (e.g., anaphylaxis/hypersensitivity reactions, rash). Unless otherwise indicated, safety analyses for Trial MK-1654-007 included in this review include follow-up through Day 42. This encompasses a single dose on Day 1 followed by a placebo dose on Day 28 [+4] for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28 [+4], for the active control group, followed by 14 days of safety follow-up.

Table 46 shows an overview of AEs reported in the safety population for Trial MK-1654-007, in RSV Season 1 (Postdose 1, Days 1 through 42). Overall, a slight imbalance was noted in the rate of any AE between the two arms, with any AE reported in 70.3% versus 66.4% of participants in the clesrovimab group versus palivizumab groups, respectively; however, most AEs were mild. SAEs were balanced between the two study groups.

Table 46. Overview of Adverse Events, Safety Population, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

Event Category	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
SAE	46 (10.3)	48 (10.7)	-0.3 (-4.4, 3.7)
SAEs with fatal outcome	2 (0.4)	1 (0.2)	0.2 (-0.8, 1.4)
Life-threatening SAEs	4 (0.9)	4 (0.9)	0.0 (-1.5, 1.5)
SAEs requiring hospitalization	45 (10.1)	47 (10.4)	-0.3 (-4.4, 3.7)

Event Category	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Any AE	313 (70.3)	299 (66.4)	3.9 (-2.2, 10.0)
Severe and worse	39 (8.8)	39 (8.7)	0.1 (-3.7, 3.9)
Moderate	60 (13.5)	60 (13.3)	0.1 (-4.3, 4.7)
Mild	214 (48.1)	200 (44.4)	3.6 (-2.9, 10.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 42 postdose.
Duration is a single dose on Day 1 followed by a placebo dose on Day 28 for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28, for the active control group, followed by 14 days of safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the Investigator.
Abbreviations: AE, adverse event; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with at least one event; RSV, respiratory syncytial virus; SAE, serious adverse event

Solicited Injection Site Reactions, Postdose 1, Season 1

Overall, injection site reactions (Days 1 through 5 following Dose 1, RSV Season 1) were reported at a higher frequency in the clesrovimab group versus the comparator (palivizumab) group, with 9.4% (42/445) of clesrovimab recipients and 6.2% (28/450) of palivizumab recipients experiencing an injection site reaction. Injection site erythema, injection site swelling, and injection site pain were reported in 4.5% (20/445) versus 2.4% (11/450), 4.7% (21/445) versus 1.6% (7/450), and 4.3% (19/445) versus 4.0% (18/450) of participants in the clesrovimab versus palivizumab groups, respectively. Most had a maximum toxicity of Grade 1 or 2 and a maximum size of ≤1 inch (injection site swelling, erythema) in either intervention group. Grade 3 solicited injection site AEs occurred in 0.4% (two participants) in each intervention group Postdose 1. No Grade 4 solicited AEs were reported. All injection site AEs were considered related to study intervention by the Investigator.

Table 47. Adverse Events, Solicited Local Administration Reactions, Within 5 Days Postdose 1, Safety Population, Trial MK-1654-007

Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	MK-1654 vs. Palivizumab Risk Difference % (95% CI)
Local administration reaction (PT)	43 (9.7)	29 (6.4)	3.2 (-0.4, 6.9)
Injection site erythema	20 (4.5)	11 (2.4)	2.0 (-0.4, 4.7)
Injection site pain	19 (4.3)	18 (4.0)	0.3 (-2.4, 3.0)
Injection site swelling	21 (4.7)	7 (1.6)	3.2 (0.9, 5.7)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the Investigator.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; PT, preferred term

Solicited Systemic Reactions, Postdose 1, Season 1

Solicited systemic reactions (Days 1 through 5 following Dose 1, RSV Season 1) were reported at a higher frequency in the treatment group, occurring in 29.7% (132/445) of clesrovimab recipients and 24.2% (109/450) of palivizumab recipients. Irritability, somnolence, and decreased appetite were reported in 21.6% (96/445) versus 17.6% (79/450), 13.3% (59/445) versus 10.7% (48/450), and 8.8% (39/445) versus 6.0% (27/450) of participants in the clesrovimab versus palivizumab group, respectively. Most solicited systemic reactions were

Grade 1 or 2 in severity. Grade 3 solicited systemic AEs Postdose 1 occurred in 0.9% (4/445) in the clesrovimab group and 0.4% (2/450) in the palivizumab group. No Grade 4 solicited AEs were reported.

Temperature Analyses Postdose 1, Season 1

Fever was defined in the protocol as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C) from Days 1 through 5 after each dose; ≤1.2% of participants in either study group met the protocol-specified definition of fever. Most (≥96%) participants in either intervention group had a maximum body temperature <100.4°F (38.0°C) from Days 1 through 5 postdose. Of those participants with a maximum body temperature ≥100.4°F (38.0°C), most in either intervention group had a maximum body temperature <102.2°F (39.0°C).

As shown in the tables below, the FDA conducted additional temperature analyses looking at temperature values through Days 2 and 7 postdose and assessing fever using the more conservative temperature cutoffs as defined by the AAP.

Fever: Protocol-Defined

Using the definition of fever included in the MK-1654-007 protocol, fevers were generally uncommon but occurred slightly more frequently among participants in the clesrovimab arm compared to the palivizumab arm.

Table 48. Participants With One or More Elevated Temperature Values Defined by the Protocol as Rectal Temperature ≥102.2°F or Axillary Temperature ≥101.7°F, Safety Population, Trial MK-1654-007

Number of Days After Dose 1	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
2 days	1 (0.2)	0 (0.0)	0.2 (-0.6, 1.3)
5 days	4 (0.9)	1 (0.2)	0.7 (-0.4, 2.1)
7 days	4 (0.9)	1 (0.2)	0.7 (-0.4, 2.1)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event

Fever: AAP-Defined

When evaluating fever using the AAP definition, an increased number of fevers was observed within 2 days after Dose 1, with a higher proportion of fevers occurring in the clesrovimab group versus the palivizumab group; however, the imbalance resolved beyond this timepoint.

Table 49. Participants With One or More Elevated Temperature Values Defined by the AAP as Rectal Temperature ≥100.4°F or Axillary Temperature ≥98.4°F, Safety Population, Trial MK-1654-007

Number of Days After Dose 1	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
2 days	125 (28.1)	118 (26.2)	1.9 (-4.0, 7.7)
5 days	171 (38.4)	172 (38.2)	0.2 (-6.2, 6.6)
7 days	175 (39.3)	176 (39.1)	0.2 (-6.2, 6.6)

Source: advs.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AAP, American Academy of Pediatrics; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with given characteristic

Fever Adverse Events

As previously noted, fever was defined per the protocol as any rectal temperature ≥102.2°F or axillary temperature ≥101.7°F. According to the Applicant, elevated body temperature measurements that met the protocol-specified definition of fever were to be reported as pyrexia," and "elevated body temperature measurements that did not meet the protocol-specified definition of fever but met AE criteria were to be reported as body temperature increased.

Within 5 days Postdose 1, there were three participants in the clesrovimab group and two participants in the palivizumab group who were reported to have the AE of pyrexia; most events were mild. In the clesrovimab group, there was one participant who experienced an AE of pyrexia that was life-threatening and one (different) participant who experienced an SAE of pyrexia.

Per the case narrative reviewed, the SAE of pyrexia occurred in a 67-day-old Asian male infant with a history of respiratory distress and bronchopulmonary dysplasia (CLD), was Grade 1, with onset on Study Day 4. On Day 4, the participant had fever without URI symptoms, with temperature 38.8 axillary, was evaluated in the emergency department, and was diagnosed with Grade 1 pyrexia (mild), prompting hospitalization on Day 5 for observation. Labs were within normal limits. SARS CoV-2 test was negative. Chest X-ray or blood cultures were not available. No specific viral infection was detected. The pyrexia resolved on Day 6 and the participant was discharged.

Per the FDA's review, it is unclear whether the SAE of pyrexia could possibly have been related to study drug intervention, given that no specific underlying etiology for the pyrexia SAE was established from the available work-up and given the close timing of onset of pyrexia after study drug administration.

There were no additional pyrexia events after Day 5 through Day 7 postdose.

Nonserious AEs, Days 1 Through 42 Postdose

Nonserious AEs from Days 1 through 42 postdose were reported in 67.9% (302/445) in the clesrovimab group, 63.8% (287/450) in the palivizumab group. The most commonly reported nonserious AEs in RSV Season 1 (Postdose 1, through Day 42) were solicited reactions (decreased appetite, somnolence, and irritability), which were reported in higher frequency in the clesrovimab group as compared with the palivizumab group.

AEs (Including SAEs), Days 1 Through 42 Postdose

The most commonly reported AEs, including SAEs, in RSV Season 1 (Postdose 1, through Day 42) were solicited (local injection site and systemic) reactions, which were reported at a higher frequency in the clesrovimab group compared with the palivizumab group, as shown in Table 50.

A higher frequency of the systemic AEs of irritability, somnolence, and decreased appetite were observed in the clesrovimab group than in the palivizumab group. It is noted that these imbalances in solicited systemic AEs were not observed in Trial MK-1654-004 (the placebo-controlled pivotal trial). The clinical significance of these imbalances which were observed only in the more medically complex population of Trial MK-1654-007 is unclear. Solicited injection site AEs were also reported at a higher frequency in the clesrovimab group than the palivizumab group in Trial MK-1654-007, which was also observed in Trial MK-1654-004.

Table 50. Participants With Common Adverse Events Occurring at ≥5% Frequency, Safety Population, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Any AE	313 (70.3)	299 (66.4)	3.9 (-2.2, 10.0)
Somnolence	75 (16.9)	59 (13.1)	3.7 (-0.9, 8.5)
Decreased appetite	52 (11.7)	37 (8.2)	3.5 (-0.5, 7.5)
Injection site swelling	27 (6.1)	12 (2.7)	3.4 (0.8, 6.3)*
Injection site erythema	29 (6.5)	17 (3.8)	2.7 (-0.2, 5.8)
Irritability	120 (27.0)	114 (25.3)	1.6 (-4.1, 7.4)
Injection site pain	26 (5.8)	24 (5.3)	0.5 (-2.6, 3.6)
Body temperature increased	26 (5.8)	27 (6.0)	-0.2 (-3.3, 3.0)
Upper respiratory tract infection	53 (11.9)	58 (12.9)	-1.0 (-5.3, 3.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 42 postdose.
Duration is a single dose on Day 1 followed by a placebo dose on Day 28 for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28, for the active control group, followed by 14 days of safety follow-up.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; RSV, respiratory syncytial virus

Table 51 below shows all AEs occurring in at least 0.5% of participants in either arm in Trial MK-1654-007. A numerical imbalance in bronchiolitis AEs (and as described later in Section 7.6.2.3 an imbalance in bronchiolitis SAEs) was observed in Trial MK-1654-007 but was not observed in Trial MK-1654-004. See discussion of bronchiolitis SAEs below.

Slight imbalances in the AEs of vomiting and diarrhea were also reported, with 2.7% of clesrovimab recipients and 1.6% of palivizumab recipients reported to have vomiting, and 1.8% of clesrovimab recipients and 0.4% of palivizumab recipients experiencing diarrhea, in Trial MK-1654-007, in RSV Season 1, Postdose 1 (Days 1 through 42), as shown in Table 51.

Given that vomiting and diarrhea are nonspecific AEs that have commonly been reported as side effects across multiple drug classes, the possibility that these gastrointestinal events could have been related to study drug administration cannot be definitively ruled out. However, it is also possible that the slight differences in gastrointestinal AEs between study groups could have been due to chance, as it was noted that this imbalance was not also seen in Trial MK-1654-004.

Table 51. Participants With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.5% of Participants in Any Arm, Safety Population, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

System Organ Class Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Any AE	313 (70.3)	299 (66.4)	3.9 (-2.2, 10.0)
Blood and lymphatic system disorders (SOC)	8 (1.8)	5 (1.1)	0.7 (-1.0, 2.5)
Anaemia	4 (0.9)	1 (0.2)	0.7 (-0.4, 2.1)
Congenital, familial, and genetic disorders (SOC)	4 (0.9)	4 (0.9)	0.0 (-1.5, 1.5)
Plagiocephaly	1 (0.2)	3 (0.7)	-0.4 (-1.7, 0.7)
Eye disorders (SOC)	9 (2.0)	12 (2.7)	-0.6 (-2.8, 1.5)
Retinopathy of prematurity	3 (0.7)	4 (0.9)	-0.2 (-1.7, 1.2)
Dacryostenosis acquired	0	3 (0.7)	-0.7 (-1.9, 0.2)
Gastrointestinal disorders (SOC)	56 (12.6)	45 (10.0)	2.6 (-1.6, 6.8)
Diarrhoea	8 (1.8)	2 (0.4)	1.4 (-0.0, 3.1)
Vomiting	12 (2.7)	7 (1.6)	1.1 (-0.8, 3.3)
Infantile colic	6 (1.3)	4 (0.9)	0.5 (-1.1, 2.1)
Abdominal pain	4 (0.9)	2 (0.4)	0.5 (-0.8, 1.9)
Umbilical hernia	4 (0.9)	2 (0.4)	0.5 (-0.8, 1.9)
Abdominal distension	3 (0.7)	1 (0.2)	0.5 (-0.6, 1.8)
Gastrooesophageal reflux disease	6 (1.3)	6 (1.3)	0.0 (-1.7, 1.7)
Flatulence	2 (0.4)	3 (0.7)	-0.2 (-1.5, 1.0)
Inguinal hernia	2 (0.4)	5 (1.1)	-0.7 (-2.2, 0.6)
Constipation	9 (2.0)	14 (3.1)	-1.1 (-3.4, 1.1)
General disorders and administration site conditions (SOC)	74 (16.6)	56 (12.4)	4.2 (-0.4, 8.8)
Injection site swelling	27 (6.1)	12 (2.7)	3.4 (0.8, 6.3)*
Injection site erythema	29 (6.5)	17 (3.8)	2.7 (-0.2, 5.8)
Injection site pain	26 (5.8)	24 (5.3)	0.5 (-2.6, 3.6)
Pain	7 (1.6)	7 (1.6)	0.0 (-1.8, 1.8)
Swelling	2 (0.4)	5 (1.1)	-0.7 (-2.2, 0.6)
Pyrexia	3 (0.7)	7 (1.6)	-0.9 (-2.6, 0.6)
Infections and infestations (SOC)	129 (29.0)	152 (33.8)	-4.8 (-10.8, 1.3)
Bronchiolitis	16 (3.6)	11 (2.4)	1.2 (-1.2, 3.6)
Rhinitis	8 (1.8)	4 (0.9)	0.9 (-0.7, 2.7)
Rhinovirus infection	3 (0.7)	1 (0.2)	0.5 (-0.6, 1.8)
Pneumonia	7 (1.6)	6 (1.3)	0.2 (-1.5, 2.0)
Lower respiratory tract infection	4 (0.9)	4 (0.9)	0.0 (-1.5, 1.5)
COVID-19	4 (0.9)	5 (1.1)	-0.2 (-1.8, 1.3)
Gastroenteritis	4 (0.9)	5 (1.1)	-0.2 (-1.8, 1.3)
Respiratory tract infection	11 (2.5)	13 (2.9)	-0.4 (-2.7, 1.8)
Conjunctivitis	4 (0.9)	7 (1.6)	-0.7 (-2.4, 0.9)
Bronchitis	1 (0.2)	4 (0.9)	-0.7 (-2.1, 0.5)
Urinary tract infection	1 (0.2)	5 (1.1)	-0.9 (-2.4, 0.3)
Upper respiratory tract infection	53 (11.9)	58 (12.9)	-1.0 (-5.3, 3.4)
Oral candidiasis	4 (0.9)	9 (2.0)	-1.1 (-3.0, 0.5)
Nasopharyngitis	13 (2.9)	19 (4.2)	-1.3 (-3.9, 1.2)
Investigations (SOC)	28 (6.3)	35 (7.8)	-1.5 (-4.9, 1.9)
Body temperature increased	26 (5.8)	27 (6.0)	-0.2 (-3.3, 3.0)
SARS-CoV-2 test positive	0	4 (0.9)	-0.9 (-2.3, -0.0)*
Metabolism and nutrition disorders (SOC)	59 (13.3)	38 (8.4)	4.8 (0.7, 9.0)*
Decreased appetite	52 (11.7)	37 (8.2)	3.5 (-0.5, 7.5)
Weight gain poor	3 (0.7)	0	0.7 (-0.2, 2.0)

System Organ Class Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Musculoskeletal and connective tissue disorders (SOC)	5 (1.1)	3 (0.7)	0.5 (-1.0, 2.0)
Pain in extremity	4 (0.9)	2 (0.4)	0.5 (-0.8, 1.9)
Nervous system disorders (SOC)	79 (17.8)	62 (13.8)	4.0 (-0.8, 8.8)
Somnolence	75 (16.9)	59 (13.1)	3.7 (-0.9, 8.5)
Psychiatric disorders (SOC)	121 (27.2)	115 (25.6)	1.6 (-4.1, 7.4)
Irritability	120 (27.0)	114 (25.3)	1.6 (-4.1, 7.4)
Respiratory, thoracic, and mediastinal disorders (SOC)	55 (12.4)	52 (11.6)	0.8 (-3.5, 5.1)
Nasal congestion	20 (4.5)	16 (3.6)	0.9 (-1.7, 3.7)
Hypoxia	3 (0.7)	0	0.7 (-0.2, 2.0)
Cough	9 (2.0)	13 (2.9)	-0.9 (-3.1, 1.3)
Apnoea	2 (0.4)	6 (1.3)	-0.9 (-2.5, 0.4)
Rhinorrhoea	12 (2.7)	18 (4.0)	-1.3 (-3.8, 1.1)
Skin and subcutaneous tissue disorders (SOC)	40 (9.0)	55 (12.2)	-3.2 (-7.3, 0.8)
Miliaria	8 (1.8)	7 (1.6)	0.2 (-1.6, 2.1)
Dermatitis atopic	3 (0.7)	2 (0.4)	0.2 (-1.0, 1.6)
Eczema	2 (0.4)	4 (0.9)	-0.4 (-1.9, 0.8)
Seborrhoeic dermatitis	1 (0.2)	4 (0.9)	-0.7 (-2.1, 0.5)
Rash maculo-papular	0	3 (0.7)	-0.7 (-1.9, 0.2)
Rash	6 (1.3)	10 (2.2)	-0.9 (-2.9, 1.0)
Erythema	2 (0.4)	6 (1.3)	-0.9 (-2.5, 0.4)
Dermatitis diaper	5 (1.1)	17 (3.8)	-2.7 (-5.0, -0.7)*

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 42 postdose.
Duration is a single dose on Day 1 followed by a placebo dose on Day 28 for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28, for the active control group, followed by 14 days of safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; SOC, system organ class

Treatment-Related Adverse Events

According to an analysis of treatment-related AEs, RSV Season 1, Postdose 1, Days 1 through 42 (Table 52), the proportions of participants with AEs considered by the Investigator to be related to study intervention were 27.0% (120/445) in the clesrovimab group and 23.6% (106/450) in the palivizumab group. The most frequently reported AEs considered to be related to study intervention by the Investigator in both groups were injection site pain, swelling, and erythema, decreased appetite, somnolence, and irritability. All these solicited AEs, with the exception of somnolence, were reported at higher frequencies in the clesrovimab group versus the palivizumab group. No SAEs reported in Season 1 were considered related to study intervention by the Investigator.

Table 52. Participants With Adverse Events Assessed by Investigator as Treatment-Related, Safety Population, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Any treatment-related AE	120 (27.0)	106 (23.6)	3.4 (-2.3, 9.1)
Injection site swelling	27 (6.1)	12 (2.7)	3.4 (0.8, 6.3)*
Injection site erythema	29 (6.5)	17 (3.8)	2.7 (-0.2, 5.8)
Decreased appetite	27 (6.1)	18 (4.0)	2.1 (-0.8, 5.1)
Irritability	69 (15.5)	61 (13.6)	2.0 (-2.7, 6.6)
Injection site pain	26 (5.8)	24 (5.3)	0.5 (-2.6, 3.6)
Constipation	2 (0.4)	0	0.4 (-0.4, 1.6)
Flatulence	1 (0.2)	0	0.2 (-0.6, 1.3)
Hypoxia	1 (0.2)	0	0.2 (-0.6, 1.3)
Infantile spitting up	1 (0.2)	0	0.2 (-0.6, 1.3)
Injection site inflammation	1 (0.2)	0	0.2 (-0.6, 1.3)
Injection site irritation	1 (0.2)	0	0.2 (-0.6, 1.3)
Insomnia	1 (0.2)	0	0.2 (-0.6, 1.3)
Respiratory tract infection	1 (0.2)	0	0.2 (-0.6, 1.3)
Abdominal pain	1 (0.2)	1 (0.2)	0.0 (-1.0, 1.1)
Drug eruption	1 (0.2)	1 (0.2)	0.0 (-1.0, 1.1)
Nasal congestion	1 (0.2)	1 (0.2)	0.0 (-1.0, 1.1)
Somnolence	31 (7.0)	32 (7.1)	-0.1 (-3.6, 3.3)
Body temperature increased	3 (0.7)	4 (0.9)	-0.2 (-1.7, 1.2)
Erythema	1 (0.2)	2 (0.4)	-0.2 (-1.4, 0.9)
Pyrexia	1 (0.2)	2 (0.4)	-0.2 (-1.4, 0.9)
Discomfort	0	1 (0.2)	-0.2 (-1.2, 0.6)
Fatigue	0	1 (0.2)	-0.2 (-1.2, 0.6)
Haematoma	0	1 (0.2)	-0.2 (-1.2, 0.6)
Injection site warmth	0	1 (0.2)	-0.2 (-1.2, 0.6)
Oral candidiasis	0	1 (0.2)	-0.2 (-1.2, 0.6)
Rash	0	1 (0.2)	-0.2 (-1.2, 0.6)
Regurgitation	0	1 (0.2)	-0.2 (-1.2, 0.6)
Apnoea	0	2 (0.4)	-0.4 (-1.6, 0.4)
Swelling	1 (0.2)	4 (0.9)	-0.7 (-2.1, 0.5)
Pain	1 (0.2)	5 (1.1)	-0.9 (-2.4, 0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 42 postdose.
Duration is a single dose on Day 1 followed by a placebo dose on Day 28 for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28, for the active control group, followed by 14 days of safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; RSV, respiratory syncytial virus

7.6.2.2. Deaths, Trial MK-1654-007

Table 53 summarizes the AEs leading to death for participants in Trial MK-1654-007. In RSV Season 1, there were a total of 12 deaths (8 [1.8%] in the MK-1654 group, 4 [0.9%] in the palivizumab group), of which three deaths occurred within 42 days postdose (2 in the clesrovimab group, 1 in the palivizumab group). None of the deaths were considered by the Investigator to be related to study intervention. No trend was observed in the timing of death relative to study drug administration and the AE preferred terms associated with death varied across multiple SOCs.

Based on review of the case narratives for these participants, the FDA agrees with the Applicant's and Investigator's assessments that these deaths were not related to study drug administration. At the time of the original BLA submission, no deaths had been reported in RSV Season 2.

Table 53. AEs Leading to Death, Safety Population, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Any AE leading to death	2 (0.4)	1 (0.2)	0.2 (-0.8, 1.4)
Hypoxia	1 (0.2)	0	0.2 (-0.6, 1.3)
Myocardial infarction	1 (0.2)	0	0.2 (-0.6, 1.3)
Pneumonia	1 (0.2)	0	0.2 (-0.6, 1.3)
Sudden infant death syndrome	0	1 (0.2)	-0.2 (-1.2, 0.6)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that occurred from Day 1 through Day 42 postdose.
Duration is a single dose on Day 1 followed by a placebo dose on Day 28 for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28, for the active control group, followed by 14 days of safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For patient-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; RSV, respiratory syncytial virus

Table 54 shows a listing of all participant deaths in Trial MK-1654-007 in RSV Season 1 following Dose 1, through Day 42.

Table 54. Listing of All Individual Participant Deaths, Safety Population, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

Study Arm	Participant ID	Age (Days)	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death: Preferred Term	Cause of Death: Verbatim Term
MK-1654 105 mg	(b) (6)	119	F	MK-1654 105 mg	1	19	Pneumonia	Pneumonia
							Hypoxia	Hypoxic spell
MK-1654 105 mg		269	F	MK-1654 105 mg	1	6	Myocardial infarction	Heart attack
Palivizumab		28	M	N/A	30	32	Sudden infant death syndrome	Sudden infant death

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as serious adverse events that occurred from Day 1 through Day 42 postdose.
Duration is a single dose on Day 1 followed by a placebo dose on Day 28 for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28, for the active control group, followed by 14 days of safety follow-up.
Abbreviations: F, female; ID, identifier; M, male; MK-1654, clesrovimab; N/A, not applicable; RSV, respiratory syncytial virus

Table 55 shows all participant deaths in Trial MK-1654-007 following any dose of study drug in RSV Season 1. Many of the deaths of participants who received clesrovimab occurred long after clesrovimab administration.

Table 55. Listing of All Individual Participant Deaths, Safety Population, RSV Season 1, Following Any Dose, Trial MK-1654-007

Study Arm	Participant ID	Age (Days)	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death: Preferred Term	Cause of Death: Verbatim Term
MK-1654 105 mg	(b) (6)	42	F	105 mg	31	115	Cardiac dysfunction	Heart function worsened
MK-1654 105 mg		106	M	105 mg	29	43	Shunt occlusion	Blalock taussig fistula obstructed
MK-1654 105 mg		46	M	105 mg	29	50	Interstitial lung disease*	Interstitial pneumonitis
MK-1654 105 mg		128	F	105 mg	28	122	Death	Unknown cause of death
MK-1654 105 mg		39	F	105 mg	28	66	Skull fracture	Skull fractures
MK-1654 105 mg		119	F	105 mg	1	19	Pneumonia	Pneumonia
							Hypoxia	Hypoxic spell
MK-1654 105 mg		212	M	105 mg	28	65	Hypoxia	Hypoxemia
MK-1654 105 mg		269	F	105 mg	1	6	Myocardial infarction	Heart attack
Palivizuma		25	M	N/A	112	171	Pulmonary alveolar haemorrhage	Diffuse alveolar haemorrhage
Palivizuma		53	F	N/A	56	102	Brain injury	Severe hypoxic brain damage
							Pulmonary congestion	Pulmonary congestion
							Cyanosis	Cyanosis
Palivizuma		28	M	N/A	30	32	Sudden infant death syndrome	Sudden infant death
Palivizuma		60	F	N/A	57	91	Pneumonia	Pneumonia (cause to be determined)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as serious adverse events that occurred through the duration of participation in RSV Season 1.
Duration: treatment group had a single dose on Day 1 followed by a placebo dose on Day 28; active control had two doses 28 days apart followed by three to five monthly doses, followed by safety follow-up until Day 365.
* In the case of "interstitial lung disease," "postmortem testing revealed *Pneumocystis carinii/jirovecii* (PCP/PJP) and *Klebsiella pneumoniae*. *P. jirovecii* is an opportunistic infection that typically affects immune compromised infants/individuals, raising concerns for an underlying acquired or congenital immune deficiency. The case is not suggestive of drug-related interstitial lung disease.
Abbreviations: F, female; ID, identifier; M, male; MK-1654, clesrovimab; N/A, not applicable; RSV, respiratory syncytial virus

Update on Deaths From the SUR

There were no additional deaths in Trial MK-1654-007. In the cumulative dataset, the proportion of participants who died following any dose in RSV Season 1 was 1.6% (8/497) in the MK-1654 group and 0.8% (4/499) in the palivizumab group; the number of deaths was unchanged since the BLA data cutoff.

Season 2

In the cumulative dataset, one new death was reported, which occurred between the Application data cutoff date and the SUR cutoff date. The death occurred in an infant who was born at 26 weeks, birthweight 0.72 kg, with CLD and had received palivizumab in RSV Season 1; the infant was febrile 1 day prior to death on Day 25 postdose RSV Season 2 dose.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial MK-1654-007

In Trial MK-1654-007, RSV Season 1, SAEs were reported in 22.2% of participants in the clesrovimab group and 24.4% in the palivizumab group. The most frequently reported SOC for both intervention groups was Infections and infestations. No SAEs in the clesrovimab group were considered related to study intervention; two participants in the palivizumab group each had one intervention-related SAE of apnea.

In Trial MK-1654-007, a numerical imbalance was observed in the SAE of bronchiolitis, with 2.7% (12/445) of clesrovimab recipients and 1.3% (6/450) of palivizumab recipients experiencing the SAE of bronchiolitis (see Table 56).

The FDA notes this imbalance in bronchiolitis SAEs between the two arms in Trial MK-1654-007. Based on FDA's review of case narratives for participants who experienced an SAE of bronchiolitis (for the cases in which an etiology was established), the imbalance appeared to be driven by a variety of pathogens, without any trend to suggest a disproportionate incidence of RSV infections (e.g., in the clesrovimab group, there were several cases of human rhinovirus/enterovirus, parainfluenza, adenovirus, SARS-CoV2, Hemophilus influenzae, human metapneumovirus, and some with unspecified etiology, in addition to RSV etiology). An underlying pathophysiologic explanation is not apparent for the slight increase in incidence of bronchiolitis SAEs in the clesrovimab group compared with the placebo group following administration of study drug. Of note, an imbalance in bronchiolitis was not observed in Trial MK-1654-004 (which, based on trial design, would be expected to provide a more reliable comparison between study groups). It is possible that the imbalance that was observed in Trial MK-1654-007 may be due to chance or related to the underlying comorbid conditions in these high-risk infants. Routine pharmacovigilance is recommended to evaluate for any signs of disproportionate incidence of bronchiolitis/respiratory events in the postmarket setting.

Table 56. Participants With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

System Organ Class Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Any SAE	46 (10.3)	48 (10.7)	-0.3 (-4.4, 3.7)
Blood and lymphatic system disorders (SOC)	1 (0.2)	2 (0.4)	-0.2 (-1.4, 0.9)
Anaemia	1 (0.2)	0	0.2 (-0.6, 1.3)
Anaemia neonatal	0	2 (0.4)	-0.4 (-1.6, 0.4)
Cardiac disorders (SOC)	1 (0.2)	2 (0.4)	-0.2 (-1.4, 0.9)
Myocardial infarction	1 (0.2)	0	0.2 (-0.6, 1.3)
Cardiac failure	0	2 (0.4)	-0.4 (-1.6, 0.4)
Eye disorders (SOC)	1 (0.2)	2 (0.4)	-0.2 (-1.4, 0.9)
Retinopathy of prematurity	1 (0.2)	2 (0.4)	-0.2 (-1.4, 0.9)

System Organ Class Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)	7 (1.6)	4 (0.9)	0.7 (-0.9, 2.4)
Gastric haemorrhage	1 (0.2)	0	0.2 (-0.6, 1.3)
Gastritis	1 (0.2)	0	0.2 (-0.6, 1.3)
Incarcerated inguinal hernia	1 (0.2)	0	0.2 (-0.6, 1.3)
Intestinal obstruction	1 (0.2)	0	0.2 (-0.6, 1.3)
Vomiting	1 (0.2)	1 (0.2)	0.0 (-1.0, 1.1)
Inguinal hernia	2 (0.4)	3 (0.7)	-0.2 (-1.5, 1.0)
Umbilical hernia	0	1 (0.2)	-0.2 (-1.2, 0.6)
General disorders and administration site conditions (SOC)	2 (0.4)	2 (0.4)	0.0 (-1.2, 1.2)
Drug withdrawal syndrome	1 (0.2)	0	0.2 (-0.6, 1.3)
Pyrexia	1 (0.2)	0	0.2 (-0.6, 1.3)
Crying	0	1 (0.2)	-0.2 (-1.2, 0.6)
Sudden infant death syndrome	0	1 (0.2)	-0.2 (-1.2, 0.6)
Hepatobiliary disorders (SOC)	1 (0.2)	0	0.2 (-0.6, 1.3)
Hyperbilirubinaemia	1 (0.2)	0	0.2 (-0.6, 1.3)
Infections and infestations (SOC)	31 (7.0)	28 (6.2)	0.7 (-2.6, 4.1)
Bronchiolitis	12 (2.7)	6 (1.3)	1.4 (-0.5, 3.5)
COVID-19	2 (0.4)	0	0.4 (-0.4, 1.6)
Gastroenteritis rotavirus	2 (0.4)	1 (0.2)	0.2 (-0.8, 1.4)
Viral infection	2 (0.4)	1 (0.2)	0.2 (-0.8, 1.4)
Bacterial infection	1 (0.2)	0	0.2 (-0.6, 1.3)
Croup infectious	1 (0.2)	0	0.2 (-0.6, 1.3)
Enterovirus infection	1 (0.2)	0	0.2 (-0.6, 1.3)
Nasopharyngitis	1 (0.2)	0	0.2 (-0.6, 1.3)
Pulmonary sepsis	1 (0.2)	0	0.2 (-0.6, 1.3)
Respiratory syncytial virus bronchiolitis	1 (0.2)	0	0.2 (-0.6, 1.3)
Pneumonia	6 (1.3)	6 (1.3)	0.0 (-1.7, 1.7)
Gastroenteritis	2 (0.4)	2 (0.4)	0.0 (-1.2, 1.2)
Pneumonia viral	2 (0.4)	2 (0.4)	0.0 (-1.2, 1.2)
Rhinovirus infection	1 (0.2)	1 (0.2)	0.0 (-1.0, 1.1)
Viral upper respiratory tract infection	1 (0.2)	1 (0.2)	0.0 (-1.0, 1.1)
Lower respiratory tract infection	1 (0.2)	2 (0.4)	-0.2 (-1.4, 0.9)
Abscess jaw	0	1 (0.2)	-0.2 (-1.2, 0.6)
Adenovirus infection	0	1 (0.2)	-0.2 (-1.2, 0.6)
Bordetella infection	0	1 (0.2)	-0.2 (-1.2, 0.6)
Endocarditis bacterial	0	1 (0.2)	-0.2 (-1.2, 0.6)
Metapneumovirus bronchiolitis	0	1 (0.2)	-0.2 (-1.2, 0.6)
Parainfluenzae virus infection	0	1 (0.2)	-0.2 (-1.2, 0.6)
Pneumonia parainfluenzae viral	0	1 (0.2)	-0.2 (-1.2, 0.6)
Sepsis	0	1 (0.2)	-0.2 (-1.2, 0.6)
Upper respiratory tract infection	0	1 (0.2)	-0.2 (-1.2, 0.6)
Urinary tract infection	1 (0.2)	3 (0.7)	-0.4 (-1.7, 0.7)
Injury, poisoning and procedural complications (SOC)	0	1 (0.2)	-0.2 (-1.2, 0.6)
Child maltreatment syndrome	0	1 (0.2)	-0.2 (-1.2, 0.6)
Investigations (SOC)	0	1 (0.2)	-0.2 (-1.2, 0.6)
Body temperature increased	0	1 (0.2)	-0.2 (-1.2, 0.6)
Metabolism and nutrition disorders (SOC)	1 (0.2)	0	0.2 (-0.6, 1.3)
Hyponatraemia	1 (0.2)	0	0.2 (-0.6, 1.3)

System Organ Class Preferred Term	MK-1654 (N=445) n (%)	Palivizumab (N=450) n (%)	Risk Difference % (95% CI)
Nervous system disorders (SOC)	2 (0.4)	2 (0.4)	0.0 (-1.2, 1.2)
Partial seizures	1 (0.2)	0	0.2 (-0.6, 1.3)
Seizure like phenomena	1 (0.2)	0	0.2 (-0.6, 1.3)
Hydrocephalus	0	1 (0.2)	-0.2 (-1.2, 0.6)
Movement disorder	0	1 (0.2)	-0.2 (-1.2, 0.6)
Pregnancy, puerperium, and perinatal conditions (SOC)	1 (0.2)	0	0.2 (-0.6, 1.3)
Jaundice neonatal	1 (0.2)	0	0.2 (-0.6, 1.3)
Psychiatric disorders (SOC)	1 (0.2)	0	0.2 (-0.6, 1.3)
Breath holding	1 (0.2)	0	0.2 (-0.6, 1.3)
Respiratory, thoracic, and mediastinal disorders (SOC)	6 (1.3)	7 (1.6)	-0.2 (-2.0, 1.5)
Hypoxia	1 (0.2)	0	0.2 (-0.6, 1.3)
Laryngospasm	1 (0.2)	0	0.2 (-0.6, 1.3)
Respiratory disorder	1 (0.2)	0	0.2 (-0.6, 1.3)
Respiratory failure	1 (0.2)	0	0.2 (-0.6, 1.3)
Chylothorax	0	1 (0.2)	-0.2 (-1.2, 0.6)
Idiopathic interstitial pneumonia	0	1 (0.2)	-0.2 (-1.2, 0.6)
Pleural effusion	0	1 (0.2)	-0.2 (-1.2, 0.6)
Apnoea	2 (0.4)	4 (0.9)	-0.4 (-1.9, 0.8)
Vascular disorders (SOC)	1 (0.2)	1 (0.2)	0.0 (-1.0, 1.1)
Cyanosis	1 (0.2)	0	0.2 (-0.6, 1.3)
Hypotension	0	1 (0.2)	-0.2 (-1.2, 0.6)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as serious adverse events that occurred from Day 1 through Day 42 postdose.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is a single dose on Day 1 followed by a placebo dose on Day 28 for the treatment group, and two doses of palivizumab, one on Day 1 and one on Day 28, for the active control group, followed by 14 days of safety follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; RSV, respiratory syncytial virus; SAE, serious adverse event; SOC, system organ class

Update on SAEs From the SUR

In the cumulative dataset, the proportions of participants with ≥1 SAEs following any dose in RSV Season 1 were similar between the clesrovimab and palivizumab groups, and consistent with the BLA dataset. SAEs were reported across multiple SOCs in both datasets and no pattern was identified. The most frequently reported SOC was Infections and infestations in both intervention groups. From the original BLA data cutoff date through the SUR data cutoff date, ≥1 SAEs were reported for 29 (14.0%) participants in the MK-1654 group and 35 (16.2%) participants in the palivizumab group; none of these SAEs were considered related to study intervention by the Investigator. Cumulatively, ≥1 SAEs were reported in 24.3% (121/497) versus 27.5% (137/499) in the clesrovimab versus palivizumab groups, respectively.

7.6.2.4. Adverse Events of Special Interest, Trial MK-1654-007

AESIs assessed by the Applicant included anaphylaxis/hypersensitivity events (which included the following terms: anaphylaxis, angioedema, bronchospasm, drug hypersensitivity, drug-related allergic reaction, dyspnea, hypersensitivity, dysphonia, urticaria, and wheezing) and rash events (which included the following terms: acute generalized exanthematous pustulosis, drug eruption, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, generalized rash of exfoliative nature, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria). Any anaphylaxis/hypersensitivity event reported in the eDiary or during weekly surveillance contact (through 14 days Postdose 2 in RSV Season 1, within 42 days postdose in RSV Season 2, or within 42 days after an additional postsurgery dose of MK-1654 in either RSV season) may have been further assessed by the site. All AESI were Grade 1.

Anaphylaxis/Hypersensitivity

No anaphylaxis/hypersensitivity AESI were reported in Season 1 of Trial MK-1654-007.

Rash

Primary Rash AESI Analysis

Within 42 days Postdose 1 in RSV Season 1, three participants (0.7%) in the clesrovimab group and one participant (0.2%) in the palivizumab group experienced a rash AESI (see above for list of included PTs); none were serious, and all were Grade 1. Rash AESIs in the clesrovimab group included one participant with a Grade 1 drug eruption that occurred 2 days Postdose 2 (placebo dose), which was not serious and resolved in 4 days; and two participants (0.4%) with urticaria. Of these rash AESIs among clesrovimab participants, only the drug eruption event was considered to be related to study drug administration per the Investigator. One palivizumab participant had a Grade 1 drug eruption that occurred 9 days Postdose 2, that was assessed to be drug-related, was not serious, and resolved in 1.14 weeks.

No rash AESIs were reported in the ADA-positive subgroups in RSV Season 1.

Expanded Analysis of Rash AEs

In addition to the rash AESI analysis, an expanded analysis of rash AEs which occurred within 14 days Postdose 1 in RSV Season 1 was conducted. The specific rash PTs included rash, rash macular, rash papular, rash maculo-papular, rash erythematous, rash vesicular, exfoliative rash, drug eruption, toxic skin eruption, and dermatitis allergic. One or more of these rash AEs were reported in 0.7% (3/445) participants in the MK-1654 group and 1.8% (8/450) participants in the palivizumab group. All rash AESIs were nonserious and were Grade 1 toxicity in both intervention groups. No rash AESIs in the clesrovimab group were considered to be related to study intervention by the Investigator; one participant in the palivizumab group had a rash AESI that was considered to be related to study intervention per the Investigator.

An analysis of rash events using OCMQ (narrow) (not shown) did not reveal any safety concerns regarding rash events.

Update on AESIs From the SUR

Since the BLA data cutoff, no additional participants have reported anaphylaxis/hypersensitivity AESIs from Days 1 through 42 Postdose 1 in RSV Season 1.

In the Applicant's expanded rash analysis, there was one additional participant in the palivizumab group who experienced a Grade 1 nonserious rash AE that was assessed as not related to study intervention.

Season 2

Season 2 data are available for 179 participants who received a 210-mg dose of clesrovimab in RSV Season 2 and had at least 42 days of follow-up postdose by the SUR cutoff date.

In the cumulative dataset, there were no participants who reported anaphylaxis/hypersensitivity AE from Days 1 through 42 postdose in RSV Season 2.

7.7. Key Safety Review Issues

7.7.1. Hypersensitivity Reactions, Including Anaphylaxis and Rash

Issue

Immune-mediated reactions have been associated with biologic products such as monoclonal antibodies. Anaphylaxis, hypersensitivity reactions, and rash are potential serious presentations of allergic reactions to monoclonal antibodies. Therefore, the FDA carefully examined the safety database for clesrovimab in order to detect and characterize potential hypersensitivity reactions or rashes due to clesrovimab administration.

Background

Immune-mediated (allergic) adverse reactions, ranging from anaphylaxis to hypersensitivity skin reactions, are well-known adverse reactions associated with the use of monoclonal antibodies (Pintea et al. 2021). These adverse reactions have been reported during the postmarketing period with palivizumab, a monoclonal antibody against the RSV fusion protein with a similar mechanism of action as nirsevimab and clesrovimab. In addition, for nirsevimab, postmarketing reports of AEs consistent with possible hypersensitivity reactions prompted a Prescribing Information update and revised WARNINGS and PRECAUTIONS, Section 5.1 in February 2024.

Anaphylaxis, a form of severe hypersensitivity reaction, can occur within minutes to hours after administration. Anaphylaxis typically involves a cluster of clinical signs and symptoms that may include changes in the skin and/or mucosa, respiratory changes, gastrointestinal symptoms, and/or a decrease in blood pressure. See the National Institute of Allergy and Infectious Disease criteria for the diagnosis of anaphylaxis (Sampson et al. 2006).

Skin reactions and rashes have also been reported with monoclonal antibody use. Hypersensitivity skin reactions can range from mild macular rash or urticaria, to more severe forms. Severe hypersensitivity skin reactions such as Stevens-Johnson syndrome or toxic

epidermal necrolysis may be observed from 2 to 7 days after drug exposure. Other rashes typically occur within 2 to 3 weeks of starting a new medication, but the time of onset could be later with products that have a prolonged half-life (e.g., clesrovimab or nirsevimab).

Allergic reactions to drugs can also occur days after drug product administration. Immune complex diseases may occur 1 to 3 weeks after drug exposure and may result in serum sickness, fever, rash, arthralgias, urticaria, glomerulonephritis, or vasculitis (Riedl and Casillas 2003).

Assessment

Clesrovimab was administered on Day 1 in the clinical trials. In order to assess for potential hypersensitivity reactions, including anaphylaxis, adverse events of hypersensitivity reactions including anaphylaxis with onset within 42 days after dosing were examined by:

- The Applicant's identification of AESIs consistent with hypersensitivity reactions, using the following the Medical Dictionary for Regulatory Activities preferred terms: anaphylaxis, angioedema, bronchospasm, drug hypersensitivity, drug-related allergic reaction, dyspnea (difficulty breathing), hypersensitivity, dysphonia, urticaria (hives or welts), and wheezing in all trials of clesrovimab.
- Analysis of adverse events in the pivotal clesrovimab trials, MK-1654-004 and MK-1654-007, with related preferred terms for AEs of hypersensitivity using OCMQs, which are clinically meaningful groupings used by FDA/OND in premarket drug safety evaluation.

Per the Applicant's pooled safety analyses performed across the infant program (Trials MK-1654-004; MK-1654-007; MK-1654-002 Panels D and E and placebo pooled across panels; MK-1654-008 Panel C), there was one participant in the clesrovimab group (Grade 2 bronchospasm in Trial MK-1654-004 in a 246-day-old infant, onset on Day 3 after dosing, which was assessed as not related by the Investigator) and one participant in the control group (mild wheezing in a 102-day-old infant in the placebo group, onset 26 days after dose administration, with concurrent URI, in Trial MK-1654-002, Panel D, which was assessed as not related by the Investigator) who experienced a hypersensitivity AE from Days 1 through 42 Postdose 1 in RSV Season 1. Of note, FDA's pooled analysis did not identify the participant from the control group with a hypersensitivity AE.

FDA's analyses using OCMQs revealed possible additional cases of hypersensitivity; however, these cases appeared to be driven by rash events. FDA analyses of rash revealed similar findings to the Applicant's analyses, with an increased frequency of rash events/AESIs noted in the clesrovimab group compared with the placebo group. In Trial MK-1654-004, rash was reported within 14 days after dosing in 2.3% of clesrovimab recipients and 1.9% of placebo recipients. Additional possible hypersensitivity and urticaria AESIs appeared to be reflective of the imbalance in rash AESIs between the two arms in Trial MK-1654-004. There was one event of severe urticaria within 14 days after dosing in the clesrovimab group, which was assessed as not related to study drug by the Investigator. It is unclear per FDA's assessment whether this severe urticaria event could possibly have been related to study drug administration.

Conclusion

No adverse events of anaphylaxis were reported in any of the clinical trials of clesrovimab. There was one event of hypersensitivity reaction (i.e., bronchospasm, Grade 2) in a recipient of clesrovimab in Trial MK-1654-004.

Severe or serious skin reactions were uncommon in the trials of clesrovimab, as were rashes that were considered allergic reactions to clesrovimab. Only one severe rash/urticaria event was reported, this was in the clesrovimab group, and was assessed as not related to study drug administration by the Investigator; however, the FDA has not definitively ruled out the possibility of the severe urticaria event being related to study drug administration. The incidence of rashes assessed as possibly drug-related in Trial MK-1654-004 was similar between the trial arms, with 0.3% in the clesrovimab group versus 0.2% in the placebo group.

Overall, the incidence of rash in the trials of clesrovimab was low but was observed at a higher frequency in the clesrovimab group versus the placebo group, with 2.3% of clesrovimab recipients and 1.9% of placebo recipients experiencing rash.

The imbalance in rash AESIs is described in Section 6.1 of the USPI to inform prescribers of the potential risk of rash associated with clesrovimab administration.

The potential risk of hypersensitivity reactions, including anaphylaxis, with use of monoclonal antibodies (including clesrovimab) is adequately described in Section 5 of the USPI (Warnings and Precautions).

7.7.2. Potential for Interference With RSV Rapid-Test Assays

Issue

Rapid antigen testing is typically used in the clinic for the diagnosis of RSV infection. Because these types of assays use antibodies targeting the F protein for detection, there is a potential for interference by clesrovimab in samples from individuals who have received this product, as has been reported for palivizumab (Deming et al. 2013).

Background

The potential for interference by clesrovimab with rapid antigen testing was assessed by the Applicant. Data from these assessments was also reviewed through a consult with CDRH.

Assessment

Four commonly used RSV rapid antigen tests kits were evaluated for detection of RSV in the presence or absence of clesrovimab, including BinaxNOW™ RSV (Abbott, Green Oaks, IL), TRU RSV® (Meridian Bioscience, Cincinnati, OH), Remel™ Xpect® RSV (Remel, Lenexa, KS), and BD Veritor™ System (BD, Franklin Lakes, NJ).

To determine the potential for clesrovimab interference with the assay, the positive controls from each RSV kit were spiked with clesrovimab to final concentrations of 1 and 5 µg/mL, the higher concentration having been selected based on nasal concentrations determined in Phase 1 adult trials and expected pharmacokinetics at the 105-mg dose in infants.

The four commonly used rapid antigen tests were able to detect RSV A at titers as low as 10^4 or 10^5 PFU/mL. In the presence of clesrovimab, the sensitivity of the assay was reduced for the BinaxNOW™ RSV and Remel™ Xpect® RSV kits, and there was a qualitative impact on the readout for BinaxNOW™ RSV and TRU RSV® kits. In the presence of clesrovimab, the sensitivity of the BinaxNOW™ RSV, TRU RSV® and Remel™ Xpect® RSV kits was $\geq 10^5$ PFU/mL compared to the BD Veritor™ System which was 10^4 PFU/mL. Data on the impact of clesrovimab on RSV B detection by these rapid antigen tests were provided late in the review cycle and showed that interference by clesrovimab was only observed for the TRU RSV® kit at 10^4 PFU/mL and 5 µg/mL clesrovimab.

Conclusion

Interference by clesrovimab was observed with commonly used rapid antigen tests for detecting RSV. Clesrovimab interference with these immunoassays might lead to false-negative results and contribute to inappropriate use of antibiotics and unnecessary laboratory testing, prolonged hospitalizations and delay actions to limit nosocomial infections (Byington et al. 2002; Mills et al. 2011).

To mitigate these risks, it will be important for testing of individuals who have received clesrovimab prophylaxis and who present with clinical observations consistent with RSV to confirm negative results using an RT-PCR-based assay, which is not affected by the presence of clesrovimab. This recommendation will be conveyed in the Prescribing Information.

7.7.3. Pharmacovigilance

Issue

If approved, clesrovimab has the potential for widespread use for the prevention of RSV lower respiratory tract disease in neonates and infants. The pharmacovigilance strategy is important for continued assessment and risk characterization once clesrovimab is licensed for marketing.

Background

Pharmacovigilance Strategies are postmarket safety monitoring plans that the Center for Drug Evaluation and Research (CDER) develops to document its coordination of pharmacovigilance and risk management activities between or among multiple disciplines to further characterize and manage the safety of a drug product or drug class.

Assessment

CDER plans to implement a broad pharmacovigilance strategy for clesrovimab. The key focus areas of the pharmacovigilance strategy are to: 1) identify new safety signal(s); 2) monitor for increased or unusual numbers of reports of a serious adverse event; and 3) monitor for increase in the severity of an adverse event. To help identify safety signals, the Agency will focus on unlabeled adverse events with the potential for serious outcomes and labeled adverse events with unexpected characteristics such as an increase in severity. CDER plans to utilize several

platforms to monitor postmarket safety adverse events across several postmarketing surveillance data streams, including:

- Reports submitted to the FDA's Adverse Event Reporting System database, which contains spontaneous adverse event reports for human drugs and therapeutic biologics.
- Relevant reports that are submitted to the Vaccine Adverse Event Reporting System will also be screened, as applicable, because of either a concomitantly administered vaccine AE with clesrovimab administration or an error in reporting to the Vaccine Adverse Event Reporting System instead of FDA's Adverse Event Reporting System, since this product may be confused by some to be a vaccine.
- Published medical literature using Embase and PubMed for new safety signals.
- Required, periodic safety reports submitted by the manufacturer.
- Review of safety data from ongoing clinical trial(s) evaluating clesrovimab.

Based on the clinical development program and adverse events associated with monoclonal antibodies, prespecified adverse events of interest during postmarketing drug safety surveillance for clesrovimab include the following:

- Hypersensitivity reactions, including anaphylaxis and angioedema
- Immune complex disease, cytopenias (including thrombocytopenia)
- Injection site reactions, serious cutaneous adverse reactions

CDER is also exploring active surveillance approaches for clesrovimab using the Sentinel Distributed Database that can be conducted postapproval on claims-based data sources.

Conclusion

CDER has determined a pharmacovigilance strategy is necessary to support coordinated monitoring and assessment of safety information from data sources across CDER Offices and/or Divisions. If approved, the Advisory Committee on Immunization Practices will provide clinical guidelines for use of clesrovimab. The Advisory Committee on Immunization Practices recommendations will be factored into the pharmacovigilance strategy, as appropriate. The full details of the pharmacovigilance strategy will be finalized in a separate document within 90 days of marketing approval. The pharmacovigilance strategy may be modified as safety information accumulates during the postmarketing period.

8. Therapeutic Individualization

8.1. Intrinsic Factors

The effect of covariates, including time-varying body weight, age, race, sex, ethnicity, CLD, CHD, and time-varying ADA status, on the exposure of clesrovimab were assessed using a pediatric population pharmacokinetic (PopPK) model. None of these intrinsic factors have clinically meaningful effects on clesrovimab pharmacokinetics in Season 1, based on the range of clesrovimab exposures and a flat exposure-response relationship. Therefore, no dose

adjustment is needed based on weight, age, race, sex, ethnicity, comorbidities such as CHD and CLD, or ADA status. Refer to Section 6.3.1 and Section 14.5.

Based on pediatric PopPK analyses,

- Body weight was a statistically significant covariate on clesrovimab pharmacokinetics.

The analysis included 2942 participants with a median (range) baseline body weight of 5.40 kg (1.14 to 11.9 kg). In RSV Season 1, infants with body weight of ≥5 kg at the time of dosing had lower exposures in terms of $AUC_{0\text{-}150d}$, compared to infants with a baseline body weight of <5 kg with the geometric mean ratio (90% CI) of 0.72 (0.72 to 0.73).

- Age was identified as a statistically significant covariate in the final PopPK model.

Across all 2942 participants included in the analysis, the median (range) age was 3.02 months (0.07 to 12.0 months). A maturation function on clearance (CL) was included in the infant PopPK model for clesrovimab describing the additional effect of adjusted age (based on postnatal age and gestational age) on clearance maturation. The $AUC_{0\text{-}150d}$ was 23% higher in infants <3 months of age and 16% lower in infants >6 months of age, compared to the reference age group of 3 to 6 months of age.

- Race was identified as a statistically significant covariate in the final PopPK model.

Asian participants (n=735) had a 5.85% lower CL as compared to the reference participant (White, n=1327), while Black (n=426) and Multiracial (n=381) participants had 13.2% and 8.72% higher clearance, respectively. The magnitude of the effect of race on clesrovimab exposures was not considered clinically meaningful given the relatively flat exposure-response relationship across the exposure range corresponding to the recommended dose of 105 mg.

- Sex, CLD, CHD, and ADA status were not statistically significant covariates of clesrovimab pharmacokinetics.

Hepatic Impairment

No dedicated hepatic impairment study was performed. Clesrovimab is expected to be predominantly catabolized by lysosomal degradation to small peptides and amino acids, and its distribution and elimination are not mediated by cytochrome P450 or drug transporters.

Renal Impairment

No dedicated study was conducted to evaluate the impact of renal impairment. Clesrovimab is a monoclonal antibody with a molecular weight greater than 69 kDa. Therefore, impaired renal function is unlikely to alter pharmacokinetics to a clinically significant degree.

8.2. Extrinsic Factors

As a high molecular weight monoclonal antibody, clesrovimab is not renally excreted or metabolized by cytochrome P450 enzymes. Therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. Clesrovimab targets a nonendogenous antigen (RSV outer membrane F protein). No inflammatory-mediated effects on metabolic enzymes are expected. As such, no drug-drug interaction studies were performed.

8.3. Plans for Pediatric Drug Development

Clesrovimab was studied in two pediatric populations: healthy infants born during or entering their first RSV season and infants at increased risk for severe RSV disease who are born during or entering their first RSV season. Severe RSV LRTD typically occurs with the first RSV infection. Most healthy children are infected with RSV and experience RSV LRTD during their first RSV season, and almost all infants have had an RSV infection by 2 years of age. While the risk of hospitalization due to RSV LRTD is highest at 2 to 3 months of age and remains increased during the first 6 to 7 months of life, the risk of LRTI and LRTD due to RSV extends throughout the first year of life (Munoz et al. 2003). The severity of RSV disease decreases after the first year of life. In participants older than 12 months of age, primary RSV infection with LRTD is typically milder because of changes in the pulmonary anatomy with lung growth; the larger airways of older children are less likely to have pulmonary flow resistance caused by the edema, cellular sloughing and mucus in the airways that occurs with RSV LRTD (Hu et al. 2020). As a result, children older than 12 months of age have a lower incidence of infection with fewer hospitalizations and less severe disease.

The CDC defines children at high risk of severe RSV LRTD as infants and young children (the younger the age, the higher the risk), those who were born prematurely, have chronic lung disease or congenital heart disease, have weakened immune systems, or have neuromuscular disorders, including those with difficulty swallowing or clearing mucus secretions (CDC 2024a). There are currently two monoclonal antibodies approved for the prevention of RSV in infants: palivizumab and nirsevimab. Currently, nirsevimab is preferred over palivizumab due to its efficacy, duration of protection, and convenient dosing. The AAP recommends nirsevimab for infants aged <8 months born during or entering their first RSV season, whose pregnant parent did not receive the RSVpreF vaccine, whose pregnant parent's RSVpreF vaccination status is unknown, or who were born <14 days after the pregnant parent's RSVpreF vaccination. Nirsevimab use is also recommended in infants and children ages 8 through 19 months of age who remain at increased risk of severe RSV disease and are entering their second RSV season (AAP 2024; CDC 2025).

Neither the CDC nor the AAP recommend the use of RSV prophylaxis after the second year of life. Therefore, in the high-risk population, the need for RSV prevention is limited to children ≤24 months of age. Thus, prevention of RSV LRTD is most appropriate for healthy neonates and infants in their first RSV season, and in those with comorbidities such as CLD of prematurity or hemodynamically significant CHD who are ≤24 months of age.

Partial Waiver for Pediatric Studies

The Applicant and FDA agree that clesrovimab has been studied in the appropriate population, and the Applicant was granted a Pediatric Research Equity Act partial waiver (per Section 505B(a)(4)(B)(iii) of the Federal Food, Drug, and Cosmetic Act) on December 31, 2020 for the study of clesrovimab in preterm and term infants >12 months of age without underlying conditions that increase the risk for RSV disease and for pediatric patients >24 months of age with underlying conditions that increase the risk for RSV disease, based on lack of meaningful therapeutic benefit given the reduced incidence and low severity of disease in these age groups, and that clesrovimab is unlikely to be used by a substantial number of pediatric patients in these age groups.

Request for Deferral of Pediatric Studies

Trial MK-1654-007, which is being conducted in participants at increased risk for severe RSV disease, was ongoing at the time of this BLA submission. An interim clinical study report, which included approximately 600 participants with 240 days of follow-up in RSV Season 1, was submitted to the original BLA. Therefore, the Applicant requested a deferral for the final clinical study report for Trial MK-1654-007, which will include the results from all participants in RSV Season 1 and RSV Season 2. A Pediatric Research Equity Act postmarketing requirement (PMR) will be issued for the submission of the final clinical study report for Trial MK-1654-007.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

MK-1654 (clesrovimab) is not indicated for use in females of reproductive potential and in vivo DART studies were not performed. There were no signs of developmental or reproductive toxicity in the 2-week GLP repeat-dose toxicology study in Wistar Han rats and no clinically significant binding was observed in the GLP TCR studies with human adult, juvenile, and neonatal tissues.

9. Product Quality

Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761432 for ENFLONSIA (clesrovimab-cfor) manufactured by Merck Sharp & Dohme LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of ENFLONSIA (clesrovimab-cfor) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

9.1. Device or Combination Product Considerations

Device constituent parts of the combination product are approvable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The Applicant confirms that “clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate

Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed."

The results of the clinical sites inspections support the conclusion that the trials were conducted adequately, and the data generated support the proposed indication. A total of five clinical sites (Drs. Baker, Zar, Franckling-Smith, Etchegaray, and Novoa Pizarro), as well as the Applicant (Merck Sharp & Dohme, LLC) were inspected in support of BLA 761432. The sites were selected for inspection based primarily upon enrollment of large numbers of trial participants, high treatment responders, and insufficient domestic data. The clinical investigator inspections covered Protocols MK-1654-004 (Drs. Baker, Zar, Etchegaray, and Novoa Pizarro) and MK-1654-007 (Dr. Franckling-Smith), and the Applicant inspection covered both protocols. See Section 22 for additional details regarding clinical site inspections.

The Applicant adequately disclosed financial interests/arrangements with clinical investigators (see Section 25) as recommended in the FDA guidance for industry *Financial Disclosure by Clinical Investigators* (September 2018) and by 21 CFR 54.4. The Applicant provided financial disclosure information for 99.9% of the investigators (2160 of 2162) in Trials MK-1654-004 and MK-1654-007. Review of the financial disclosures did not raise concerns about the integrity of the data. See Section 25 for additional information regarding financial disclosures.

11. Advisory Committee Summary

This Application was not taken to an FDA advisory committee because this drug is not a first in class and the Application did not raise significant safety or efficacy issues that were unexpected and there were no controversial issues that would benefit from discussion by an advisory committee.

III. Additional Analyses and Information

12. Summary of Regulatory History

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck) established a pre-investigational new drug (PIND) 130097 file on July 29, 2016, with the submission of a Type B, PIND meeting request for MK-1654, a recombinant human IgG1 monoclonal antibody that targets the antigenic Site IV of the RSV fusion (F) protein and contains YTE substitutions. Merck's submission included plans to develop MK-1654 for the prevention of hospitalizations and medically attended lower respiratory tract infections caused by RSV A and B strains in infants. The purpose of the meeting was to obtain the Agency's agreement that the nonclinical toxicology studies could be used to support development of MK-1654 through Phase 3 and to discuss the overall proposed clinical development program, including the design of the Phase 1a first-in human trial and pediatric Phase 1b/2 and Phase 3 trials.

In the Agency's September 27, 2016, Written Response Only (WRO) correspondence, the Agency agreed that the nonclinical toxicology studies are of the type needed to characterize the safety profile of MK-1654 through Phase 3. In addition, the Agency agreed that the safety, tolerability, and pharmacokinetic data from the Phase 1a trial in healthy adults could be used to support a Phase 1b/2a trial in infants. However, the Agency disagreed with the pediatric population that was proposed to be enrolled in the Phase 1b/2a dose ranging trial. Instead, the Agency recommended evaluation of MK-1654 in infants born at >29 weeks to ≤35 weeks gestation since this population is at increased risk of RSV LRTD due to prematurity. In addition, the Agency recommended Merck conduct separate Phase 1 and/or Phase 2 trials; at least one trial should be a dose-finding trial in infants. It was also recommended that trials in term infants should only be conducted after Merck had obtained adequate safety data from trials conducted in the greater than 29 weeks to at least 35 weeks gestation patient population.

On December 7, 2016, Merck submitted IND 130097 for MK-1654 for the prevention of RSV infection in infants. The Agency placed the application on full clinical hold on January 6, 2017, due to the potential risk of cytokine release syndrome (based on demonstration of release of interleukins induced in human white blood cells in an in vitro cytokine release assay).

On February 24, 2017, Merck submitted a Type A meeting request to discuss their approach to addressing the clinical hold issues. The Agency's preliminary comments were sent on March 20, 2017, and a teleconference was held on March 22, 2017. Merck and the Agency reached agreement on the design of additional cytokine release studies that would be needed to address the Agency's concerns. In addition, agreement was reached on the design of a Phase 1 trial in healthy adult volunteers.

On April 12, 2017, Merck submitted a complete response to the clinical hold. On May 11, 2017, the Agency removed the full clinical hold and imposed a partial hold, informing Merck that studies with MK-1654 could only proceed in adult participants.

On October 13, 2017, Merck submitted a complete response to the partial clinical hold. Following review of additional cytokine data that showed no difference in cytokine levels between the clesrovimab group and various comparator groups when using clinical grade

clesrovimab rather than research grade clesrovimab, the Agency removed the partial hold on November 9, 2017.

On July 5, 2018, Merck submitted a request for Fast Track designation, and on August 27, 2018, the Agency granted Fast Track designation to MK-1654 for the prevention of RSV in infants.

On April 16, 2019, Merck submitted a Type C Written Response Only Meeting request to discuss their revised pediatric development plans. In the June 12, 2019, WRO correspondence, the Agency agreed with the trial design concept sheet for the Phase 2b/3 trial, Trial MK-1654-004, which included a lead-in safety cohort. In addition, the Agency agreed with the trial design concept sheet for a Phase 3 trial that will evaluate the safety and efficacy of MK-1654 against RSV-associated hospitalization in preterm and term infants and strongly recommended collection of information on RSV-associated MALRI in addition to RSV-hospitalization. The Agency disagreed with Merck's trial design concept sheet for a Phase 3 pharmacokinetics and safety trial that would evaluate MK-1654 and palivizumab in a population eligible (preterm and term infants) to receive palivizumab without evaluating efficacy. The Agency noted that the efficacy of both MK-1654 and palivizumab for prevention of RSV-associated MALRI should be assessed as a secondary endpoint. The Agency agreed with Merck's plan to study a second dose of MK-1654 in participants with chronic lung disease or chronic heart disease who are eligible for palivizumab in their second RSV season. To assess safety and efficacy trends, it was recommended that the trial be designed as a blinded, randomized, controlled trial during both years, with information on MALRI collected in both years.

On September 13, 2019, Merck submitted an MIDD meeting request to discuss the use of MIDD approaches for the Phase 2b/3 dose selection and trial design. Preliminary comments for the initial meeting were sent on February 14, 2020, and the initial meeting was held on February 20, 2020. The FDA requested clarification on the proposed dose determination strategy and the single dose for infants of all weight and ages and requested a sensitivity analysis and model comparisons. Merck clarified that they plan to conduct Trial MK-1654-004 first followed by Trial MK-1654-007. The preliminary comments for the follow-up meeting were sent on June 25, 2020, and the follow-up teleconference was held on June 29, 2020. The Agency agreed with Merck's analysis used to justify their dose selection plan for Trials MK-1654-004 and MK-1654-007 for Season 1 and the Agency agreed with the extrapolation approach for infants at risk (i.e., palivizumab-eligible infants) and sparse PK sampling plan.

On January 27, 2020, Merck submitted a Type C meeting request to discuss and reach agreement on their revised Phase 2b/3 and Phase 3 programs and to obtain additional clarification from the Agency on feedback that was provided in the June 12, 2019, WRO correspondence. The Preliminary Comments correspondence was sent on April 1, 2020, and the teleconference was held on April 14, 2020. Agreements were reached on Merck's plan to increase the number of pediatric participants enrolled in MK-1654-004 to 3300; the plan for collecting AEs and monitoring plans for hypersensitivity and anaphylaxis for Trials MK-1654-004 and MK-1654-007; the blinding strategy for the palivizumab-controlled trial (Trial MK-1654-007); and the revised definition of MALRI. The Agency agreed that neonates from birth to 2 weeks of age could be enrolled in Trials MK-1654-004 and MK-1654-007, however, they recommended that enrollment of these participants be initiated during the Phase 3 portion of Trial MK-1654-004. Given the rapid changes in this population, the Agency requested Merck conduct subgroup analysis for safety, pharmacokinetics, and efficacy by age group. The Agency noted that the

inclusion of data from the secondary endpoint in Trial MK-1654-004 in the Prescribing Information will be a review issue.

On July 1, 2020, Merck submitted an initial Pediatric Study Plan (iPSP) and the agreed iPSP was issued on December 30, 2020. Per the agreed iPSP, Merck will submit an assessment for infants who are entering their first RSV season, and infants and children less than 2 years of age at increased risk for severe RSV disease, entering their second RSV. A partial waiver for other pediatric age groups will be requested.

On August 25, 2020, Merck submitted a Type C, WRO meeting request to obtain Agency feedback on their chemistry, manufacturing, and controls (CMC) plans for the MK-1654 product that will be used in the Phase 2b/3 clinical trials (vial presentation) and the to-be marketed dosage form (prefilled syringe). In the November 6, 2020, WRO correspondence, the Agency concurred with Merck's analytical comparability plans for Process 1 versus Process 2 and the vial presentation versus the prefilled syringe presentation, drug substance container closure system, new manufacturing site, and container closure system for the to-be marketed presentation, i.e., the prefilled syringes. To support the use of the prefilled syringe presentation, Merck was informed that they would need to conduct a human factors study.

On October 21, 2020, Merck submitted a request for preliminary breakthrough therapy Designation Request Advice. During the November 5, 2020, teleconference, the Agency agreed that the preliminary or interim efficacy results from Trial MK-1654-002 should be submitted with the request for breakthrough therapy designation.

On July 14, 2021, Merck submitted a Type C meeting request to discuss their antidrug-antibody sample collection and testing plans, dosing regimen for Trial MK-1654-007, and the safety database to support licensure. Preliminary comments were sent on September 15, 2021, and the teleconference was held on September 23, 2021. Merck agreed to incorporate the Agency's recommendations for blood serum collection in the ADA sample collection plan. Agreement was reached on the use of the PK liquid chromatography–mass spectrometry assay, ADA assay, and RSV serum neutralizing activity method data to inform the neutralization activity of MK-1654 in Trials MK-1654-004 and MK-1654-007. Agreement was reached on the administration of a single 210-mg dose of MK-1654 for the second RSV season prophylaxis in high-risk participants enrolled in Trial MK-1654-007. In addition, participants who received 100 mg of Process 1 manufactured material could be included in the safety data base provided the exposures are similar to the 105 mg (Process 2 material) dose.

On July 27, 2021, the Applicant submitted a proposed use-related risk analysis and justification for not submitting human factors validation study results. The Agency later concluded, and the Applicant was notified on November 10, 2021, that a HF validation study was not needed to support the use of the prefilled syringe presentation.

On October 26, 2022, Merck submitted a Type C WRO, meeting request to discuss their CMC plans for the MK-1654 prefilled syringe presentation (to-be-marketed presentation). In the January 9, 2023, WRO correspondence, the Agency provided feedback on the drug product Process Performance Qualification plan, the overall comparability plan to support the changes associated with the plan to market prefilled syringes instead of product supplied in vials and the combination product assembly Process Performance Qualification proposal.

On August 29, 2023, Merck submitted a type C WRO meeting request to gain additional feedback on nonclinical, clinical, and regulatory issues associated with their future BLA submission. In the November 9, 2023, WRO correspondence, the Agency agreed that the completed nonclinical safety studies appeared sufficient to support a BLA submission and that a clinical PK comparability study may not be needed if the analytical comparability data supported bridging between the Phase 2b/Phase 3 product provided in vials and the to-be-marketed prefilled syringe product. In addition, the Agency generally agreed that the data from Trial MK-1654-007 could be included in the original BLA and that an amended iPSP should be submitted for review.

On February 29, 2024, Merck submitted an amended iPSP. On September 20, 2024, the Agency issued an agreed-amended iPSP that included an assessment for neonates and infants who are born during or entering their first RSV season and infants and children up to 2 years of age who remain vulnerable to severe RSV disease in their second RSV season. In addition, Merck planned to submit a request for a deferral for submission of the final study reports for Trial MK-1654-007 and Trial MK-1654-004 and a request for a waiver from evaluating MK-1654 for all remaining pediatric patient populations.

On March 20, 2024, Merck submitted a request for proprietary name review. On September 13, 2024, the proposed name was deemed unacceptable because the name was vulnerable to medication errors due to name confusion with an approved product.

On June 13, 2024, Merck submitted a Type B pre-BLA meeting request to reach agreement on the content and format of their BLA. Preliminary comments were sent August 20, 2024, and the teleconference was held on August 23, 2024. The Agency agreed that the clinical data obtained to date could be used to support the BLA. While foreign data from Trials MK-1654-004 and MK-1654-007 could support use of MK-1654 in the U.S. patient population, additional subgroup analysis of efficacy and safety would be needed. Agreements were reached on the clinical virology data, the content and format of the Safety Update Report, the content of the Integrated Summary of Safety (as well as the content and timeline for submitting the pooled analysis reviewer's guide), and the overall content and format of Modules 1 through 5. The pooled analysis reviewers guide could be submitted within 30 days of receipt of the final BLA submission as a Clinical – Late Component.

On July 2, 2024, Merck notified the Agency of their intent to submit the BLA for clesrovimab-cfor (MK-1654) with a Tropical Disease Priority Review voucher.

On October 10, 2024, BLA 761432 was submitted for clesrovimab-cfor, injection for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season (b) (4) .

The BLA was filed on December 6, 2024, and granted a priority review. The Filing Review Issues Identified letter included a list of virology and clinical pharmacology potential review issues. The Prescription Drug User Fee Act goal date for BLA 761432 is June 10, 2025.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The nonclinical safety studies conducted to support MK-1654 (clesrovimab) were originally submitted to and reviewed under IND 130097. All pertinent studies were also submitted to the present BLA and are reviewed in this section.

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

MK-1654 is a human anti-RSV F protein IgG1 monoclonal antibody. It is identical to its predecessor, RB-1, except for YTE substitutions in its Fc region (M252Y/S254T/T256E) which increases neonatal Fc receptor binding affinity and serum half-life. MK-1654 and RB-1 bind to the same epitope on the F protein with similar affinities. MK-1654 demonstrated antiviral activity in cotton rats, and the breadth of activity has been demonstrated across temporally distinct RSV isolates. See the virology review (refer to Section 18) for more information.

13.1.1.2. Secondary Pharmacology

The binding affinity of MK-1654 to human and rhesus monkey red blood cells and platelets was evaluated in vitro. MK-1654 binding was similar to controls in both cell types and species at the concentrations and conditions tested. No binding of clinical concern to red blood cells and platelets was observed.

13.1.1.3. Safety Pharmacology

Safety pharmacology of MK-1654 was assessed as a component of the GLP 2-week repeat dose toxicology study in Wistar Han rats (Study # TT #16-1029). In that study, functional observational battery performed on the first six males from each IV group, approximately 1 hour following the first dose on Day 1, showed no treatment-related adverse effects on functional nervous system parameters at all dose levels tested (up to 300 mg/kg). There was a slight decrease in overall activity (19% and 26% decrease in the number of lines crossed in the 100 mg/kg and 300 mg/kg groups, respectively) during the open-field observations. These findings were within historical control limits and were not associated with other findings, so were considered incidental. In addition, there were no clinical signs nor microscopic findings indicating any MK-1654 related effects on the central nervous system, cardiovascular or respiratory systems in rats. Refer to the GLP 2-week toxicology study review in Section 13.1.2.1 for more information.

13.1.1.4. ADME/PK

Absorption

The pharmacokinetics/toxicokinetics of MK-1654 were evaluated in a GLP 2-week IV and IM repeat-dose toxicology study in Wistar Han rats (Study TT #16-1029), and the toxicokinetic parameters from this study are presented in Section 13.1.2.1.

The pharmacokinetics of MK-1654 were evaluated in single-dose studies in male Wistar Han rats (Study PK006MK1654) and female rhesus monkeys (Study PK002MK1654), with four animals/group administered 3, 10, or 30 mg/kg IV in both rats and monkeys, or 3 mg/kg IM in rats and 10 mg/kg IM in monkeys. The PK parameters for IV and IM dose groups are presented in Table 57 and Table 58. Dose-linear PK parameters were observed for MK-1654 in both male Wistar Han rats and female rhesus monkeys following a single IV dose up to 30 mg/kg. Bioavailability was 90.1% for the 3 mg/kg IM dose in male Wistar rats, and 94.7% for the 10 mg/kg IM dose in female rhesus monkeys. The PK profile of MK-1654 was similar to that of a motavizumab-YTE analog in a 10-day study in male rhesus monkeys with a 10 mg/kg IV dose. An extended terminal half-life of 44.0 days for MK-1654 was observed in human infants (refer to the clinical pharmacology review in Section 14 for more information).

The pharmacokinetics of MK-1654 were also evaluated in female rhesus monkeys (four/group) following single IM doses of four different formulations and lots of MK-1654 (0.5 mL/animal) (Study PK007MK1654). Dosing was conducted on Day 0 and all animals were euthanized on Day 91. The MK-1654 concentrations and formulations for each group are presented in Table 59. The formulations for Groups 1 and 2 appear to be identical to those in Groups 4 and 3, respectively, aside from the difference in toxicology product lots used. PK data are presented in Table 60. Data for all four formulations were similar.

Table 57. PK Parameters Estimates for MK-1654 Following IV and IM Administration in Wistar Han Rats

		Parameter Estimates (Mean ± Standard Deviation)		
Group	Dose (mg/kg)	$AUC_{0\text{-}inf}$ (day*µg/mL)	CL (mL/day/kg)	Vd_{ss} (mL/kg)
1 (IV)	30	3350±190	8.98±0.522	51.6±4.14
2 (IV)	10	1060±157	9.58±1.30	95.5±15.8
3 (IV)	3	352±24.8	8.55±0.615	91.4±27.2
4 (IM)	3	317±49.8	9.64±1.54	96.1±12.8

Source: Applicant table; Study PK006MK1654; page 9 of pharmkin-written-summary
Results presented as "mean ± SD."
Blood (plasma) samples were collected at Day 0 (0.5, 1, 3, 6 h), Day 1, Day 3, Day 5, Day 8, Day 11, and Day 14 postdose.
CL and Vd_{ss} following IM administration represent apparent CL and apparent Vd_{ss}, respectively.
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated from time 0 to infinity; CL, clearance; h, hour(s); IM, intramuscular; IV, intravenous; MK-1654, clesrovimab; PK, pharmacokinetic; SD, standard deviation; Vd_{ss}, apparent volume of distribution at steady state

Table 58. PK Parameters Estimates for MK-1654 Following IV and IM Administration in Rhesus Monkeys

		Parameter Estimates (Mean ± Standard Deviation)		
Group	Dose (mg/kg)	$AUC_{0\text{-}inf}$ (day*µg/mL)	CL (mL/day/kg)	Vd_{ss} (mL/kg)
1 (IV)	1	329±51.5	3.10±0.511	77.3±20.0
2 (IV)	10	3950±512	2.57±0.345	71.9±10.8
3 (IV)	30	13,500±1440	2.24±0.236	78.1±11.7
4 (IM)	10	4300±998	2.43±0.567	78.1±11.3

Source: Applicant table; Study PK002MK1654; page 10 of pharmkin-written-summary
Results presented as "mean ± SD."
Blood (Serum) samples were collected at Predose, Day 0 (30 minutes and 1, 3, 8 h), Day 1, Day 2, Day 3, Day 4, Day 7, Day 10, Day 14, Day 17, and Day 21 postdose.
CL and Vd_{ss} following IM administration represent apparent CL and apparent Vd_{ss}, respectively.
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated from time 0 to infinity; CL, clearance; h, hour(s); IM, intramuscular; IV, intravenous; MK-1654, clesrovimab; PK, pharmacokinetic; SD, standard deviation; Vd_{ss}, apparent volume of distribution at steady state

Table 59. MK-1654 Formulations Used in the Single IM Dose[a] Monkey PK Study

Group	N/Gender	Test Article	Lot No.
Species: antibody-naïve rhesus monkey			
1	4/F	100.8 mg/mL MK-1654, 10mM histidine, pH 6.0, 7% (w/v) sucrose, 0.02% (w/v) PS80	5017056-0013
2	4/F	163 mg/mL MK-1654, 10mM histidine, 70mM arginine, pH 6.0, 5% (w/v) sucrose, 0.02% (w/v) PS80	5017056-0014
3	4/F	188.8 mg/mL MK-1654, 10mM histidine, 70mM arginine, pH 6.0, 5% (w/v) sucrose, 0.02% (w/v) PS80	5017056-0015
4	4/F	169.1 mg/mL MK-1654, 10mM histidine, pH 6.0, 7% (w/v) sucrose, 0.02% (w/v) PS80	5017056-0016

Source: Applicant table; Study PK007MK1654; page 17
[a] Dose administration will be carried out as intramuscular (IM) injection. Total dose volumes (mL) are fixed to 0.5 mL for each animal.
Abbreviations: F, female; MK-1654, clesrovimab; N, number of animals per group; No., number; PK, pharmacokinetic; PS80, polysorbate 80

Table 60. Pharmacokinetic Parameters Estimates of MK-1654 Following IM Administration of Four Different Formulations to Rhesus Monkeys (Doses Were Normalized to 15 mg/kg)

Group Formulation	$t_{½}$ (Day)	C_{max} (µg/mL)	$AUC_{0\text{-}last}$ (Day·µg/mL)	$AUC_{0\text{-}inf}$ Predicted (Day·µg/mL)	CL (mL/Day/kg)	Vd_{ss} (mL/kg)
1	36.3±7.73	144±17.5	5030±615	6030±907	2.54±0.436	122±18.9
2	38.4±11.4	118±11.3	4530±693	5710±1560	2.76±0.684	144±9.01
3	32.3±3.54	134±16.4	4530±656	5260±796	2.90±0.409	132±17.0
4	37.6±4.24	132±9.62	5270±306	6430±583	2.35±0.209	122±2.84

Source: Applicant table; Study PK007MK1654; page 18
Results presented as "mean ± SD"
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated from time 0 to infinity; $AUC_{0\text{-}last}$, area under the concentration-time curve from time zero to the last quantifiable concentration; CL, clearance; C_{max}, maximum plasma concentration; IM, intramuscular; MK-1654, clesrovimab; SD, standard deviation; $t_{½}$, terminal half-life; Vd_{ss}, volume of distribution at steady state

Biodistribution, Metabolism, and Excretion

The biodistribution of MK-1654 labeled with DyLight™ 650 was characterized in healthy female CD-1 mice for up to 14 days following a single 3 mg/kg IV dose of MK-1654 (PK003MK1654). MK-1654 is predominately located in the intravascular compartment (as evidenced by the volume of distribution at steady state values described in the above tables), with tissue-to-blood ratios lower or approaching 1.0 for most organs except the spleen and the lungs. A slight increase in tissue uptake was observed primarily in the spleen after 14 days (2:1

tissue: blood ratio). No evidence of catabolism was observed in female CD-1 mice following a single 3 mg/kg IV dose of fluorescent-labeled MK-1654. MK-1654 is a protein therapeutic consisting entirely of naturally occurring amino acids and typical proteolytic pathways are expected to be the primary route of catabolism. No metabolism or mass balance excretion studies were conducted per ICH S6(R1) guidance.

In Vivo Stability

Stability and recovery of MK-1654 were similar among human, rhesus monkey, Wistar Han rat and C57BL/6 mouse plasma (~80-90%) after 28 days (Study PK007MK1654).

13.1.1.5. Toxicokinetic Data

Blood samples for toxicokinetic analysis were collected from satellite animals (IV dose groups) 0.25-, 24-, and 72-hours postdose on Day 1, and 0.25, 6, 24, 48, 72, 192, 360, 528, and 696 hours postdose on Day 13. Toxicokinetic parameters for MK-1654 are presented in Table 61. Maximum plasma concentration (C_{max}) values on Day 1 were approximately dose-proportional, while C_{max} and $AUC_{0\text{-}72hr}$ on Day 13 were generally less than dose-proportional. C_{max} values on Day 13 were also slightly higher than on Day 1 (1.2- to 1.6-fold), and time to maximum concentration (T_{max}) values generally peaked around 0.25 hours post-treatment. Serum half-life of MK-1654 was approximately 10.8 to 15.0 days. No substantial differences in exposure were observed between sexes.

Table 61. MK-1654 TK Parameters From the 2-Week Rat Study

		Day 1		Day 13			
Dose (mg/kg)	Sex	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}72hr}$ (µg•Day/mL)	C_{max} (µg/mL)	$t_{1/2}$ (hr)	T_{max} (hr)
30	Female	718±46.2	0.25±NC	1940±ID	1140±180	10.2±ID	0.25±NC
	Male	776±14.2	0.25±NC	2470±ID	1280±23.3	13.2±ID	0.25±NC
	All	747±25.3	0.25±NC	2210±ID	1210±87.2	11.9±ID	0.25±NC
100	Female	2190±ID	0.25±NC	4920±ID	3250±30.6	9.93±ID	0.25±NC
	Male	2530±111	0.25±NC	5800±ID	3870±128	11.6±ID	0.25±NC
	All	2390±115	0.25±NC	5360±ID	3560±151	10.8±ID	0.25±NC
300	Female	6600±103	0.25±NC	8990±ID	7970±103	16.8±ID	0.25±NC
	Male	7650±307	0.25±NC	10,800±ID	9680±262	14.1±ID	0.25±NC
	All	7120±276	0.25±NC	9890±ID	8830±401	15.0±ID	0.25±NC

Source: Applicant tables; Study TT #16-1029; pages 180-181
Abbreviations: $AUC_{0\text{-}72hr}$, area under the concentration-time curve from time 0 to 72 hours; C_{max}, maximum plasma concentration; hr, hour(s); ID, insufficient data; MK-1654, clesrovimab; NC, not calculated; TK, toxicokinetic; T_{max}, time to maximum concentration; $t_{1/2}$, terminal half-life

13.1.2. Toxicology

13.1.2.1. General Toxicology

Study Number/Title

TT 16-1029/Two-Week Intravenous and Intramuscular Toxicity Study in Rats With Functional Observational Battery Followed by a 4-Week Treatment-Free Period

Key Study Findings

- No adverse findings up to highest dose of MK-1654 tested (300 mg/kg/dose, IV).
- In IV groups, decreased neutrophils (~40%) and increased eosinophils (50%) in 300 mg/kg females only at Day 42. Increased ALT (33%) in 100 mg/kg females at Day 42 compared to the control animals.
- Minimal organ weight decreases in IV groups, spleen weight decreased 12% in 300 mg/kg females at Day 16, up to 16% liver weight decrease in 100 and 300 mg/kg females at Day 42, 15% decrease in testis weight in 300 mg/kg males at Day 42. These findings are not considered adverse and are likely incidental.
- MK-1654 was well tolerated at all dose levels at the IV and IM injection sites.
- The NOAEL was determined at 300 mg/kg/day (IV).

Table 62. Study Information of the 2-Week IV/IM Toxicity Study in Rats, TT 16-1029

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	IV (Groups 2 to 5): 0, 30, 100, 300 mg/kg once every 3 days (Days 1, 4, 7, 10, 13) IM (Group 1 and 6): 0, 25 mg/kg on Days 1 & 13
Route of administration:	Intravenous and intramuscular
Formulation/vehicle:	100 mg/mL MK-1654 in vehicle containing 0.698 mg/mL L-histidine, 1.153 mg/mL L-histidine HCl monohydrate, 70 mg/mL sucrose, and 0.20 mg/mL polysorbate 80, pH 6.0.
Species/strain:	Crl:WI(Han) rats
Number/sex/group:	15/sex/group, 10/sex/group euthanized on Day 16 (treatment), 5/sex/group on Day 42 (recovery).
Age:	Approximately 7 weeks.
Satellite groups/unique design:	6/sex/group for IV groups (No. 2 to 5) only/none.
Deviation from study protocol affecting interpretation of results:	The deviations reported did not have a significant impact on the interpretation of the study.

Source: Reviewer analysis
Abbreviations: Crl:WI(Han), Charles River Laboratories Wistar Hannover (rat); GLP, good laboratory practice; HCl, hydrochloride; IM, intramuscular; IV, intravenous; MK-1654, clesrovimab

Table 63. Observations and Results of the 2-Week IV/IM Toxicity Study in Rats, TT 16-1029

Parameters	Major Findings
Mortality	No test article-related deaths were observed.
Clinical signs	Assessed daily on Days 1 to 16, and on each weekday excluding holidays and days of necropsy on Day 17 to 41. No test article-related findings.
Body weights	Assessed prior to treatment and once weekly throughout the study. No test article-related findings.
Ophthalmoscopy	Slit-lamp biomicroscopy and indirect ophthalmoscopy were performed on Day 15 (2 days following the last dose) on all IV group animals. No test article-related findings.
ECG	Not evaluated.
Hematology	Hematology parameters were assessed on Days 12 and 42. Decreased neutrophils (~40%) and increased eosinophils (50%) were observed in 300-mg/kg females only at Day 42 (compared to controls). These findings were considered incidental and unrelated to treatment.
Clinical chemistry	Unremarkable. Fasted blood samples were collected on Days 12, 16, and 42. Clinical chemistry parameters were assessed on Days 12 and 42 only. The following observations were noted: • Increased total protein (4%), albumin (~5%) and globulin (7%; males only) in 300-mg/kg group at Day 12 • Increased ALT (33%) in 100-mg/kg group females at Day 42 • Increased potassium (30%) in 300-mg/kg group females at Day 42 • Decreased phosphorus (19%) in 100 to 300-mg/kg group males at Day 42
Urinalysis	Assessed on Days 12 and 42. No test article-related findings.
Gross pathology	Discoloration in stomach were observed in both treatment and control groups, with slightly higher incidence in high-dose groups. The significance of the stomach discoloration is unknown. All clinical signs and variations in food consumption and body weights were considered incidental and unrelated to treatment.
Organ weights	IV groups: • Spleen, 12% weight decreased in 300-mg/kg females at Day 16 • Liver, up to 16% weight decrease in 100 and 300-mg/kg females at Day 42 • Testis, 15% weight decrease in 300-mg/kg males at Day 42 IM groups: • Decreased ovary weight (13%) in 25-mg/kg females and prostate weight (10%) in 25-mg/kg males at Day 16 • Increased heart (11%) and thymus weight (19%) in 25-mg/kg females at Day 42 These findings were considered incidental and unlikely treatment related.

Parameters	Major Findings
Histopathology Adequate battery: Yes	Microscopic examination was performed on all animals in control and high-dose groups in IV and both control and treatment groups in IM during necropsy on either Day 16 or 42. IV: • Minimal focal congestion in stomach in 0M/1F in HD group at Day 16. Dark/red focal discoloration in glandular mucosa of stomach in 2M/0F in HD group at Day 42 (also 3M/0F controls). • Minimal focal perivascular hemorrhage at injection site in 0M/4F in HD group (also 2M/2F controls). IM: • Minimal-to-mild iliac lymphoid hyperplasia in 6M/5F, and minimal inguinal lymphoid hyperplasia in 1M/1F, in 25-mg/kg dosing group at Day 16. • Minimal subcutis inflammation at injection site in 3M/2F, minimal muscle inflammation at injection site in 6M/3F (also 2M/1F controls), and minimal inflammation in right quadriceps in 0M/1F, all in 25-mg/kg group at Day 16. These findings were considered incidental and unlikely treatment related.
Functional observational battery (FOB)	An FOB was performed on the first six males from each IV groups approximately 1 hour following the first dose on Day 1. There was a decrease in the number of lines crossed (19% in Group 4, 26% in Group 5) during the open-field observations. These findings were within historical control limits and were not associated with other findings, so were considered incidental.

Source: Reviewer analysis
Abbreviations: ALT, alanine aminotransferase; ECG, echocardiogram; F, female; HD, high dose; IM, intramuscular; IV, intravenous; M, male

Study Number/Title

TT 20-9012/Single-Dose Intramuscular Local Tolerability Study in Rats

The objective of this study was to assess the local tolerability of the MK-1654 in the drug product formulation in Wistar Han rats following a single IM administration.

Key Study Findings

- No premature deaths or drug-related finding in clinical signs, body weight, gross pathology and histopathology of the injection sites and draining lymph nodes.
- The no-observed-effect-level is 25 mg/kg. The test article and the drug product formulation are locally tolerated.

Table 64. Study Information of the Single-Dose IM Local Tolerability Study in Rats

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 25 mg/kg, single dose on Day 1 and euthanized on Day 4.
Route of administration:	Intramuscular
Formulation/vehicle:	25 mg/kg MK-1654 (150 mg/mL) in vehicle containing 0.78 mg/mL L-histidine, 1.05 mg/mL L-histidine mono-HCl monohydrate, 50 mg/mL sucrose, 14.75 mg/mL of L-arginine HCl and 0.20 mg/mL polysorbate 80, pH 6.0
Species/strain:	Crl:WI(Han) rats
Number/sex/group:	10
Age:	Approximately 9 weeks old
Satellite groups/unique design:	No
Deviation from study protocol affecting interpretation of results:	The deviations reported did not have a significant impact on interpretation of the study.

Source: Reviewer analysis
Abbreviations: Crl:WI(Han), Charles River Laboratories Wistar Hannover (rat); GLP, good laboratory practice; HCl, hydrochloride; IM, intramuscular; MK-1654, clesrovimab

13.1.2.2. Genetic Toxicology

Genotoxicity studies have not been conducted with MK-1654. In accordance with ICH S6(R1), genotoxicity studies are not needed for biologics as they are not anticipated to interact with deoxyribonucleic acid (DNA) or other genetic material.

13.1.2.3. Carcinogenicity

Carcinogenicity studies have not been conducted with MK-1654. In accordance with ICH S1A and ICH S6(R1), carcinogenicity studies are not needed because MK-1654 will be administered as a single dose. Additionally, MK-1654 binds a nonendogenous foreign virus-specific target that is not expressed in nonclinical species or in humans.

13.1.2.4. Reproductive and Developmental Toxicity

Dedicated in vivo DART studies have not been conducted with MK-1654. In accordance with ICH S6(R1), DART studies are generally not needed for biologics to exogenous targets. In addition, no male or female reproductive toxicities were observed in the 2-week repeat-dose toxicology study in rats (Study TT #16-1029), and no off-target binding was observed in the tissue cross-reactivity studies in any of the adult, juvenile or neonatal human tissues (Study TT #16-9012). Lastly, MK-1654 is not indicated for use in females of reproductive potential.

13.1.2.5. Other Toxicology/Specialized Studies

Evaluation of MK-1654 for Tissue Cross-Reactivity in Normal Human Tissues by Immunohistochemistry (Non-GLP, Study 15-7811)

A preliminary non-GLP tissue cross-reactivity study was conducted in a limited number of normal adult human tissues. No off-target binding of MK-1654 was observed.

A Tissue Cross-Reactivity Study in Normal Adult Human and Select Juvenile and Neonatal Human Tissues (GLP, Study TT 16-9012)

The potential tissue cross-reactivity of MK-1654 was evaluated in cryosections of 36 normal adult human tissues (3 separate adult donors), 20 juvenile human tissues (1 to 4 donors per tissue, where available), and 19 neonatal human tissues (1 to 2 donors per tissue, where available) at concentrations of 2 and 5 μg/mL. Positive (cryosections of EXP1 NJII RSV-F-transfected cells) and negative controls (cryosections of EXP1-293 control cells) produced appropriate responses; the control article (human IgG1 antibody [HuIgG1]) also produced an appropriate response (no binding).

No off-target binding was observed with MK-1654 in any tissue observed under the conditions of this study.

MK-1654: Assessment of In Vitro Cytokine Release Induced by MK-1654 in Human Peripheral Blood Mononuclear Cell and Whole Blood Cell Assays (Study PD005)

An in vitro cytokine release assay in human peripheral blood mononuclear cells (PBMCs) and whole blood was conducted to assess the potential risk of cytokine storm in humans. PMBCs were analyzed using the solid-phase method, while whole blood was analyzed using the soluble-phase method. An analog of theralizumab (TGN1412), a humanized anti-CD28 IgG4 antibody, and an analog of Muromonab-CD3 (OKT3), a mouse anti-CD3 IgG2a antibody, were used as positive controls. Trastuzumab, a human antihuman epidermal growth factor receptor 2 (HER2) IgG1 antibody, was used as a negative control. The concentrations of test and control antibodies ranged from 0.1 to 1000 μg/mL.

MK-1654 did not exacerbate cytokine release in human PBMCs upon exposure to MK-1654 in vitro. Increased release of IL-1β, IL-6, IL-8 and TNF-α release (2 to 4-fold) were observed in human whole blood in vitro following exposure to MK-1654. These increases were similar to those observed with the positive control, TGN1412, but were inconsistent among individual donors. PBMCs with plate-bound MK-1654 is considered a more sensitive assay than human whole blood cell assay. As a follow-up, the Applicant conducted another in vitro cytokine release assay using human whole blood with soluble MK-1654 as requested by the FDA (Study PD007).

MK-1654: Assessment of In Vitro Cytokine Release Induced by a MK-1654 in a Human Whole Blood Cell Assay (Study PD007)

The whole blood cytokine release assay was conducted using soluble clinical-grade MK-1654 instead of research-grade material used in the previous cytokine release assays (Study PD005). Blood from nine healthy human donors were used in this study. The known stimulatory antibodies anti-CD3 (OKT3 analog) and anti-CD28 (TGN1412 analog) were used as positive controls. The innate immune stimulator lipopolysaccharide was also included as a positive control. The therapeutic mAb trastuzumab (anti-HER2), the therapeutic antibody palivizumab (anti-RSV), and a research-grade mAb containing the Fc YTE mutations and targeting a virus unrelated to RSV (anticytomegalovirus YTE) were used as comparators. These comparators have not been associated with cytokine release syndrome in humans.

The positive controls (lipopolysaccharide and the TGN1412 and OKT3 analogs) induced production of multiple cytokines as expected. No differences in cytokine production were observed with MK-1654 up to the highest concentration tested relative to the blood alone and

phosphate buffered saline (PBS) control groups. Further, cytokine levels in the MK-1654 group were similar to those in the palivizumab, trastuzumab (anti-HER2), and anticytomegalovirus YTE antibody comparator groups.

Overall, these data indicated that the risk of cytokine release in human participants with MK-1654 is minimal.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Excipients/Impurities/Degradants

No excipient-related issues with the MK-1654 drug product have been identified. No novel excipients are used in the drug product, and they were also tested in the toxicology study and considered qualified. The qualification of actual and potential impurities that may arise during manufacture and storage of MK-1654 drug substance and product are categorized into process and product impurities and may arise from raw materials, manufacturing, and/or degradation. Product-related impurities include high- and low-molecular-weight species and charged variants. Process-related impurities include host cell protein and DNA, residual (b) (4) endotoxin, and bioburden. Comparison of data from the drug substance and drug product clinical lots to the toxicology lots indicate that the material tested in toxicology studies was comparable to the clinical material, with respect to product quality attributes. Overall, the proposed specifications, or lack of specifications, are considered acceptable from a pharmacology/toxicology perspective.

13.2.2. Extractables/Leachables

From the pharmacology/toxicology perspective, there are no safety concerns regarding extractables/leachables.

The biological risk assessment for the primary container closure system was performed per ISO 10993. The formulation contacting components of the clesrovimab prefilled syringe, the (b) (4) syringe barrel assembly, and the (b) (4) plunger stopper met the established ISO 10993 criteria for the relevant biological safety endpoints including cytotoxicity, sensitization, irritation, systemic toxicity, and materials mediated pyrogenicity.

Controlled studies to characterize potential leachables were performed. Three leachables ((b) (4) up to (b) (4) µg/mL ((b) (4) µg/day), elemental (b) (4) up to (b) (4) µg/mL ((b) (4) µg/day) and (b) (4) up to (b) (4) µg/mL ((b) (4) µg/day) were above the safety concern threshold of 1.5 µg/day as recommended for parenteral products by the Product Quality Research Institute. The Applicant conducted pediatric-specific health risk assessments of (b) (4) based on a literature review. Permitted daily exposure values were derived for all applicable age cohorts, including premature infants, neonates, and older infants using conservative body weights of 0.5 kg, 3.5 kg, and 10 kgs, respectively. The estimated margin of exposures for (b) (4) leachables are considered acceptable (ranged from (b) (4)) for parenteral administration using the most conservative estimates. In addition, the daily exposure to (b) (4) is well below the parenteral permitted daily exposure of (b) (4) µg/day, as

described in ICH Q3D(R2). The daily exposures to [redacted] are also well below the qualification threshold in ICH Q3B(R2) and the [redacted] µg/day level in ICH M7(R2). Therefore, the presence of [redacted] leachables at the observed levels are not a significant safety concern from the pharmacology/toxicology perspective.

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Clinical studies providing clinical pharmacology information of clesrovimab in neonates and infants who are born during or entering their first RSV season are summarized in Table 65.

Table 65. Overview of Clinical and Clinical Pharmacology Trials

Trial	Trial Title	Trial Participants	Dosing Regimen (Single-Dose)
MK-1654-001 (Section 14.2.1) Phase 1	A Single Rising Dose Clinical Trial To Study the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MK-1654 in Healthy Subjects	Healthy adult male participants and women of nonchildbearing potential (WONCBP) (N=114) clesrovimab (N=38) placebo	100 mg (IM) 300 mg (IM) 300 mg (IV) 1000 mg (IV) 3000 mg (IV) Placebo (IV and IM)
MK-1654-002 (Section 14.2.3) Phase 1b/2a	A Double-Blind, Randomized, Placebo-Controlled, Single-Ascending Dose Study To Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1654 in Preterm and Full-Term Infants	Infants with GA either ≥29 to 35 weeks or >35 weeks, chronological age ≥2 weeks to 8 months, and weighing ≥2 kg at the time of screening (N=143) clesrovimab (N=38) placebo	Preterm 20 mg (IM) Preterm 50 mg (IM) Preterm 75 mg (IM) Preterm 100 mg (IM) Full-term 100 mg (IM) Placebo (IM)
MK-1654-003 (Section 14.2.2) Phase 1	A Single Rising-Dose Clinical Trial To Study the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MK-1654 in Healthy Japanese Male Adult Subjects	Healthy Japanese adult male participants (N=33) clesrovimab (N=5) placebo IM (N=6) placebo IV	100 mg (IM) 300 mg (IM) 300 mg (IV) 1000 mg (IV) Placebo (IM or IV)
MK-1654-004 (Section 14.2.4) Phase 2b/3	A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study To Evaluate the Efficacy and Safety of MK-1654 in Healthy Preterm and Full-Term Infants	Healthy male and female infants who had a chronological age from birth up to 1 year and who were entering their first RSV season at the time of consent (N=3614, 2:1)	MK-1654: 105 mg

Trial	Trial Title	Trial Participants	Dosing Regimen (Single-Dose)
MK-1654-007 (Section 14.2.5) Phase 3	A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab- Controlled Study To Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease	Infants and children at increased risk for severe RSV disease (N=896, 1:1)	MK-1654: 105 mg ^ Palivizumab: 15 mg/kg

Source: 2.7.2 Summary of Clinical Pharmacology Studies.
^ Participants randomized to the palivizumab group received 3 to 5 monthly doses of palivizumab in RSV Season 1.
Trial MK-1654-005 (a non-IND RSV challenge study evaluating single IV administration of clesrovimab 100 mg to 900 mg to healthy adults inoculated with experimental RSV) is not included in this review as the objective of the study was not relevant to the proposed indication).
Abbreviations: GA, gestational age; IM, intramuscular; IND, investigational new drug; IV, intravenous; MK-1654, clesrovimab; N, number of participants; RSV, respiratory syncytial virus

Data Supporting Final To-Be-Marketed Formulation and Presentation

Process 1 formulation ((b) (4) mg/mL) was used in the Phase 1 and Phase 2a trials (MK-1654-001, MK-1654-002, and MK-1654-003), and Process 2 formulation was used in the Phase 2b and 3 trials (MK-1654-004 and MK-1654-007). Process 2 formulation consists of a higher clesrovimab concentration (150 mg/mL), to allow for a reduced injection volume of 0.7 mL in infants, and the addition of excipient L-arginine hydrochloride. The associated changes (Process 2 versus Process 1) were bridged by analytical comparability data and further supported by the comparable PK parameters (i.e., observed concentrations and PopPK based dose-normalized $AUC_{0\text{-}150d}$) in Trial MK-1654-002 and Trial MK-1654-004, which did not suggest a significant impact of formulation change on clesrovimab pharmacokinetics.

The intended commercial clesrovimab formulation is identical to the Process 2 formulation except that the commercial formulation is prepared in a single-use, prefilled syringe whereas solution in vial presentation was used in the late-stage clinical trials. The change in the presentations (vial versus prefilled syringe) was bridged by analytical comparability data. This is acceptable from a clinical pharmacology perspective.

14.2.1. Trial MK-1654-001, Healthy Adults

Trial MK-1654-001 is a Phase 1, randomized, placebo-controlled, double-blind, single-ascending-dose trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics (RSV SNA titer) of clesrovimab in healthy adult participants. A total of 152 participants were randomized to receive a single dose of clesrovimab 100 mg IM (n=12), 300 mg IM (n=48), 300 mg IV (n=12), 1000 mg IV (n=30), 3000 mg IV (n=12), or placebo (n=38). IM doses were administered as either a single-bolus injection (100 mg) in vastus lateralis or equally divided bolus injections (300 mg) in either vastus lateralis or deltoid. IV doses were administered as a single infusion over 2.5 hours.

PK Assessment

Serum PK sampling was performed at predose and 0.5, 1, 2.5, 4, 8, 12, 24, 30 hours, and Days 3, 5, 7, 14, 28, 60, 90, 120, 150, 210, 270, and 360 postdose. Serum samples were assayed using a validated high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) method (refer to Section 14.3 for details).

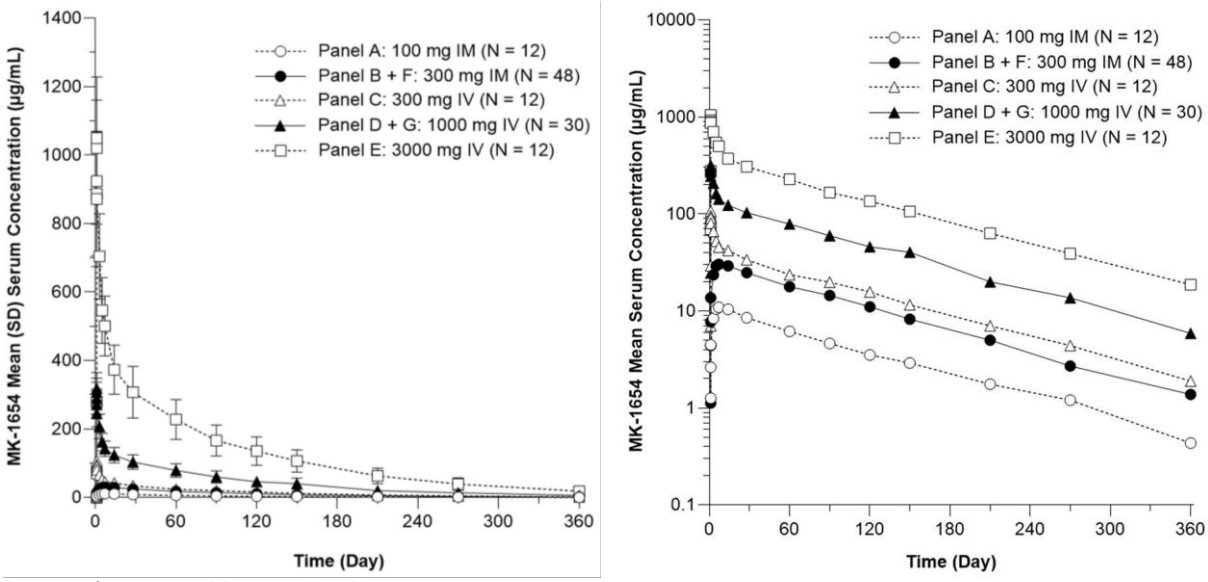
A summary of PK results is shown in Table 66. The mean serum concentration-time profiles of clesrovimab are shown in Figure 9. The observed median T_{max} was 6 days for IM doses and 4 hours for IV doses. The apparent terminal half-life ranged from 73 to 88 days. Clesrovimab C_{max} and $AUC_{0\text{-}inf}$ appeared to increase in a dose-proportional manner following a single IV dose ranging 300 mg to 3000 mg. Based on PK data from 300 mg IV and 300 mg IM cohorts, the absolute bioavailability of clesrovimab was approximately 69% in healthy adults.

Table 66. Clesrovimab PK Parameters Following Single IM or IV Doses in Healthy Adults

					Geometric Mean (% GCV)									
Matrix	**Route**	**Panel**	**Dose (mg)**	**N**	**AUC0-inf (day*µg/mL)**	**AUC0-3d (day*µg/mL)**	**AUC0-59d (day*µg/mL)**	**AUC0-150d (day*µg/mL)**	**Cmax (µg/mL)**	**C90d (µg/mL)**	**C150d (µg/mL)**	**Tmax[a] (day)**	**t1/2 (day)**	**Bioavailability (%)[b]**
Serum	IM	A	100	12	1220 (17.5)	16.9 (29.3)	483 (12.8)	857 (13.0)	11.1 (18.1)	4.59 (15.2)	2.85 (23.1)	5.97 (2.00 - 11.99)	87.6 (14.1)	--
		B+F[c]	300	48	3450 (21.4)	48.2 (33.5)	1380 (18.5)	2520 (18.9)	30.9 (23.2)	14.1 (24.6)	8.03 (23.4)[d]	5.98 (2.00 - 28.96)	78.0 (19.2)	68.9
	IV	C	300	12	5000 (17.0)	221 (13.6)	2100 (12.7)	3670 (14.0)	107 (12.3)	19.5 (18.1)	11.3 (22.3)	0.17 (0.10 - 0.17)	79.8 (13.6)	--
		D+G	1000	30	15100 (33.5)	673 (15.2)	6460 (18.4)	11200 (26.0)	322 (14.4)	55.5 (52.7)	34.5 (93.4)	0.17 (0.10 - 0.33)	72.8 (29.3)	--
		E	3000	12	45000 (30.6)	2280 (16.9)	19800 (18.5)	33300 (23.4)	1050 (15.8)	159 (36.2)	97.1 (59.9)	0.17 (0.10 - 0.17)	83.6 (16.0)	--

Source: Table 2.7.2-rsvmabproph1:1, page 16, Summary of Clinical Pharmacology Studies
[a] Median (Minimum-Maximum).
[b] Bioavailability was calculated by using the following formula: 300 mg IM Geometric Mean $AUC_{0\text{-}inf}$ (Panel B + F, N=48)/300 mg IV Geometric Mean $AUC_{0\text{-}inf}$ (Panel C, N=12).
[c] For one participant in Panel F, the date and time of collection of Day 360 sample indicated it was collected before dosing. Due to the discrepancy, this sample was excluded from analysis.
[d] N=47, as one participant in Panel B had missing concentration data at Day 150. Therefore, C150d was not calculated for one participant.
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated from time 0 to infinity; $AUC_{0\text{-}3d}$, area under the concentration-time curve from Day 0 to 3; $AUC_{0\text{-}59d}$, area under the concentration-time curve from Day 0 to 59; $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; C90d, serum concentration on Day 90; C150d, serum concentration on Day 150; C_{max}, maximum plasma concentration; d, day; GCV, geometric coefficient of variation; IM, intramuscular; IV, intravenous; N, number of participants; PK, pharmacokinetic; T_{max}, time to maximum concentration; $t_{1/2}$, terminal half-life

Figure 9. Mean Serum Concentration-Time Profiles of Clesrovimab Following Single IM or IV Administrations to Healthy Adults



Source: Figure 11-1, CSR MK-1654-001, page 54
Left Panel: Linear Scale; Right Panel: Semi Log Scale.
Abbreviations: CSR, clinical study report; IM, intramuscular; IV, intravenous; MK-1654, clesrovimab; N, number of participants

Nasal epithelial lining fluid PK samples were collected as an exploratory endpoint in the 3000 mg IV cohort to determine partitioning of clesrovimab to nasal mucosa after dosing. The Applicant reported geometric mean serum to nasal mucosal (urea corrected) concentration ratios were 37.4, 32.6, and 30.0 on Days 3, 14, and 60, respectively, following a single IV dose of clesrovimab 3000 mg (Source, Table 11-5 clinical study report MK-1654-001); clesrovimab concentrations in epithelial lining fluid were calculated to be 2.7% (i.e., 1/37.4), 3.1% (i.e., 1/32.6), and 3.3% (i.e., 1/30.0) of the respective serum concentration on Days 3, 14, and 60 following IV administration of clesrovimab 3000 mg.

Immunogenicity

Of the 114 participants who received clesrovimab in Trial MK-1654-001, 3 developed treatment-emergent ADA (1 each in the 300 mg IM, 300 mg IV, and 3000 mg IV dose cohorts). The earliest detection of treatment-emergent ADA after dosing was at Day 120 in a participant from the 3000 mg IV cohort.

14.2.2. Trial MK-1654-003, Healthy Japanese Adults

Trial MK-1654-003 is a Phase 1, randomized, placebo-controlled, double-blind, single-ascending-dose trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of clesrovimab in healthy male Japanese participants. A total of 44 participants were randomized to receive a single dose of clesrovimab 100 mg IM (n=6), 300 mg IM (n=9), 300 mg IV (n=9), 1000 mg IV (n=9), or placebo (IM or IV). IM dosing was administered as either a single (100 mg) or equally divided (300 mg) bolus injections in the vastus lateralis. IV intervention was administered as a single infusion over 2.5 hours.

PK Assessment

Serum PK sampling was performed at predose, and 0.5, 1, 2.5, 4, 8, 12, 24 hours and Days 3, 5, 7, 14, 28, 60, 90, 120, 150, 210, 270, and 360 postdose. Serum samples were assayed using a validated HPLC-MS/MS method (refer to Section 14.3 for details).

A summary of PK results is shown in Table 67. The observed median T_{max} was 6.0 to 9.5 days for IM doses and 2.50 to 4.00 hours for IV doses. The apparent terminal half-life ranged from 76 to 91 days. Clesrovimab C_{max} and $AUC_{0\text{-}inf}$ appeared to increase in a dose-proportional manner following single IM or IV doses. Based on PK data from 300 mg IV and 300 mg IM cohorts, the absolute bioavailability of clesrovimab was about 77.4% in healthy Japanese adults.

Table 67. Clesrovimab PK Parameters Following Single IM or IV Doses in Healthy Japanese Adults

				Geometric Mean (% GCV)					
Matrix	Route	Dose (mg)	N	AUC0-inf (day*ug/mL)	Cmax (ug/mL)	C150d (ug/mL)	Tmax[a] (day)	t1/2 (day)	Bioavailability(%)[b]
SERUM	IM	100	6	1540 (15.0)	11.2 (24.2)	4.05 (11.2)	9.53 (4.02 - 27.09)	90.6 (14.6)	-
		300	9[c]	4170 (19.8)	33.2 (18.4)	9.60 (23.2)	6.03 (0.10 - 13.20)	86.4 (21.0)	77.4
	IV	300	9	5390 (14.4)	112 (9.2)	11.0 (27.8)	0.17 (0.10 - 0.17)	75.9 (18.8)	-
		1000	9	17300 (10.2)	370 (13.3)	36.0 (14.1)	0.10 (0.10 - 0.17)	91.2 (6.9)	-

Source: Table 14.2-9, page 21, CSR MK-1654-003.
[a] Median (Minimum-Maximum).
[b] Bioavailability was calculated by using the following formula: 300 mg IM Geometric Mean $AUC_{0\text{-}inf}$ (N=9) / 300 mg IV Geometric Mean $AUC_{0\text{-}inf}$ (N=9).
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated from time 0 to infinity; C_{150d}, serum concentration on Day 150; C_{max}, maximum plasma concentration; CSR, clinical study report; d, day; GCV, geometric coefficient of variation; IM, intramuscular; IV, intravenous; N, number of participants; PK, pharmacokinetic; T_{max}, time to maximum concentration; $t_{1/2}$, terminal half-life

Immunogenicity

One out of 33 (3.0%) participants who received clesrovimab in Trial MK-1654-003 developed treatment-emergent ADA (100 mg IM cohort). The earliest detection of ADA in this participant was on Day 90 and the maximum titer was detected on Day 210 postdose. This participant with treatment-emergent ADA demonstrated a PK profile comparable to those of ADA-negative participants.

The Applicant developed an adult PopPK model based on data from Trials MK-1654-001 and MK-1654-003. The Applicant stated that IM injection to the arm yielded faster absorption than administration to the thigh with 79.6% higher absorption rate constant (K_a), along with a 17.5% decrease in bioavailability. The PopPK based absolute bioavailability was 77.8% in adults following IM administration to the thigh, which was consistent with the observed bioavailability for individual Trials MK-1654-001 and MK-1654-003. Additionally, race was not identified as a significant covariate in the model after accounting for body weight. The higher concentrations observed in Trial MK-1654-003 could be attributed to the lower median body weights and body mass index in participants in Trial MK-1654-003 than participants in Trial MK-1654-001 (66.9 kg and 22.7 kg/m^2 versus 83.9 kg and 27.4 kg/m^2, respectively) (Merck 2024c). Those results were not verified by the review division, as the relevance of these results to the target population is unclear due to physiological differences between adults and infants (the target population).

14.2.3. Trial MK-1654-002, Dose-Ranging Trial in Preterm and Term Infants

Trial MK-1654-002 was a Phase 1b/2a, randomized, placebo-controlled, single-ascending dose, double-blind trial to evaluate the safety, tolerability, and pharmacokinetics of clesrovimab in healthy preterm and term infants with GA either 29 to ≤35 weeks or >35 weeks, chronological age ≥2 weeks to 8 months and weighing ≥2 kg. A total of 181 infants were randomized and received a single IM dose of clesrovimab (20, 50, 75, or 100 mg) or placebo. Doses were IM administered as either a single bolus injection in the thigh (for the 25 mg and 50 mg cohorts) or divided as two injections, one per thigh (75 mg and 100 mg cohorts). Baseline demographic characteristics for dosed infants in the trial are provided in Table 68.

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Table 68. Demographic and Baseline Characteristics for Dosed Participants

Participants in Population n (%)	20 mg	50 mg	75 mg	100 mg (29-≤35 Weeks)	100 mg (>35 Weeks)	Placebo	Total
Randomized at Day 1	8	31	41	32	33	38	183
Dosed at Day 1	8 (100.0)	31 (100.0)	40 (97.6)	32 (100.0)	32 (97.0)	38 (100.0)	181(98.9)
Gender							
Male	2 (25.0)	16 (51.6)	20 (50.0)	15 (46.9)	19 (59.4)	19 (50.0)	91 (50.3)
Female	6 (75.0)	15 (48.4)	20 (50.0)	17 (53.1)	13 (40.6)	19 (50.0)	90 (49.7)
Age (days)							
n	8 (100.0)	31 (100.0)	40 (100.0)	32 (100.0)	32 (100.0)	38 (100.0)	181 (100.0)
Median	68.0	109.0	93.5	139.5	167.0	128.0	126.0
Range	31 to 257	23 to 255	24 to 245	14 to 239	46 to 250	26 to 275	14 to 275
Race							
Asian	0 (0.0)	1 (3.2)	0 (0.0)	5 (15.6)	0 (0.0)	0 (0.0)	6 (3.3)
African American	4 (50.0)	8 (25.8)	9 (22.5)	14 (43.8)	14 (43.8)	11 (28.9)	60 (33.1)
White	4 (50.0)	20 (64.5)	14 (35.0)	8 (25.0)	11 (34.4)	14 (36.8)	71 (39.2)
Multiple	0 (0.0)	1 (3.2)	16 (40.0)	2 (6.3)	6 (18.8)	9 (23.7)	34 (18.8)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (2.5)	1 (3.1)	1 (3.1)	2 (5.3)	5 (2.8)
Missing[a]	0 (0.0)	1 (3.2)	0 (0.0)	2 (6.3)	0 (0.0)	2 (5.3)	5 (2.8)
Ethnicity							
Hispanic	1 (12.5)	12 (38.7)	24 (60.0)	9 (28.1)	13 (40.6)	18 (47.4)	77 (42.5)
Not Hispanic	7 (87.5)	19 (61.3)	16 (40.0)	23 (71.9)	19 (59.4)	20 (52.6)	104 (57.5)
Gestational age							
29 to ≤35 weeks	8 (100.0)	31 (100.0)	40 (100.0)	32 (100.0)	0 (0.0)	30 (78.9)	141 (77.9)
>35 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	32 (100.0)	8 (21.1)	40 (22.1)
Weight at randomization (kg)							
n	8	31	40	32	32	38	181
Mean	5.2	5.2	5.1	5.9	7.6	5.8	5.9
SD	2.0	2.0	2.0	2.3	1.7	1.9	2.1
Median	4.7	5.3	4.8	6.0	7.6	5.8	5.8
Range	3.1 to 8.1	2.1 to 9.6	2.4 to 9.5	2.2 to 11.7	4.1 to 11.1	2.5 to 9.5	2.1 to 11.7
Weight group at randomization							
2 to <5 kg	5 (62.5)	15 (48.4)	21 (52.5)	12 (37.5)	3 (9.4)	13 (34.2)	69 (38.1)
>5 kg	3 (37.5)	16 (51.6)	19 (47.5)	20 (62.5)	29 (90.6)	25 (65.8)	112 (61.9)

Source: Tables 10-1 and 10-3, CSR MK-1654-002
[a] Includes 5 participants from South Africa who have race reported as “Colored” which is not a standard category on the form.
Abbreviations: CSR, clinical study report; n, number of participants with given characteristic; SD, standard deviation

PK Assessment

Serum PK sampling was performed on Days 7, 14, 90, 150, and 365 postdose. Serum samples were assayed using a validated HPLC-MS/MS method (refer to Section 14.3 for details).

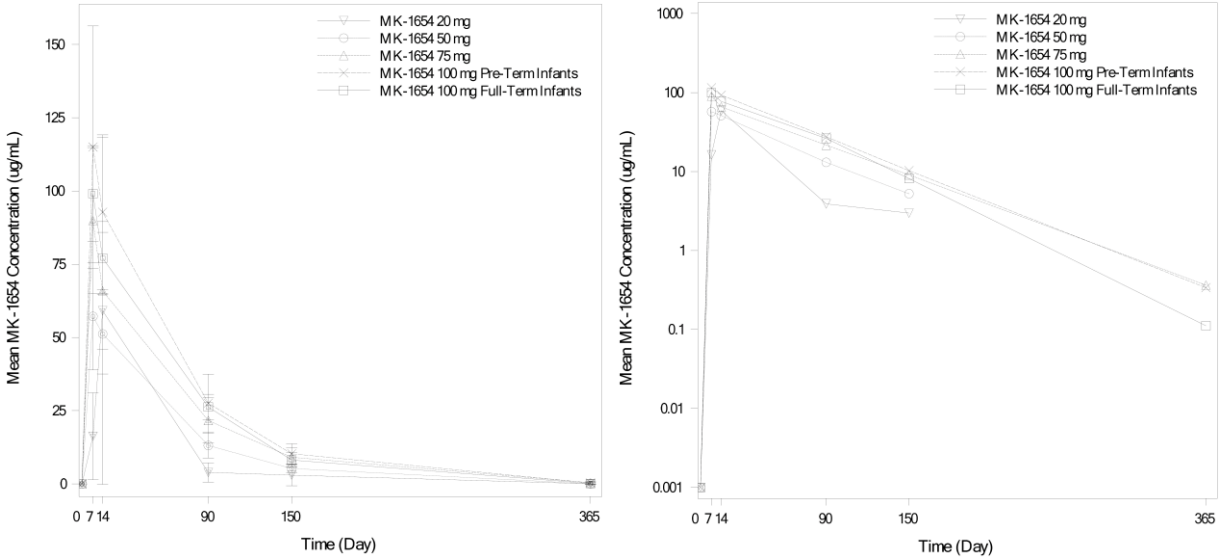
A summary of clesrovimab PK results is shown in Table 69. The mean serum concentration-time profiles of clesrovimab are shown in Figure 10.

Table 69. Clesrovimab PK Parameters Following Single IM Doses, 20 to 100 mg in Infants

				Geometric Mean (%GCV)[a]									
Population	Panel	Total MK-1654 Dose (mg)	n	Cmax (µg/mL)	Tmax[b] (day)	AUC0-inf (day*µg/mL)	AUC0-150 (day*µg/mL)	t1/2 (day)	C7 (µg/mL)	C14 (µg/mL)	C90 (µg/mL)	C150 (µg/mL)	C365 (µg/mL)
Pre-term	A	20	5	26.3 (19.3)	4.00 (3.80 - 4.60)	1560 (43.5)	1370 (32.9)	48.8 (34.6)	24.4 (20.4)	19.4 (22.1)	5.60 (49.5)	2.24 (80.6)	0.0953 (362)
Pre-term	B	50	33	61.7 (21.8)	4.20 (3.70 - 5.30)	3530 (22.8)	3200 (21.5)	44.6 (10.9)	57.8 (21.6)	46.8 (20.6)	13.0 (25.4)	4.98 (34.2)	0.177 (79.4)
Pre-term	C	75	40	94.5 (20.5)	4.20 (3.00 - 5.80)	5510 (22.4)	4950 (20.5)	46.1 (15.1)	88.1 (20.4)	71.1 (19.7)	20.4 (25.8)	8.05 (37.7)	0.313 (107)
Pre-term	D	100	32	117 (23.5)	4.10 (3.70 - 6.00)	6790 (25.4)	6120 (23.6)	45.2 (13.7)	109 (23.0)	88.6 (21.8)	25.2 (28.6)	9.70 (40.2)	0.355 (104)
Full-term	E	100	31	99.9 (13.7)	4.10 (3.70 - 4.90)	5690 (15.9)	5180 (14.6)	43.0 (9.72)	92.8 (13.3)	75.4 (12.9)	21.1 (18.8)	7.96 (26.7)	0.248 (63.1)

Source: Table 14.2-2, CSR MK-1654-002, Page 177.
[a] A PopPK model was used to predict full PK profiles based on sparse observed data, and noncompartmental analysis was performed on simulated profiles to estimate PK parameters for each infant.
[b] Median (min-max)
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated from time 0 to infinity; $AUC_{0\text{-}150}$, area under the curve from time zero to Day 150; n, number of participants in the per-protocol population; C7, C14, C90, C150, C365, serum concentrations on Days-7, 14, 90, 150, and 365, respectively; C_{max}, maximum serum concentration; CSR, clinical study report; GCV, geometric coefficient of variation; IM, intramuscular; max, maximum; min, minimum; MK-1654, clesrovimab; PK, pharmacokinetic; PopPK, population pharmacokinetic(s); T_{max}, time to maximum serum concentration; $t_{1/2}$, terminal half-life

Figure 10. Mean Serum Concentration-Time Profiles of Clesrovimab Following a Single IM Dose to Infants



Source: Figure 11-1, CSR MK-1654-002, page 58
Left Panel: Linear Scale; Right Panel: Semi Log Scale
Abbreviations: CSR, clinical study report; IM, intramuscular; MK-1654, clesrovimab

Immunogenicity

The proportion of infants with ADA to clesrovimab was 13.1% through Day 150, 22.8% through Day 365, and 36.7% through Day 545.

14.2.4. Trial MK-1654-004, Phase 3 Trial in Healthy Preterm and Term Infants

Trial MK-1654-004 is a Phase 2/3, randomized, double-blind, multicenter, placebo-controlled trial to evaluate the efficacy and safety of 105 mg clesrovimab administered as a single IM injection in healthy preterm and term infants born during or entering their first RSV season. Approximately 3300 eligible infants, from birth up to 1 year of age, were randomized in a 2:1 ratio to receive a single dose of clesrovimab or placebo on Day 1. Participants who were either an early or moderate preterm infant (GA 29 to <35 weeks) or a late preterm or term infant (GA ≥35 weeks) were eligible to enroll in the trial. For a detailed description of the design of Trial MK-1654-004, refer to Section 15.1.

PK Assessment

Dosed infants were randomized to one of two serum sampling groups. One group had serum PK samples collected on Day 7, and the other group had serum PK samples collected on Day 240. All participants had serum PK samples collected at predose (Day 1) and Day 150 postdose. Serum samples were assayed using a validated HPLC-MS/MS method (refer to Section 14.3 for details). PK data were included in analyses of PopPK and exposure-response analyses.

Following IM administration of clesrovimab 105 mg, median T_{max} of clesrovimab was approximately 6.7 days, the geometric mean (% coefficient of variation [CV]) $AUC_{0\text{-}150d}$ was 6260 mcg·day/mL (21.2%), C_{max} was 115 mcg/mL (23.3%), and the concentration at Day 150 (C_{150d}) was 10.1 mcg/mL (36.4%).[4] A summary of clesrovimab PK results is shown in Table 70. The mean serum concentration-time profiles of clesrovimab are shown in Figure 11.

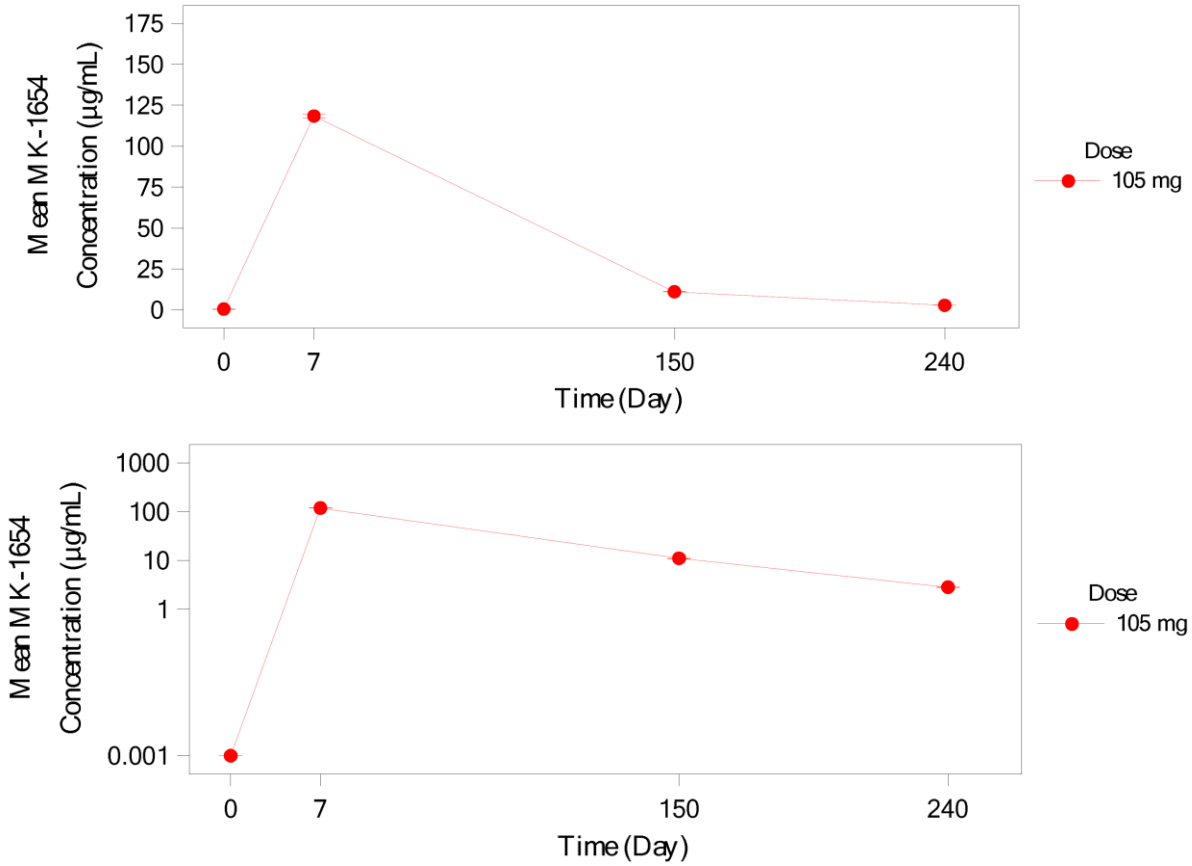
Table 70. Summary of Observed Clesrovimab Serum Concentrations (mcg/mL) Following Administration of a Single IM Dose to Infants

	MK-1654 105 mg (N=2411)		
Time Point	n	Geometric Mean	95% CI [a]
Day 7	1064	108.8	(104.7, 113.1)
Day 150	2107	10.2	(10.0, 10.4)
Day 240	992	2.4	(2.3, 2.5)

Source: Table 14.2-45, CSR MK-1654-004, Page 447.
[a] The 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=number of participants randomized and dosed with MK-1654.
n=number of participants eligible for inclusion in the per-protocol population with a result at the given timepoint.
Abbreviations: CI, confidence interval; CSR, clinical study report; IM, intramuscular; MK-1654, clesrovimab

[4] Infant PopPK Report Table 6-21

Figure 11. Mean Serum Concentration-Time Profiles of Clesrovimab Following a Single IM Dose to Infants



Source: Figure 14.2-7, CSR MK-1654-004, page 448
Top Panel: Linear Scale; Bottom Panel: Semi Log Scale
Abbreviations: CSR, clinical study report; IM, intramuscular; MK-1654, clesrovimab

PK Subgroup Analysis

The serum concentrations of clesrovimab at all timepoints were higher in participants who were <6 months of age than in participants ≥6 months of age at randomization (Table 71). The serum concentrations of clesrovimab at all timepoints were higher in participants who were <5 kg than in participants ≥5 kg at randomization (Table 72).

Table 71. Observed Clesrovimab Serum Concentrations (mcg/mL) by Age Group at Randomization

	<6 Months of Age (N=1923)			≥6 Months of Age (N=488)		
Time Point	n	Geometric Mean	95% CI [a]	n	Geometric Mean	95% CI [a]
Day 7	844	117.2	(112.8, 121.7)	220	82.1	(73.7, 91.4)
Day 150	1696	10.8	(10.6, 11.1)	411	7.9	(7.6, 8.2)
Day 240	787	2.6	(2.5, 2.7)	205	1.7	(1.6, 1.9)

Source: Table 14.2-46, CSR MK-1654-004, Page 449
[a] The 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=number of participants randomized and dosed with MK-1654 in the given age group.
n=number of participants eligible for inclusion in the per-protocol population with a result at the given timepoint.
Abbreviations: CI, confidence interval; CSR, clinical study report; MK-1654, clesrovimab

Table 72. Observed Clesrovimab Serum Concentrations (mcg/mL) by Weight Group at Randomization

	<5 kg (N=863)			≥5 kg (N=1548)		
Time Point	n	Geometric Mean	95% CI [a]	n	Geometric Mean	95% CI [a]
Day 7	386	141.7	(136.2, 147.4)	678	93.7	(88.8, 98.7)
Day 150	759	11.7	(11.3, 12.0)	1348	9.4	(9.2, 9.7)
Day 240	344	2.8	(2.6, 3.0)	648	2.2	(2.1, 2.3)

Source: Table 14.2-47, CSR MK-1654-004, Page 450.
[a] The 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=number of participants randomized and dosed with MK-1654 in the given body weight group.
n=number of participants eligible for inclusion in the per-protocol population with a result at the given timepoint.
Abbreviations: CI, confidence interval; CSR, clinical study report; MK-1654, clesrovimab

Immunogenicity

Refer to Section 14.4.

14.2.5. Trial MK-1654-007, Phase 3 Trial in Infants at Increased Risk

Trial MK-1654-007 is an ongoing Phase 3, multicenter, partially blinded, randomized, palivizumab-controlled trial to evaluate the safety, efficacy, and pharmacokinetics of a single 105 mg IM dose of clesrovimab in palivizumab-eligible infants and children born during or entering their first RSV season. In RSV Season 1, a total of 896 eligible infants received their assigned dose of study intervention (n=446 for clesrovimab and n=450 for palivizumab Day-1). Of the 896 dosed participants, 495 (55.2%) were stratified as neither CLD nor CHD ≥29 weeks GA, 250 (27.9%) as CLD, 101 (11.3%) as CHD, and (50) 5.6% as neither CLD nor CHD <29 weeks GA. The median age was 2.5 months with 89.2% of the participants in the <6-months age range, and the median body weight was 3.3 kg (1.1 to 9.6 kg). For a detailed description of the design of Trial MK-1654-007, refer to Section 15.2.

PK Assessment

Serum PK sampling was performed on Days 7, 150, and 240 postdose. An additional postsurgery PK sample might be collected if the participants received an additional postsurgery dose of clesrovimab. Serum samples were assayed using a validated HPLC-MS/MS method (refer to Section 14.3 for details).

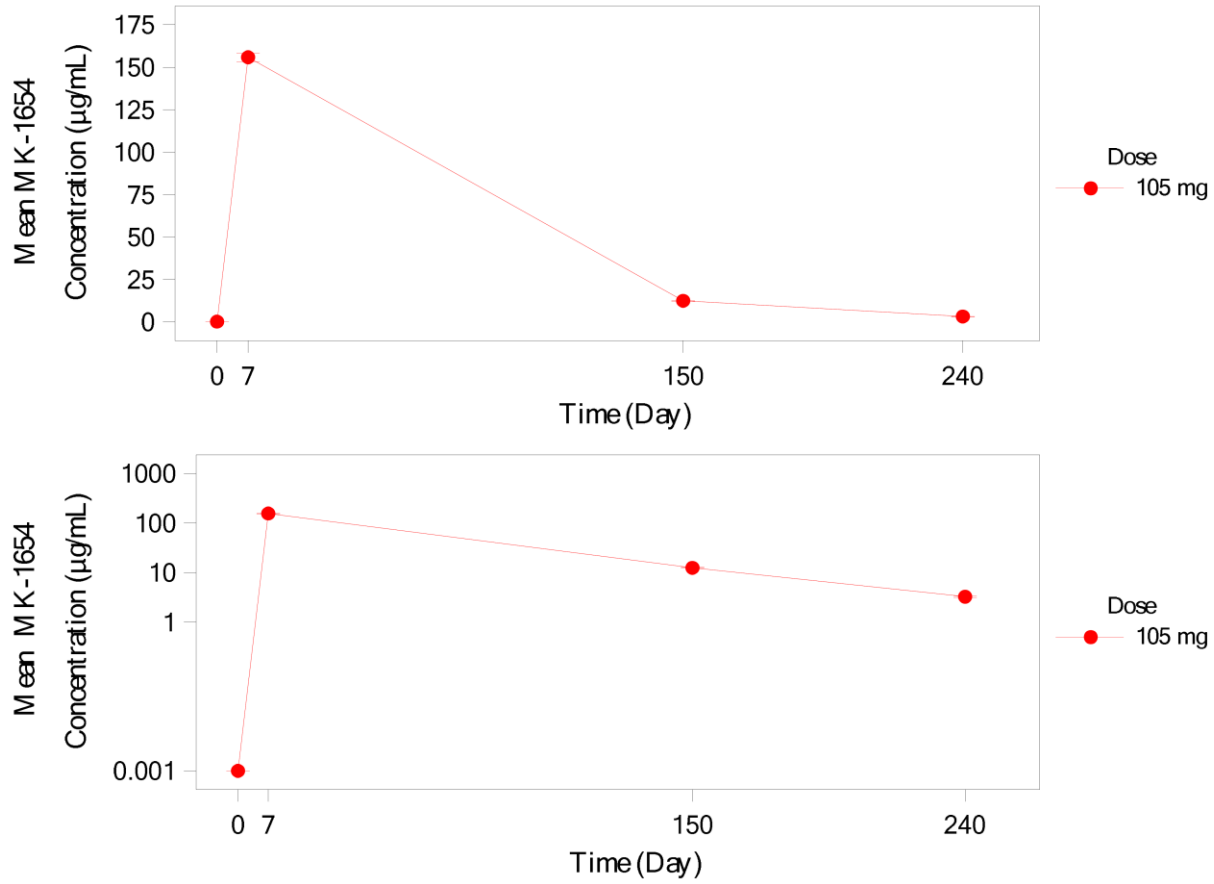
Following IM administration of clesrovimab 105 mg in RSV Season 1, the median T_{max} of clesrovimab was approximately 6.6 days, the geometric mean (%CV) $AUC_{0\text{-}150d}$ was 7740 mcg·day/mL (20.4%), C_{max} was 150 mcg/mL (24.0%), and the concentration at Day 150 (C_{150d}) was 11.5 mcg/mL (35.2%) (Source, Infant PopPK Report Table 6-21). Median $AUC_{0\text{-}150d}$ from Trial MK-1654-007 was approximately 27% higher than in Trial MK-1654-004, when comparing exposures in RSV Season 1. The difference in exposure between studies is due to the lower median body weight associated with the lower median gestational and chronological age in Trial MK-1654-007. A summary of clesrovimab PK results is shown in Table 73. The mean serum concentration-time profiles of clesrovimab are shown in Figure 12.

Table 73. Summary of Observed Clesrovimab Serum Concentrations (mcg/mL) Following Administration of a Single IM Dose to Infants in RSV Season 1

	MK-1654 105 mg (N=446)		
Time Point	n	Geometric Mean	95% CI [a]
Day 7	399	145.4	(138.6, 152.5)
Day 150	301	11.4	(10.7, 12.0)
Day 240	257	2.8	(2.6, 3.0)

Source: Table 14.2-38, CSR Trial MK-1654-007, Page 387
[a] The 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=number of participants randomized and dosed with MK-1654.
n=number of participants eligible for inclusion in the per-protocol population with a result at the given timepoint.
Abbreviations: CI, confidence interval; CSR, clinical study report; IM, intramuscular; MK-1654, clesrovimab; RSV, respiratory syncytial virus

Figure 12. Mean Serum Concentration-Time Profiles of Clesrovimab Following a Single IM Dose to Infants, RSV Season 1, Trial MK-1654-007



Source: Figure 14.2-7, CSR MK-1654-007, page 388
Top Panel: Linear Scale; Bottom Panel: Semi Log Scale.
Abbreviations: CSR, clinical study report; IM, intramuscular; MK-1654, clesrovimab; RSV, respiratory syncytial virus

PK Subgroup Analysis

The serum concentrations of clesrovimab at all timepoints were higher in participants who were <6 months of age than participants ≥6 months of age at randomization (Table 74). The serum concentrations of clesrovimab at all timepoints were higher in participants who were <5 kg than participants ≥5 kg at randomization (Table 75).

Table 74. Observed Clesrovimab Serum Concentrations (mcg/mL) by Age Group at Randomization in RSV Season 1

	<6 Months of Age (N=409)			≥6 Months of Age (N=37)		
Time Point	n	Geometric Mean	95% CI [a]	n	Geometric Mean	95% CI [a]
Day 7	368	148.7	(141.4, 156.4)	31	111.2	(101.8, 121.3)
Day 150	275	11.7	(11.0, 12.4)	26	8.5	(6.8, 10.7)
Day 240	232	2.9	(2.7, 3.2)	25	2.0	(1.5, 2.7)

Source: Table 14.2-40, CSR MK-1654-007, Page 392
[a] The 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=number of participants randomized and dosed with MK-1654 in the given age group.
n=number of participants eligible for inclusion in the per-protocol population with a result at the given timepoint.
Abbreviations: CI, confidence interval; CSR, clinical study report; IM, intramuscular; MK-1654, clesrovimab; RSV, respiratory syncytial virus

Table 75. Observed Clesrovimab Serum Concentrations (mcg/mL) by Weight Group at Randomization in RSV Season 1

	<5 kg (N=349)			≥5 kg (N=97)		
Time Point	n	Geometric Mean	95% CI [a]	n	Geometric Mean	95% CI [a]
Day 7	316	157.0	(148.5, 166.1)	83	108.5	(103.8, 113.3)
Day 150	238	12.0	(11.2, 12.8)	63	9.2	(8.3, 10.3)
Day 240	198	3.0	(2.8, 3.3)	59	2.1	(1.8, 2.5)

Source: Table 14.2-41, CSR MK-1654-007, Page 393.
[a] The 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
N=number of participants randomized and dosed with MK-1654 in the given body weight group.
n=number of participants eligible for inclusion in the per-protocol population with a result at the given timepoint.
Abbreviations: CI, confidence interval; CSR, clinical study report; MK-1654, clesrovimab

Immunogenicity

Refer to Section 14.4.

14.3. Bioanalytical Method Validation and Performance

The current section focuses on review of bioanalytical method used to determine clesrovimab concentrations in serum samples for PK analyses in clinical studies. Three validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods were utilized at several testing facilities during clinical development. A cross-validation was performed demonstrating the comparability of the data generated across the testing sites.

Samples were prepared via protein precipitation followed by trypsin digestion. Stable isotope-labeled clesrovimab was used as an internal standard (ISTD) and was added to the sample prior to the precipitation/digestion steps. A peptide from the variable region of the antibody that resulted from the digestion served as a surrogate for the analyte, with a corresponding peptide from the ISTD serving as a surrogate for the ISTD. The surrogate peptides were analyzed and quantified using the fully validated LC-MS/MS method, which demonstrated acceptable precision and accuracy over a calibration range of 0.500 to 500 mcg/mL. See more details of validation parameters for each method in Table 76. The trial sample analyses met precision and accuracy acceptance criteria. See in-trial performance in Table 77.

Table 76. Summary of Bioanalytical Method Validation for Determination of Clesrovimab Concentrations in Human Serum

Method Parameters	Method Details		
Method type	HPLC- MS/MS	HPLC- MS/MS	HPLC- MS/MS
Method number	BDTM-000105	(b) (4) 838-19	K654HSP
Validation report	VR-BT00169, 080208	08J5YL, 08J5YV, 08K0BV	08LNKF, 08JC2H (cross-validation)
Testing site	Merck, West Point, PA; Merck Research Lab, Kenilworth, NJ	(b) (4)	
Clinical study supported	MK-1654-001, MK-1654-002, MK-1654-003	MK-1654-004, MK-1654-007	MK-1654004
Bioanalytical study reports	MK-1654-001 (058JT9) MK-1654-002 (08895H) MK-1654-003 (05F4BK)	08LN2K pg. 3710 08LNXJ pg. 878	08LNJK pg. 7667
Biological matrix	*Human serum*	*Human serum*	*Human serum*
Method validation summary			
Validation range (mcg/mL)	0.500 to 500	0.500 to 500	0.500 to 500
Within-run accuracy (all QC concentrations)	%Bias −10.0% to −14.8%	%Actual 90.0% to 115.7%	%Bias −4.7% to 9.0%
Within-run precision (all QC concentrations)	4.2% to 10.1%	4.8% to 10.1%	1.0% to 14.4%
Inter-run accuracy (all QC concentrations)	%Bias −10.4 to −3.0%	%Actual 102.0 to 105.7%	%Bias −1.3 to 7.0%
Inter-run precision (all QC concentrations)	≤8.6%	≤8.8%	≤8.9%
Long-term storage stability	761 days at −70°C; 196 days at −20°C	917 days at −80±15°C; 12 days at −25±10°C	402 days at −20±10°C and at −70±10°C;

Source: Summary of Biopharmaceutical Studies, Table 2.7.1: 2, Appendix 1Appendices 1 to 4, and Bioanalytical method validation reports:080208, 08J5YL, 08J5YV, 08K0BV, 08LNKF, 08JC2H
Abbreviations: HPLC, high-performance liquid chromatography tandem mass spectrometry; QC, quality control

Table 77. In-Trial Performance of Method BDTM-000105

Method BDTM-000105

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Bias (%)	CV (%)	Bias (%)	CV (%)	
MK-1654-001	98% (44/45)	-1.8 to 2.0	5.6 to 7.0	0.3 to 5.7	7.1 to 8.4	98% (150/153)
MK-1654-002	97% (37/38)	-4.1 to 2.4	3.7 to 7.5	-1.6 to 2.0	4.6 to 10.8	88% (53/60)
MK-1654-003	100% (17/17)	-5.6 to 2.8	4.2 to 7.9	-0.8 to 7.3	9.3 to 37.6	Not assessed

Method PMRI-1838-19

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Accuracy (%)	CV (%)	Accuracy (%)	CV (%)	
MK-1654-004	95% (142/150)	97.4 to 103.0	2.8 to 5.8	98.2 to 101.0	4.6 to 7.3	99% (417/422)
MK-1654-007	91% (48/53)	97.4 to 102.0	2.5 to 5.5	97.1 to 99.7	4.6 to 6.3	98% (130/132)

Method K654HSP

Study #	Run Acceptance Rate	Std. Curve Performance		QC Performance		ISR Passing Rate (%)
		Relative Error (%)	CV (%)	Relative Error (%)	CV (%)	
MK-1654-004	96% (22/23)	-1.0 to 1.0	3.7 to 6.2	-2.9 to 0.7	4.4 to 6.0	99% (91/92)

Source: Summary of Biopharmaceutical Studies, Appendices 5 to 7
Abbreviations: CV, coefficient of variation; ISR, incurred sample reanalysis; QC, quality control

In addition, dried blood samples from Trials MK-1654-001 and MK-1654-002 were collected and analyzed using an LC-MS/MS method (0802L6) and nasal fluid samples from Trial MK-1654-001 were collected and analyzed using an electrochemiluminescence immunoassay method (04V3Q3) as exploratory endpoints.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Summary of Findings

Immunogenicity of clesrovimab was assessed throughout clinical development. In Trial MK-1654-004 and Trial MK-1654-007, after receiving 105 mg IM of clesrovimab in RSV-Season 1, 5.7% (120/2112) and 5% (13/291) of participants were ADA-positive (ADA+) on Day 150, respectively; and 12% (124/1033) and 13% (34/261) of participants were ADA-positive through Day 240, respectively. The rates of ADA positivity were generally similar in other trials. There was no identified impact of ADA on pharmacokinetics, pharmacodynamics (RSV serum-neutralizing activity) or safety of clesrovimab during RSV Season 1. While a trend of lower efficacy was observed in ADA-positive participants as compared to ADA-negative (ADA-) participants, the impact of ADA on efficacy cannot be determined due to the low rates of MALRI and ADA.

Overview of the Immunogenicity Assessment

The current submission provides immunogenicity data up to Day 515 in Trial MK-1654-004 and Day 240 in Trial MK-1654-007. The evaluation of the impact of immunogenicity on the pharmacokinetics of clesrovimab relied on timepoints with both PK and ADA samples collected (i.e., Days 150 and 240). Table 78 provides an overview of the trial information, the results of ADA incidence, and trial results for pharmacokinetics, for the two trials. ADA-positive is defined as treatment-emergent or treatment-boosted positive.

Table 78. Summary of Trials MK-1654-004 and MK-1654-007 and Immunogenicity Incidence

	Clinical Trial	
Clinical Trial Information	**MK-1654-004**	**MK-1654-007 (Season 1)**
Dosing regimen	A single 105-mg dose, IM	A single 105-mg dose, IM
PK and ADA sampling	Pharmacokinetics: Days 1, 7[a], 150, and 240[a] ADA: Days 1, 150, 240[a], 365[a], and 515[a]	Pharmacokinetics: Day 1, 7, 150, 240 ADA: Day 1, 150, 240 In addition, there is an optional ADA and PK sample at postsurgery follow-up[b]
Trial status and the last timepoint with available data as of the data cutoff date	Ongoing; Data are available up to Day 515	Ongoing; Data are available up to Day 240
No. of participants who received clesrovimab	2411[c]	446[d]
Applicant-reported ADA incidence at Day 150	5.7% (120/2112)[e]	4.5% (13/291)[f]
Applicant-reported ADA incidence through Day 240	12.0% (124/1033)[g]	13.0% (34/261)[h]

Clinical Trial Information	Clinical Trial	
	MK-1654-004	**MK-1654-007 (Season 1)**
Applicant-reported ADA incidence (based on all ADA data of the trial)	22.8% (515/2254)[i]	13.0% (34/261)[h]
Applicant-reported NAb incidence	Not evaluated[j]	Not evaluated[j]
FDA-calculated ADA incidence	22.8% (517/2264)	11.5% (39/338)
FDA-calculated NAb incidence	Not assessed	Not assessed
Clesrovimab concentration (mcg/mL); mean ± SD		
Applicant analysis of clesrovimab concentration[k]	8.3±5.1	8.6±6.3
Day 150 (FDA's analysis)	11.0±4.0 (n=2185)	12.7±5.4 (n=361)
Day 240 (FDA's analysis)	2.8±1.5 (n=1043)	3.8±1.6 (n=280)

Source: Reviewer analysis of the CSR: Integrated Summary of Immunogenicity.
[a] The noted sampling timepoints were not applicable to all the sampling groups. The trial assigned participants into four different blood sampling groups (i.e., 1a, 1b, 2a, and 2b). All participants had ADA and PK samples collected at predose on Day 1 and on Day 150. A subgroup of participants (assigned to Group 2b) had ADA and PK samples collected on Day 240. Only groups 1a and 2a have additional ADA samples collected on Days 365 and 515.
[b] Additional blood samples may be collected based on Applicant consultation if participants underwent extracorporeal membrane oxygenation (ECMO) or surgical intervention for congenital heart disease.
[c] Table 10-1 (page 53) in CSR of Trial MK-1654-004
[d] Table 10-1 (page 66) in CSR of Trial MK-1654-007
[e] Table 14.2-49 (page 452) in CSR of Trial MK-1654-004
[f] Table 14.2-43 (page 396) in CSR of Trial MK-1654-007
[g] Table 14.2-50 (page 453) in CSR of Trial MK-1654-004
[h] Table 14.2-44 (page 397) in CSR of Trial MK-1654-007; the denominator is the numbers of participants with a Day 240 result.
[i] Table 14.2-48 (page 451) in CSR of Trial MK-1654-004; ADA status is defined based on available ADA results at any of the timepoints in the trial.
[j] The Applicant did not develop a NAb assay. The Applicant proposed using a serum-neutralizing antibody (SNA) as a PD biomarker to evaluate the PD response of the drug and rely on SNA to analyze the relationship between PK and PD response.
[k] The results were calculated using the clesrovimab concentrations at Days 150 and 240 in the adpc dataset.
Abbreviations: ADA, antidrug antibody; CSR, clinical study report; IM, intramuscular; n, number of participants in treatment group; Nab, neutralizing antibody; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation

Highlights of Key Characteristics of Immunogenicity Assays Relevant to This Review

Table 79 provides an overview of the trial information, the results of ADA incidence, and trial results for pharmacokinetics, for the two trials. ADA-positive (ADA+) is defined as treatment-emergent or treatment-boosted positive. The Applicant used one ADA assay for the analysis of immunogenicity samples in Trials MK-1654-004 and MK-1654-007. The ADA assay was validated at two sites. The ADA assay at both analytical sites evaluated drug tolerance using the recommended concentration (100 ng/mL) of positive control. All postdose ADA samples at Day 150 and Day 240 contained clesrovimab concentrations lower than the drug-tolerance level validated at 100 ng/mL. Therefore, the ADA assay is considered adequate in terms of drug tolerance and can reliably detect ADA to clesrovimab. Table 80 contains the key assay characteristics for the ADA assay that are relevant to the clinical pharmacology review of the immunogenicity data. The Applicant did not develop a NAb assay. In lieu of a NAb assay, the Applicant proposed using a SNA as a pharmacodynamic (PD) biomarker to evaluate the PD response of the drug and to analyze the relationship between PK and PD response, which was accepted by the review team.

Table 79. Key ADA Assay Characteristics Related to Current Immunogenicity Assessment

Trial Number	MK-1654-004	MK-1654-007	
Validation report number (bioanalytical site)	SH-M14-R3735 (b) (4)	2282-14666 (b) (4)	
Method	*Electrochemiluminescent immunoassay (ECLIA)*		
Drug tolerance	700 mcg/mL, at 100 ng/mL of PC	400 mcg/mL, at 100 ng/mL of PC	
Percentage of samples with clesrovimab concentration > drug tolerance[a]	0.0%	0.0%	0.0%

Source: Reviewer analysis.
[a] The assessment was conducted using PK samples that are time-matched with the corresponding ADA samples at Days 150 and 240.
Abbreviations: ADA, antidrug antibody; PC, positive control; PK, pharmacokinetic

Impact of Immunogenicity on Pharmacokinetics of Clesrovimab

To evaluate the impact of immunogenicity on pharmacokinetics, the observed clesrovimab concentrations were compared between the ADA-positive (ADA+) versus ADA-negative (ADA-) groups, for participants with time-matched PK and ADA data in Trials MK-1654-004 and MK-1654-007, using the immunogenicity specimen (IS) tool developed by the Office of Clinical Pharmacology. At each timepoint, the clesrovimab geometric mean concentrations were calculated for ADA+ participants and ADA- participants. The results of the IS tool analysis in Trials MK-1654-004 and MK-1654-007 are presented in Table 80. The geometric mean ratios (ADA+/ADA-) for Day 150 and Day 240 were 0.90 and 0.84 in Trial MK-1654-004, and 0.72 and 0.98 in Trial MK-1654-007, respectively. Figure 13 provides a visual comparison of the clesrovimab concentrations between the ADA+ and ADA- groups.

Table 80. Comparison of Clesrovimab Concentrations by ADA Status at Each Visit

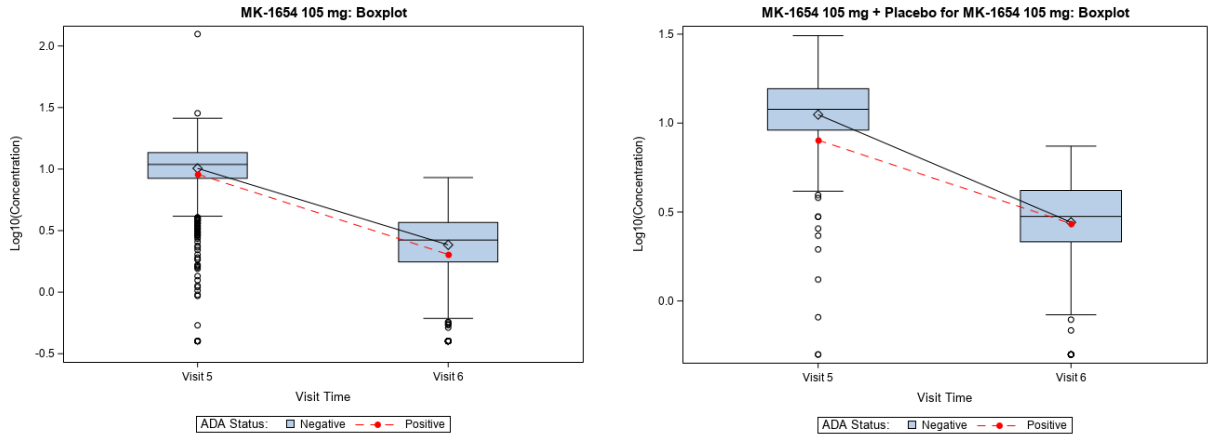
		Geometric Mean Concentration (ng/mL)				ADA+ to ADA- Ratio	
Trial	Timepoint	ADA+ Group	N	ADA- Group	N	GMR	90% CI
MK-1654-004	Day 150	9.088	126	10.134	2020	0.897	(0.835, 0.963)
	Day 240	2.025	108	2.421	924	0.836	(0.754, 0.927)
MK-1654-007	Day 150	8.018	16	11.154	300	0.719	(0.572, 0.903)
	Day 240	2.722	34	2.770	232	0.983	(0.821, 1.176)

Source: Reviewer analysis.
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio, N, number of participants in treatment arm

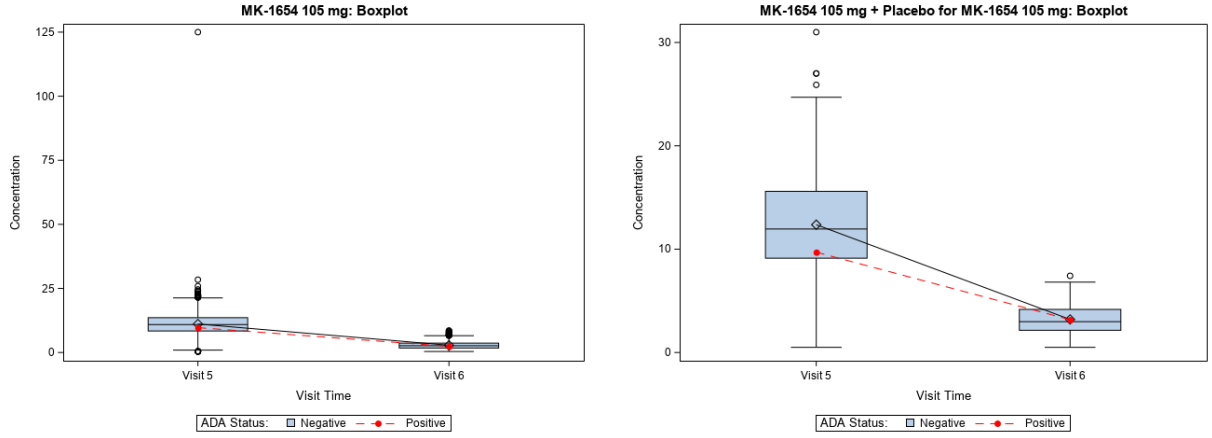
Figure 13. Comparison of Clesrovimab Concentrations (mcg/mL) in ADA-Positive and ADA-Negative Samples in Participants Receiving Clesrovimab Treatment, Trials MK-1654-004 and MK-1654-007

Trial -MK-1654-004 | **Trial MK-1654-007**

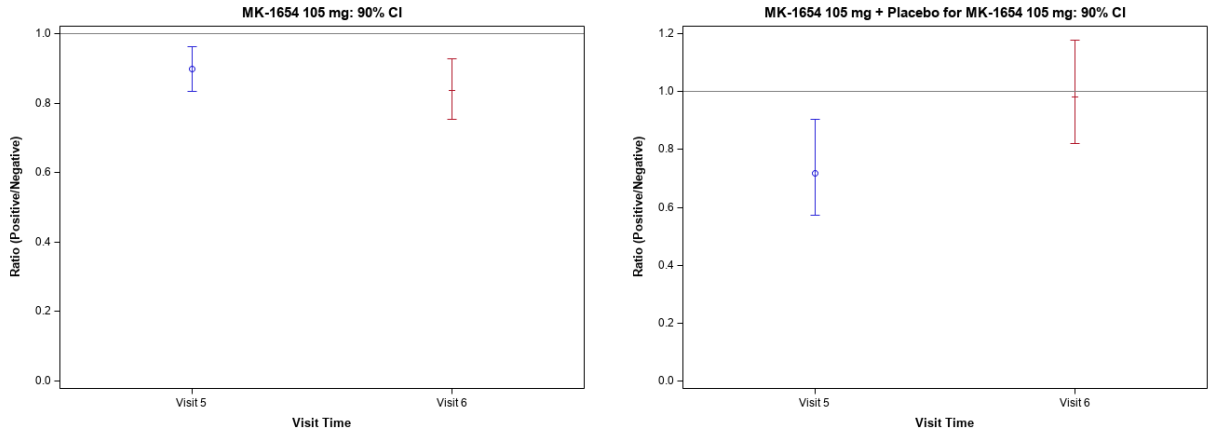
Log scale



Linear scale for y-axis



GMR (ADA+/ADA-) and 90% CI



Source: Reviewer analysis
Upper Panel: semilogarithmic scale; Middle Panel: linear scale; Bottom Panel: 90% CIs of the GMR of clesrovimab concentrations
Visit 5: Study Day 150; Visit 6: Study Day 240
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; MK-1654, clesrovimab

Based on IS tool analysis, among clesrovimab-treated participants with time-matched PK and ADA data in Trials MK-1654-004 and MK-1654-007 Season 1, concentrations in the ADA+ group were 2 to 28% lower compared to the ADA- group. The impact of ADA on clesrovimab pharmacokinetics was also assessed as part of the infant PopPK model. During model development, ADA was evaluated as a time-varying covariate on CL and found not to be significant. Overall, the review team concluded that ADA did not significantly alter the pharmacokinetics of clesrovimab (refer to Section 14.5).

Impact of ADA on Clesrovimab Pharmacodynamics

The impact of ADA on clesrovimab pharmacodynamics was assessed by comparing RSV-A SNA titers by ADA status in Trials MK-1654-004 and MK-1654-007. SNA titer was measured with a cell-based virus reduction neutralization test assay (method TSOP.119.00987) in Trials MK-1654-004 and MK-1654-007, which is acceptable as an assay for exploratory endpoints.

Based on ADA status at Day 150 (Table 81) and through Day 240 (Table 82), the observed SNA titers are comparable between the ADA+ and ADA- groups at all timepoints, with the exception of Day 365, which was higher in the ADA+ group than in the ADA- group. Overall, there was no apparent evidence of changes in pharmacodynamics among ADA+ participants relative to participants who did not develop ADAs during RSV Season 1.

Table 81. Observed RSV A SNA Titers in Season 1 by ADA Status at Day 150 in Trials MK-1654-004 and MK-1654-007

		ADA-Negative at Day 150			ADA-Positive at Day 150		
Trial	Timepoint	N	GMT	95% CI	N	GMT	95% CI
MK-1654-004	Predose	907	259.1	(236.6, 283.6)	52	124.7	(83.3, 186.6)
	Day 7	409	30289.3	(27458.1, 33412.4)	20	17329.3	(7345.0, 40885.7)
	Day 150	911	2474	(2340.2, 2615.5)	58	2384.1	(1927.6, 2948.7)
	Day 240	393	554.3	(504.9, 608.5)	26	668.5	(469.5, 951.9)
	Day 365	457	255.4	(222.6, 292.9)	30	383.6	(189.7, 775.8)
	Day 515	473	223.5	(188.8, 264.4)	31	240.2	(129.8, 444.5)
MK-1654-007	Predose	239	200.7	(161.3, 249.7)	12	90.9	(39.1, 211.2)
	Day 7	244	43324.8	(36937.0, 50817.3)	11	30098.8	(19168.9, 47260.6)
	Day 150	253	3113.4	(2741.6, 3535.7)	13	3608.8	(2308.5, 5641.5)
	Day 240	208	805.3	(713.4, 909.1)	11	490.1	(218.8, 1097.6)

Source: CSR MK-1654-005 Table 14.2-65 and CSR MK-1654-007 Table 14.2-67
Abbreviations: ADA, antidrug antibody; CI, confidence interval; CSR, clinical study report; GMT, geometric mean titer; N, number of participants in treatment arm at given timepoint; RSV, respiratory syncytial virus; SNA, serum-neutralizing antibody

Table 82. Observed RSV A SNA Titers in Season 1 by ADA Status Through Day 240 in Trials MK-1654-004 and MK-1654-007

		ADA-Negative Through Day 240			ADA-Positive Through Day 240		
Trial	**Timepoint**	**N**	**GMT**	**95% CI**	**N**	**GMT**	**95% CI**
MK-1654-004	Predose	391	265.6	(230.5, 306.2)	55	118.7	(81.9, 172.1)
	Day 150	371	2473.5	(2277.6, 2686.3)	51	2132.3	(1683.7, 2700.3)
	Day 240	382	552.1	(502.3, 606.9)	56	703.5	(566.8, 873.0)
	Day 365	204	272.7	(219.1, 339.3)	30	301	(177.9, 509.2)
	Day 515	213	255	(199.2, 326.4)	28	217.9	(113.0, 420.1)
MK-1654-007	Predose	182	169.9	(135.8, 212.6)	31	105.5	(65.2, 170.6)
	Day 7	191	41147.3	(34687.9, 48809.7)	30	41291.8	(33178.0, 51389.7)
	Day 150	185	2918.2	(2474.3, 3441.7)	32	3297	(2472.3, 4396.9)
	Day 240	203	810.5	(711.5, 923.2)	31	844.6	(593.5, 1201.9)

Source: CSR MK-1654-005 Table 14.2-66 and CSR MK-1654-007 Table 14.2-68
Abbreviations: ADA, antidrug antibody; CI, confidence interval; CSR, clinical study report; GMT, geometric mean titer; N, number of participants in treatment arm at given timepoint; RSV, respiratory syncytial virus; SNA, serum-neutralizing antibody

Impact of ADA on Clinical Outcomes

Table 83 summarizes the incidence rates and proportion of participants who had the clinical endpoint disease by ADA status. The incidence rates of RSV-associated disease endpoints were higher in the ADA+ subgroup compared with the ADA- subgroup, in both Trials MK-1654-004 and MK-1654-007. The potential impact of ADA development on the efficacy of clesrovimab is discussed in Section 6.3.5. There was no evidence of a clinical impact of ADA status on the safety profile of clesrovimab.

Table 83. Summary of Incidence Rate for RSV-Associated Disease Endpoints and Proportion of Participants Having RSV-Associated Disease Endpoints by ADA Status in Participants Treated With Clesrovimab, Full Analysis Set Population, Trials MK-1654-004 and MK-1654-007

	ADA+				ADA-			
Endpoint	n	No. of Cases	Proportion of Participants With Endpoint Disease	Incidence Rate Over 5 Months	n	No. of Cases	Proportion of Participants With Endpoint Disease	Incidence Rate Over 5 Months
Trial MK-1654-004								
MALRI150 by ADA at D150	120	14	0.117	0.125	1898	41	0.022	0.125
MALRI150 by ADA through D240	123	11	0.089	0.095	846	12	0.014	0.014
MALRI180 by ADA at D150	120	15	0.125	0.135	1898	43	0.023	0.023
MALRI180 by ADA through D240	123	12	0.098	0.104	846	13	0.015	0.016
Hospitalization150 by ADA at D150	120	3	0.025	0.025	1898	6	0.003	0.003
Hospitalization150 by ADA through D240	123	2	0.016	0.016	846	2	0.002	0.002
Hospitalization180 by ADA at D150	120	3	0.025	0.025	1898	7	0.004	0.004
Hospitalization180 by ADA through D240	123	3	0.024	0.025	846	2	0.002	0.002
Trial MK-1654-007								
MALRI150 by ADA at D150	13	3	0.231	0.256	273	8	0.029	0.030
MALRI150 by ADA through D240	34	3	0.088	0.092	212	7	0.033	0.034
MALRI180 by ADA at D150	13	3	0.231	0.262	273	9	0.033	0.034
MALRI180 by ADA through D240	34	3	0.088	0.092	212	7	0.033	0.034
Hospitalization150 by ADA at D150	13	2	0.154	0.167	273	1	0.004	0.004
Hospitalization180 by ADA at D150	13	2	0.154	0.169	273	2	0.007	0.007
Hospitalization150 by ADA through D240	34	2	0.059	0.061	212	1	0.005	0.005
Hospitalization180 by ADA through D240	34	2	0.059	0.061	212	1	0.005	0.005

Source: CSR MK-1654-004, Tables 14.2-55 to 62; and CSR MK-1654-007 Table 14.2-51 to 54, and 57 to 60
MALRI150 by ADA at D150: RSV-associated MALRI Days 1 to 150 postdose by ADA status at Day 150
MALRI150 by ADA through D240: RSV-associated MALRI Days 1 to 150 postdose by ADA status though Day 240
MALRI180 by ADA at D150: RSV-associated MALRI Days 1 to 180 postdose by ADA status at Day 150
MALRI180 by ADA through D240: RSV-associated MALRI Days 1 to 180 postdose by ADA status though Day 240
Hospitalization150 by ADA at D150: RSV-associated hospitalization Days 1 to 150 postdose by ADA status at Day 150
Hospitalization150 by ADA through D240: RSV-associated hospitalization Days 1 to 150 postdose by ADA status though Day 240
Hospitalization180 by ADA at D150: RSV-associated hospitalization Days 1 to 180 postdose by ADA status at Day 150
Hospitalization180 by ADA through D240: RSV-associated hospitalization Days 1 to 180 postdose by ADA status though Day 240
Abbreviations: ADA, antidrug antibody; CSR, clinical study report; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm with given characteristic; No. number; RSV, respiratory syncytial virus

14.5. Pharmacometrics Assessment

The Applicant's population pharmacokinetics and exposure-response analyses are considered acceptable for describing and predicting clesrovimab exposure in infants from birth to 12 months at enrollment. More specifically, the developed PK and exposure-response models were utilized to support the current submission as outlined below.

Table 84. Utility of the Population Pharmacokinetics and Exposure-Response Modeling

Utility of the Final Model		Reviewer's Comments
Derive exposure metrics and PK parameters	The PK model was used to characterize the pharmacokinetics of clesrovimab in infants (baseline chronological age for birth up to 12 months) entering their first or second RSV season, from three clinical trials (MK-1654-002, MK-1654-004 and MK-1654-007). Time-varying body weight, and maturation function on apparent clearance (based on time-varying adjusted age) were the most clinically relevant covariates on clesrovimab exposure. The PK model was used to derive the individual PK parameters and predict clesrovimab exposure metrics (AUC from 0 to Day 150 or 180 and C_{trough} on Day 150 or 180) after a single 105 mg IM dose of clesrovimab for the first RSV season, to support the exposure-efficacy response analyses.	The PK model reasonably predicted median and individual observed concentrations of clesrovimab and their variability across age and weight groups, and 2 RSV seasons. Accordingly, the model was considered acceptable for generating the exposure metrics of AUC from days 0 to 150 and C_{trough} on Day 150. Antidrug antibody (ADA) status and ADA titer were first measured at Day 150 postdose in clinical trials MK-1654-002, MK-1654-004 and MK-1654-007. ADA status and ADA titer were not found to affect clesrovimab exposure metrics single 105 mg IM dose of clesrovimab for the first RSV season (proposed indication and dosage).

Utility of the Final Model		Reviewer's Comments
Exposure-response analyses to support dosage and Prescribing Information	The final PK model was used to predict exposure metrics used in the exposure-response analyses for efficacy endpoints, including the primary endpoint [RSV-associated MALRI (Days 1 to 150)], and the secondary endpoints [RSV-associated MALRI (Days 1 to 180) and RSV-associated hospitalization (Days 1 to 150)]. The exposure-efficacy analyses did not find a significant relationship between the primary and secondary efficacy endpoints and the exposure metrics, (AUC from 0 to Day 150 or 180), supporting the efficacy of the studied and proposed single clesrovimab dose of 105 mg IM for the first RSV season.	Most of RSV-associated MALRI events in the clesrovimab arm occurred before Day 150 (60 events in 2291 participants with evaluable exposure), with 4 additional events between Day 150 and Day 180. Therefore, exposure-response analyses for the efficacy endpoints up to Day 150 were considered more relevant. Although, no significant relationship was observed between $AUC_{0\text{-}150d}$ and the efficacy endpoints, the reviewer's assessment of the exposure-efficacy relationship for the primary endpoint with C_{trough} on Day 150, as the exposure metric, found a statistically significant trend (p-value of 0.04 for the slope coefficient parameter) between C_{trough} and RSV-associated MALRI (Days 1 to 150). Even though, there was a trend towards statistical significance, the relationship was not considered clinically meaningful to suggest that other doses higher than 105 mg would offer meaningful improvement. This was supported in particular by the largely overlapping C_{trough} values between participants with and without RSV-associated MALRI (Days 1 to 150) event, and the flat relationship when considering the proportion of participants with RSV-associated MALRI (Days 1 to 150) across most of the quantiles of C_{trough} (representing more than 75% of C_{trough} observations), except for eight participants at the highest three quantiles of C_{trough} driving the trend towards statistical significance in the logistic regression. Given the trend of lower exposure in older participants or participants with higher body weight, the reviewer evaluated the exposure-response relationship for RSV-associated MALRI (Days 1 to 150), after adjustment for baseline weight groups or baseline chronological age groups. Weight groups and chronological age were not found to be significant predictors of the exposure-response relationship, no significant difference in the proportion and probability of RSV-associated MALRI (Day 1 to 150) across the clesrovimab exposure ranges (for AUC or C_{trough}) in the different baseline weight and age groups, supporting the efficacy of the single clesrovimab dose of 105 mg IM for the first RSV season.

Source: FDA Reviewer
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; C_{trough}, trough concentration; IM, intramuscular; MALRI, medically attended lower respiratory infection; PK, pharmacokinetic; RSV, respiratory syncytial virus

14.5.1. Applicant's Population PK Analysis

The Applicant developed an infant population PK model to characterize the PK properties of clesrovimab administered IM in preterm and full-term infants through their first or second RSV season. The data for PK modeling were collected from three clinical trials (Table 85), with a Phase 1b/2a trial in healthy preterm and full-term infants (Trial MK-1654-002), a Phase 2b/3 trial in healthy preterm and full-term infants (Trial MK-1654-004), and a Phase 3 trial in preterm and full-term infants and children at increased risk for severe RSV disease (Trial MK-1654-007). Table 86 summarizes clesrovimab dosing and PK sampling from Trials MK-1654-002, MK-1654-004, and MK-1654-007.

The final PK dataset used for the analysis comprised a total of 5831 quantifiable concentrations from 2939 participants. The limit of quantification for clesrovimab was 0.5 mg/L. Below-the-limit-of-quantification samples (N=118) represented about 2% of the PK data, and therefore were excluded from the analysis.

Table 87 summarizes the demographic characteristics of the participants from the trials included in the PK analysis. Most participants (79.5%) were negative for ADAs, with only 8.5% being treatment-emergent positive and 0.2% being treatment boosted positive.

Table 85. Trials Included in the Population PK Analysis

Study ID	Study Title	Study Design	Study Population
MK-1654-002 P002 *(Completed)*	A Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1654 in Pre-Term and Full-Term Infants	Randomized (4:1), double-blind, placebo-controlled, multicenter, single-ascending-dose Study duration: 4 years	Males/females Age: Pre-term infants (born at 29-35 weeks gestational age); Full-term infants (born at >35 weeks gestational age), all with chronological age: 2 weeks to 8 months. Healthy infants
MK-1654-004 P004 *(Ongoing)*	A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Pre-Term and Full-Term Infants	Randomized (2:1), double-blind, placebo-controlled, single dose efficacy study Planned Study duration: 3.5 years	Healthy male/female infants Pre-term (born at 29-<35 weeks GA) Full-term infants (born at ≥35 weeks GA) Postnatal age (Ph 2b): 2 weeks to 12 months Postnatal age (Ph 3): birth to 12 months
MK-1654-007 P007 *(Ongoing)*	A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab- Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease	Randomized (1:1), double-blind, active comparator, study for 1 or 2 RSV seasons Planned Study duration: 3.5 years	Male/female and infants and children up to 1 yr at increased risk for severe RSV disease who are either pre-term (≤35 weeks GA eligible to receive palivizumab) or have CLD/CHD

Source: Applicant's Modeling and Simulation Report (08khn9), Table 3-1, page 27
Abbreviations: CHD, congenital heart disease; CLD, chronic lung disease; GA, gestational age; MK-1654, clesrovimab; RSV, respiratory syncytial virus

Table 86. Clesrovimab Dosing and Pharmacokinetic Sampling

Study ID	Dosing Regimen	Pharmacokinetic/Pharmacodynamic Sampling Strategy
MK-1654-002 P002 *(Completed)*	A single ascending IM dose of clesrovimab or matching placebo in: Pre-term infants: Panel A: 20 mg IM; Panel B: 50 mg IM; Panel C: 75 mg IM; or Panel D: 100 mg IM Full-term infants: Panel E: 100 mg IM	Serum PK samples at predose and postdose either on 1) days 7, 90, 150, 2) days 7, 150, 365, or on 3) days 14, 150, 365 SN samples at predose and postdose either on 1) day 150, 2) days 150, 365, or on 3) days 150, 365, 545
MK-1654-004 P004 (Ongoing)	A single 105 mg IM dose of clesrovimab or matching placebo	Serum PK samples at predose and postdose either on days 7, 150 or on days 150, 240 SN samples at predose and postdose either on days 7, 150, or on days 150, 240; and on days 365 and 515 (only in the first 750 participants continuing in RSV season 2)
MK-1654-007 P007 (Ongoing)	Season 1: a single 105 mg IM dose of clesrovimab or 5 weight-based doses of palivizumb (15 mg/kg) Season 2: a single 210 mg IM dose of clesrovimab	Season 1: • Serum PK samples at predose and postdose on days 7, 150, 240 • SN samples at predose and postdose on days 7, 150, 240 Season 2: • Serum PK samples at postdose on days 7, 150 • SN samples at postdose on days 7, 150

Source: Applicant's Modeling and Simulation Report (08khn9), Table 3-2, page 2
Abbreviations: ID, identifier; IM, intramuscular; PK, pharmacokinetic; SN, RSV serum neutralizing titer; RSV, respiratory syncytial virus

Table 87. Demographic Characteristics of Participants in the Population PK Analysis

Demographic Characteristics	MK-1654-002 (N=141)	MK-1654-004 (N=2305)	MK-1654-007 (N=496)	Overall (N=2942)
Sex, n (%)				
Male	72 (51.1%)	1184 (51.4%)	254 (51.2%)	1510 (51.3%)
Female	69 (48.9%)	1121 (48.6%)	242 (48.8%)	1432 (48.7%)
Age (months)				
Mean (SD)	4.30 (2.42)	3.66 (2.63)	3.11 (2.03)	3.60 (2.54)
Median	4.07	3.02	2.73	3.02
[min, max]	[0.490, 8.39]	[0.0700, 11.9]	[0.200, 12.0]	[0.0700, 12.0]
Adjusted age (months)				
Mean (SD)	3.13 (2.55)	3.11 (2.71)	1.12 (2.01)	2.77 (2.70)
Median	2.75	2.56	0.510	2.20
[min, max]	[-0.990, 8.20]	[-1.68, 11.9]	[-2.00, 11.5]	[-2.00, 11.9]
Gestational age (weeks)				
Mean (SD)	34.9 (2.58)	37.6 (2.67)	31.4 (3.55)	36.4 (3.68)
Median	34.1	38.3	31.6	37.9
[min, max]	[30.3, 41.0]	[29.0, 43.0]	[23.0, 41.1]	[23.0, 43.0]
Baseline body weight (kg)				
Mean (SD)	5.86 (2.21)	5.82 (2.01)	3.76 (1.46)	5.48 (2.08)
Median	5.66	5.80	3.40	5.40
[min, max]	[2.07, 11.7]	[1.70, 11.9]	[1.14, 9.60]	[1.14, 11.9]
Baseline body mass index (kg/m^2)				
Mean (SD)	16.2 (2.93)	16.0 (2.92)	13.7 (2.97)	15.7 (3.05)
Median	16.3	16.1	13.6	15.8
[min, max]	[9.90, 25.6]	[6.80, 45.4]	[0, 33.4]	[0, 45.4]

Demographic Characteristics	MK-1654-002 (N=141)	MK-1654-004 (N=2305)	MK-1654-007 (N=496)	Overall (N=2942)
Race, n (%)				
American Indian/Alaskan Native	3 (2.1%)	48 (2.1%)	5 (1.0%)	56 (1.9%)
Asian	6 (4.3%)	630 (27.3%)	99 (20.0%)	735 (25.0%)
Black/African American	47 (33.3%)	310 (13.4%)	69 (13.9%)	426 (14.5%)
Multiracial	25 (17.7%)	290 (12.6%)	66 (13.3%)	381 (13.0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (0.0%)	5 (1.0%)	6 (0.2%)
White	57 (40.4%)	1018 (44.2%)	252 (50.8%)	1327 (45.1%)
Missing	3 (2.1%)	8 (0.3%)	0 (0%)	11 (0.4%)
Ethnicity, n (%)				
Hispanic/Latino	59 (41.8%)	654 (28.4%)	151 (30.4%)	864 (29.4%)
Not Hispanic/Latino	82 (58.2%)	1588 (68.9%)	332 (66.9%)	2002 (68.0%)
Not reported	0 (0%)	15 (0.7%)	8 (1.6%)	23 (0.8%)
Unknown	0 (0%)	46 (2.0%)	5 (1.0%)	51 (1.7%)
Missing	0 (0%)	2 (0.1%)	0 (0%)	2 (0.1%)
Chronic lung disease				
No	141 (100%)	2305 (100%)	323 (65.1%)	2769 (94.1%)
Yes	0 (0%)	0 (0%)	173 (34.9%)	173 (5.9%)
Congenital heart disease				
No	141 (100%)	2305 (100%)	438 (88.3%)	2884 (98.0%)
Yes	0 (0%)	0 (0%)	58 (11.7%)	58 (2.0%)
ADA status, n (%)				
Negative	84 (59.6%)	1907 (82.7%)	348 (70.2%)	2339 (79.5%)
Inconclusive	0 (0%)	39 (1.7%)	9 (1.8%)	48 (1.6%)
Nontreatment-emergent positive	1 (0.7%)	52 (2.3%)	7 (1.4%)	60 (2.0%)
Treatment-emergent positive	51 (36.2%)	164 (7.1%)	36 (7.3%)	251 (8.5%)
Treatment-boosted positive	2 (1.4%)	4 (0.2%)	0 (0%)	6 (0.2%)
Missing	3 (2.1%)	139 (6.0%)	96 (19.4%)	238 (8.1%)
Drug product				
Clesrovimab 100 mg/mL	141 (100%)	0 (0%)	0 (0%)	141 (4.8%)
Clesrovimab 150 mg/mL + L- arginine HCL	0 (0%)	2305 (100%)	496 (100%)	2801 (95.2%)

Source: Adapted from Applicant's Pharmacometric Modelling Report (08khn9), Table 6-5, page 46
Adjusted age was derived by postnatal age + gestational age - 40 weeks
Abbreviations: ADA, antidrug antibody; HCL, hydrochloride; max, maximum; min, minimum; N, number of participants in treatment arm; n, number of participants with given characteristic; PK, pharmacokinetic; SD, standard deviation

Final Population PK Model

The pharmacokinetics of clesrovimab was described by a two-compartment disposition model, with first order absorption and elimination. The PK model was parameterized in terms of apparent clearance (CL/F), apparent central and peripheral volumes of distribution (Vc/F and Vp/F), apparent intercompartmental clearance, and the K_a. Interindividual variability was estimated for clesrovimab CL/F, Vc/F and K_a, using a diagonal variance-covariance matrix. The residual variability was described by a combined (proportional and additive) error model.

Due to sparse PK data in Trials MK-1654-002, MK-1654-004 and MK-1654-004, informative prior from an adult PK model were included on K_a, Vp/F, as well as on the interindividual variability on K_a and Vc/F, to improve parameters estimation.

Covariate Analysis

The following covariates were included in the PK model:

- Time-varying body weight (standardized to a weight of 5 kg) on clearances and volumes of distribution, using a power function with estimated power exponents.
- A maturation function on CL/F based on the time-varying adjusted age (footnote of Table 88), as follows:

Equation 1. Maturation Function on CL/F Based on the Time-Varying Adjusted Age

$$CL_{i,t} = TVCL * (\frac{WT_{i,t}}{WT_{ref}})^{\theta 1} * (1 - (1 - \beta_{CL}) * e^{-\left(PAGE_i - \frac{40}{4.35}\right) * \frac{\ln(2)}{T50CL}})$$

Source: Applicant's Modeling and Simulation Report (08khn9), page 39
Where $CL_{i,t}$ is the individual time varying apparent CL/F, TVCL is the typical value of CL/F, $WT_{i,t}$ is the time-varying body weight, WT_{ref} is the reference body weight of 5 kg, θ_1 is the estimated allometric scaling exponent for clearance, β_{CL} is the fractional difference in CL/F of a full-term infant at birth (i.e., gestational age of 40 weeks) compared with complete maturation, PAGEi is the individual time-varying adjusted age in months (calculated as the sum of gestational age and postnatal age), T50CL is the maturation half-life for CL/F.
Abbreviation: CL/F, apparent clearance

The parameter estimates from the final PK model describing clesrovimab pharmacokinetics in infant (from birth to 12 months) are listed in Table 88.

Figure 14 shows the goodness-of-fit (GOF) plots from the final PK model. The GOF plots were acceptable and there were no critical trends in the observed versus the individual predicted concentrations, and in the conditional weighted residuals versus either clesrovimab predicted concentrations or time. The prediction-corrected visual predictive check for the final model (Figure 15) showed that the models could adequately predict the median and variability of the observed data.

Table 88. Parameter Estimates From the Final Population PK Model

Parameter	Estimate	RSE (%)	Shrinkage (%)	95% CI
CL/F (L/day)[a]	0.0197	21.3		[0.0115-0.0278]
Vc/F (L)[c]	0.514	2.04		[0.494-0.535]
Q/F (L/day)[b]	0.0406	8.32		[0.0340-0.0473]
Vp/F (L)[c]	0.316	2.17		[0.303-0.330]
Ka (1/day)	0.286	3.13		[0.269-0.304]
β_{CL}[a]	0.579	20.5		[0.346-0.811]
T50CL (months)[a]	20.3	21.1		[5.81-70.8]
Body weight effect on clearances (CL, Q)[a, b]	0.524	4.06		[0.482-0.566]
Body weight effect on volumes (Vc, Vp)[c]	0.662	1.76		[0.639-0.685]
Race effect on CL/F, percentage shift for Asian[a, d]	-5.85	11.7		[-7.19 - -4.51]
Race effect on CL/F, percentage shift for Black[a, d]	13.2	8.18		[11.1-15.3]
Race effect on CL/F, percentage shift for Multi-racial[a, d]	8.72	11.4		[6.77-10.7]
IIV Ka (%)	23.5	5.49	74.6	[20.8-25.9]
IIV Vc/F (%)	8.12	5.6	71.9	[7.18-8.97]
IIV CL/F (%)	14.4	2.58	12.3	[13.6-15.1]
prop. error (%)	14.3	2.98		[13.4-15.1]
add. error (µg/mL)	0.231	12.8		[0.163-0.284]

Source: Applicant's Pharmacometric Modelling Report (08khn9), Table 8-4, page 51
Notes: CV% calculated as $\sqrt{e^{\omega^2}-1}\cdot 100$. CV% for residual error calculated as $\sqrt{\sigma^2}\cdot 100$.

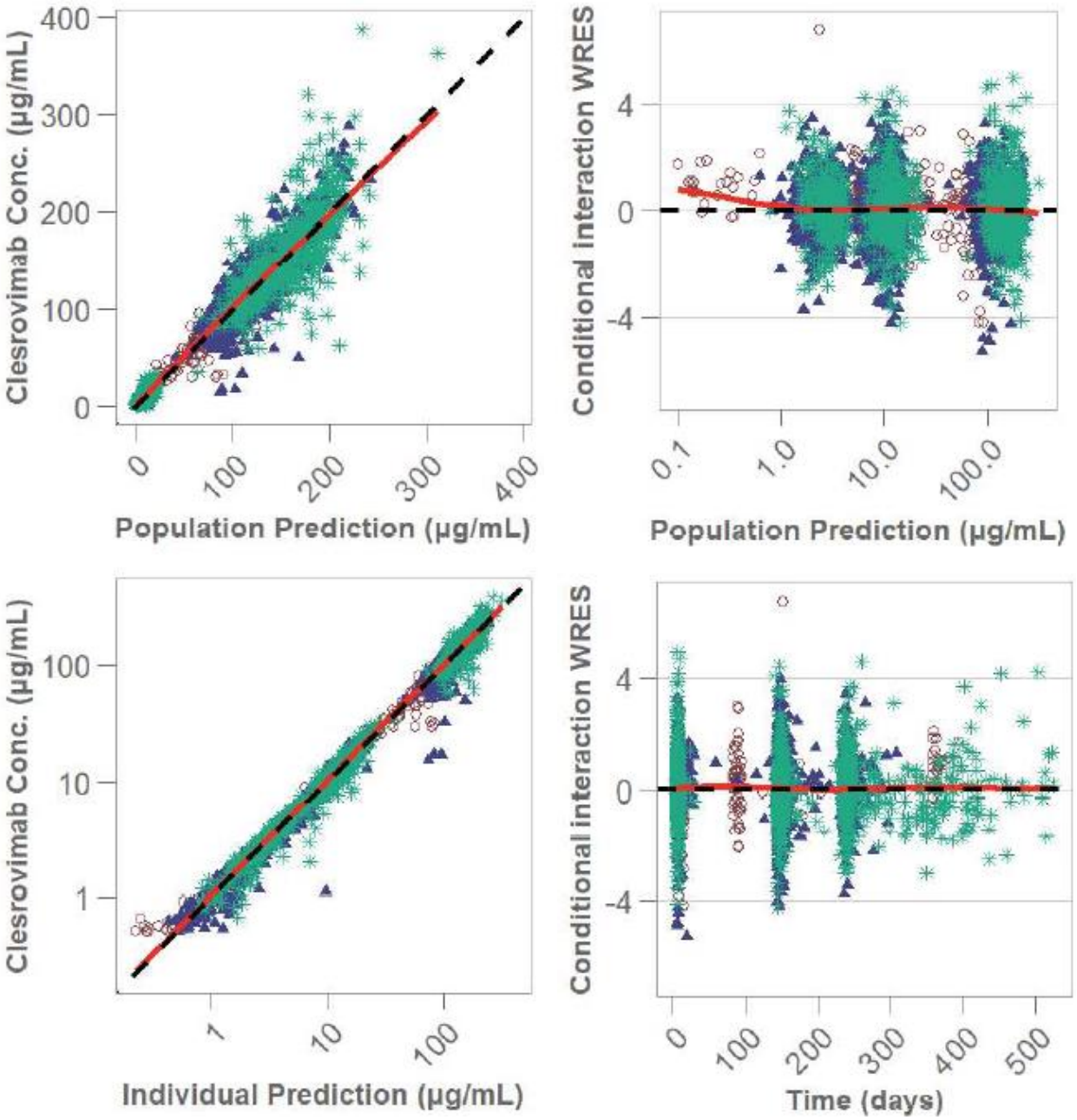
[a] The typical value of apparent clearance $\widehat{CL/F}$, for an individual with body weight = WTKG, adjusted age = AGEADJTV, and race=White can be calculated as follows.

$$\widehat{CL/F} = 0{,}0197 \cdot \left(\frac{WTKG}{5}\right)^{0.524} \cdot \left(1-(1-0{,}579)\cdot e^{-AGEADJTV\cdot\frac{\ln(2)}{20{,}3}}\right).$$

T50CL was originally estimated as a logarithmic value (original estimate: 3.01), but was exponentiated for the parameter table as 20.3.

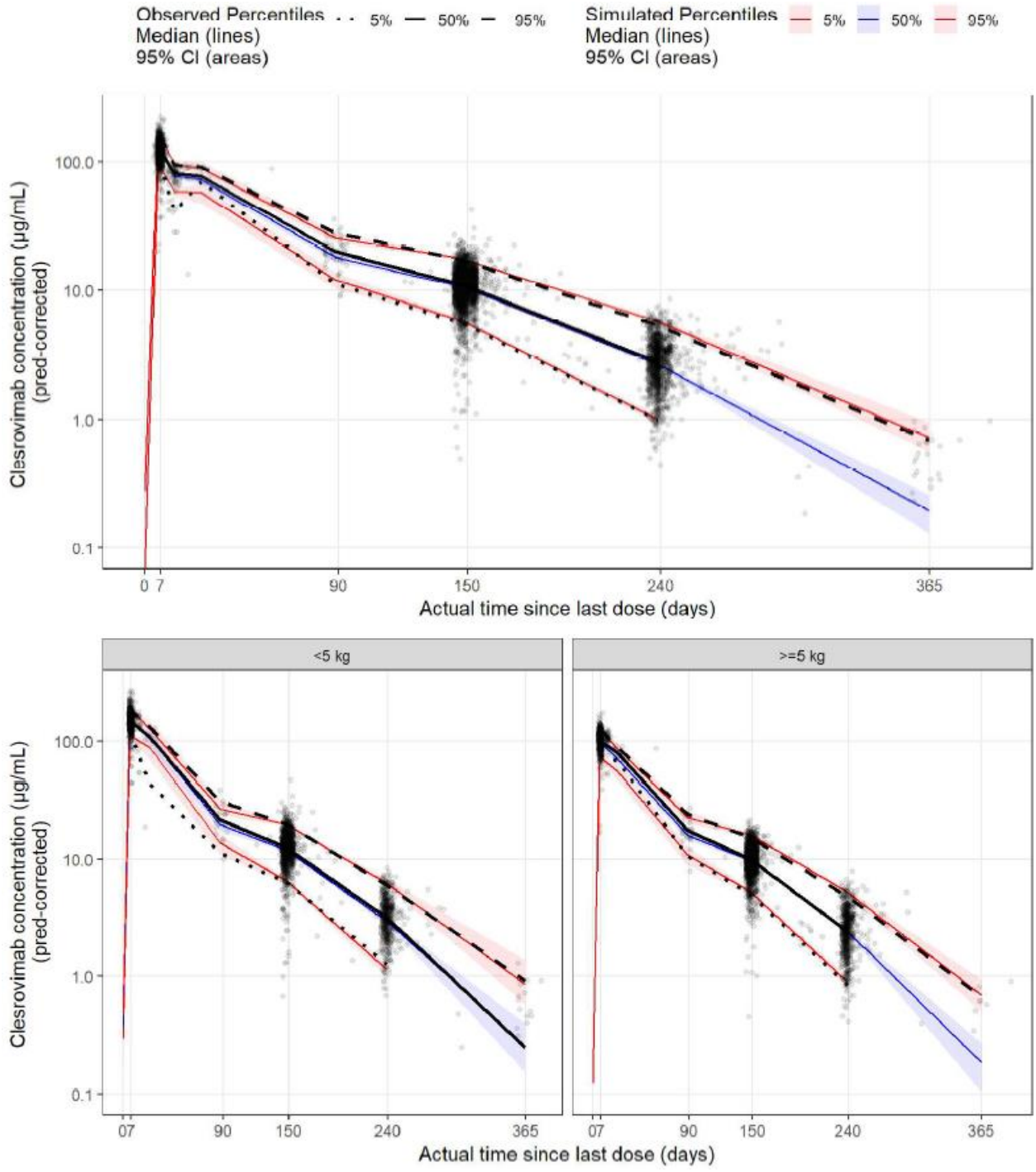
The time-varying adjusted age (AGEADJTV) expressed in months was calculated as adjusted age (AGEADJ) + (Study Day x 12/365.24), where AGEADJ = postnatal age (in months) + ((gestational age in weeks – 40 weeks) ×7×12/365.24).
Abbreviations: CI, confidence interval; β_{CL}, fractional difference in CL/F of a full-term infant at birth (i.e., gestational age of 40 weeks) compared with complete maturation; CL, clearance; CL/F, apparent clearance; CV, coefficient of variation; K_a, absorption rate constant; Q, intercompartmental clearance; Q/F, apparent intercompartmental clearance; PK, pharmacokinetic; RSE, relative standard error; T50CL, maturation half-life for CL/F; Vc, volume of distribution in the central compartment; Vc/F, apparent volume of distribution in the central compartment at steady-state; Vp, volume of distribution in the peripheral compartment

Figure 14. Goodness of Fit Plot From the Final PK Model



Source: Applicant's Pharmacometric Modelling Report (08khn9), Figure 6-5, page 60
Empty red circles, filled blue triangles and green crosses represent individual observations from Trials MK-1654-002, MK-1654-004 and MK-1654-007, respectively. Solid red lines are smoothed LOESS lines. Dashed black lines are reference lines to indicate zero or line of unity.
Abbreviations: conc, concentration; LOESS, locally weighted scatterplot smoothing; PK, pharmacokinetic; WRES, weighted residuals

Figure 15. Visual Predictive Check Plots From the Final PK Model, Overall and Stratified by Body Weight

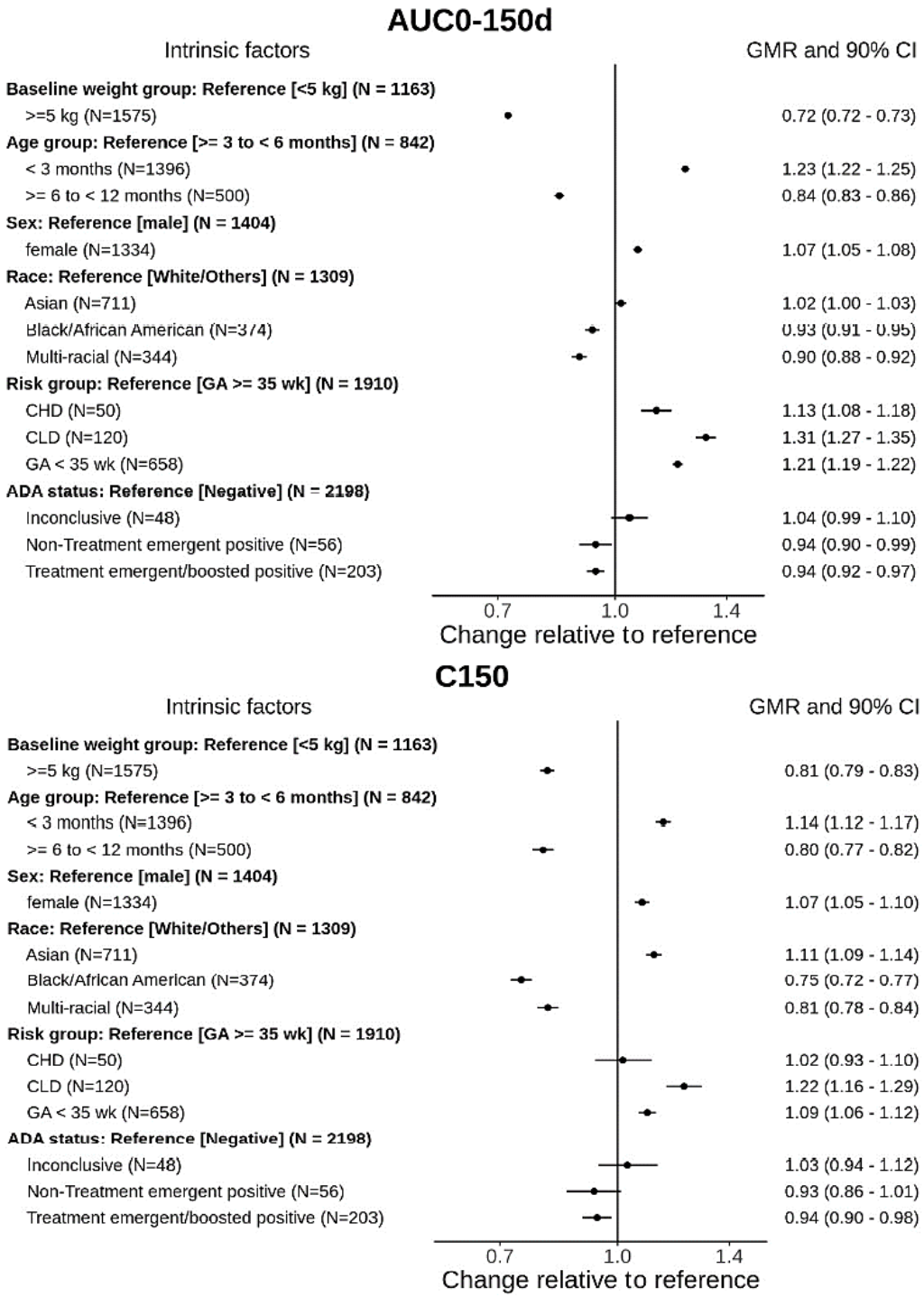


Source: Applicant's Pharmacometric Modelling Report (08khn9), Figure 6-6, page 63
Abbreviations: PK, pharmacokinetic; pred, prediction

Figure 16 shows the effect of different intrinsic factors on the model-derived exposure metrics ($AUC_{0\text{-}150d}$ and C_{trough} on Day 150) from Trials MK-1654-004 and MK-1654-007. Although body weight and race were found to be statistically significant covariates, they were not considered to have a clinically meaningful effect and resulted in about 30% relative change in exposure metrics

compared to the reference covariate group (Figure 16). ADA status had not significant effect on exposure metrics.

Figure 16. Forest Plot of Covariate Effects on Clesrovimab Exposure Average Steady-State Concentration



Source: Applicant's Pharmacometric Modelling Report (08khn9), Figure 6-17 and Figure 10-47, pages 81 and 262
Abbreviations: ADA, antidrug antibody; $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; C_{150}, serum concentration on Day 150; CHD, congenital heart disease; CI, confidence interval; CLD, chronic lung disease; GA, gestational age; GMR, geometric mean ratio; N, number of participants

FDA's Assessment of the Population PK Analysis

The Applicant's PK model reasonably describes the observed clesrovimab concentrations in infants and was considered acceptable for deriving exposure metrics for comparison of exposure between covariate groups in infants and conducting exposure-response analyses.

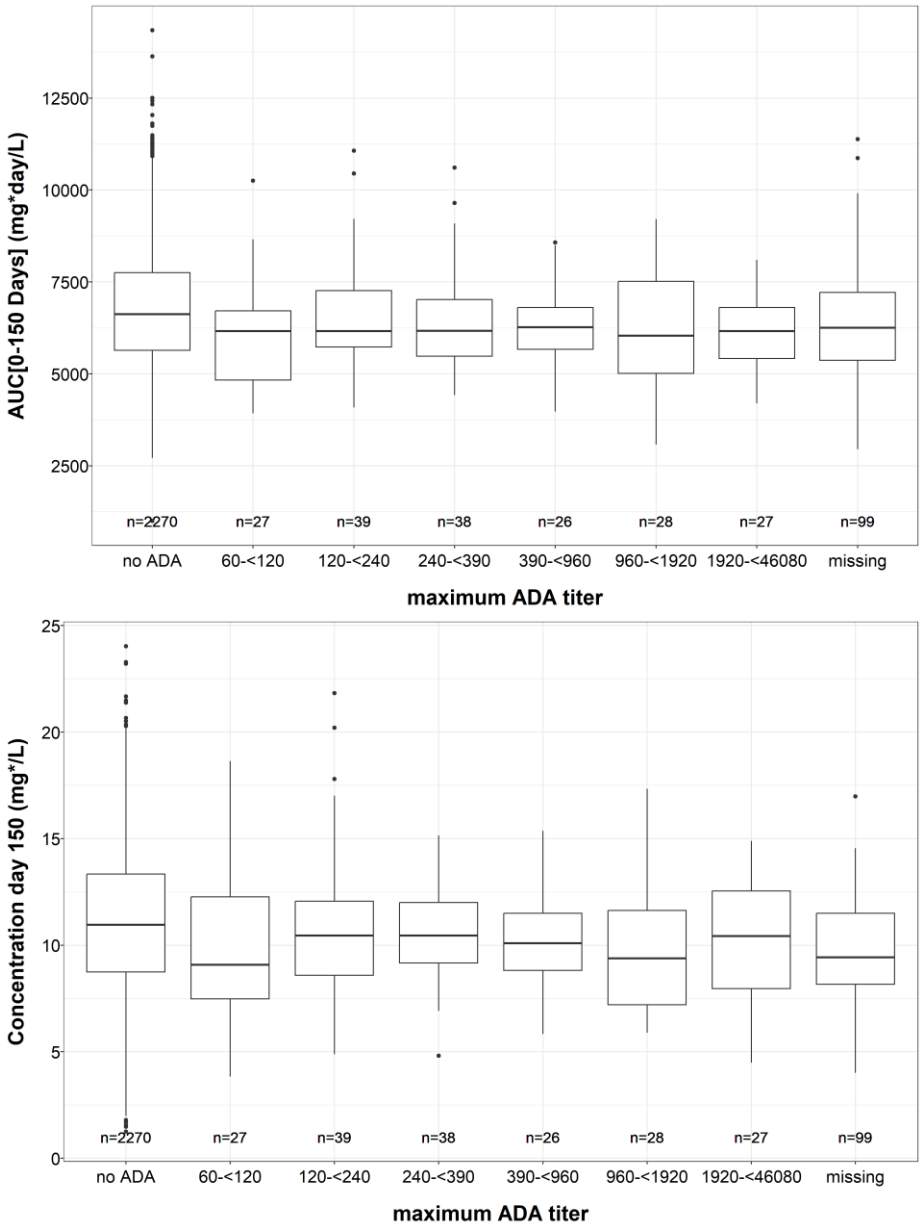
The PK parameters from the final model were estimated with a good precision (relative standard error ≤25%). The interindividual random effect shrinkages on CL/F was low (<30%), allowing reliable assessment of covariate effects on CL/F and exposure ($AUC_{0\text{-}150d}$). The residual error (Epsilon) shrinkage was low (<10%), indicating the informativeness of the GOF to diagnose structural and residual error model misspecifications.

The visual-predictive-check plots and GOF plots stratified by body weight and trial are acceptable and did not show major trends or bias.

The Applicant's estimated a terminal half-life of 44 days for clesrovimab, based on a noncompartmental analysis of observed and additional model-predicted concentrations (for specific time points). The reviewer estimated a median terminal half-life of approximately 80 days, either based on individual PK model parameters or typical PK model parameters.

The Applicant's PK model did not investigate the effect of ADA titer on clesrovimab exposure after a single IM dose of 105 mg in Trials MK-1654-004 and MK-1654-007 (where ADA and ADA titers were measured first at Day 150). The reviewer's graphical exploratory evaluation did not find an effect of ADA titer on clesrovimab exposure with no trend of ADA titer on Day 150 or maximum ADA titer and clesrovimab $AUC_{0\text{-}150d}$ and C_{trough} on Day 150 (Figure 17).

Figure 17. Clesrovimab Exposure Metrics, Stratified by Maximum ADA Titer During First RSV Season



Source: FDA reviewer
Abbreviations: ADA, antidrug antibody; $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; RSV, respiratory syncytial virus

14.5.2. Applicant's Exposure-Response Analyses

The Applicant characterized the relationship between clesrovimab exposure ($AUC_{0\text{-}150d}$) and efficacy endpoints from Trial MK-1654-004. The primary endpoint was RSV-associated MALRI (Days 1 to 150), and the secondary endpoints were RSV-associated MALRI (Days 1 to 180) and RSV-associated hospitalization (Days 1 to 150). The exposure metrics evaluated were the PK model-derived clesrovimab AUC from Day 1 to Day 150 ($AUC_{0\text{-}150d}$) or Day 180 ($AUC_{0\text{-}180d}$), depending on the endpoint.

Of note, most of RSV-associated MALRI events in the clesrovimab arm occurred before Day 150 (60 events in 2291 participants with evaluable exposure), with four additional events between Day 150 and Day 180. Therefore, exposure-efficacy analyses for the RSV-associated MALRI endpoints up to Day 150 were considered more relevant.

Of the 2399 participants dosed with clesrovimab with efficacy endpoints assessment (in Season 1 of Trial MK-1654-004), 2291 participants had at least one evaluable PK concentration and individual exposure estimates derived from the PK model.

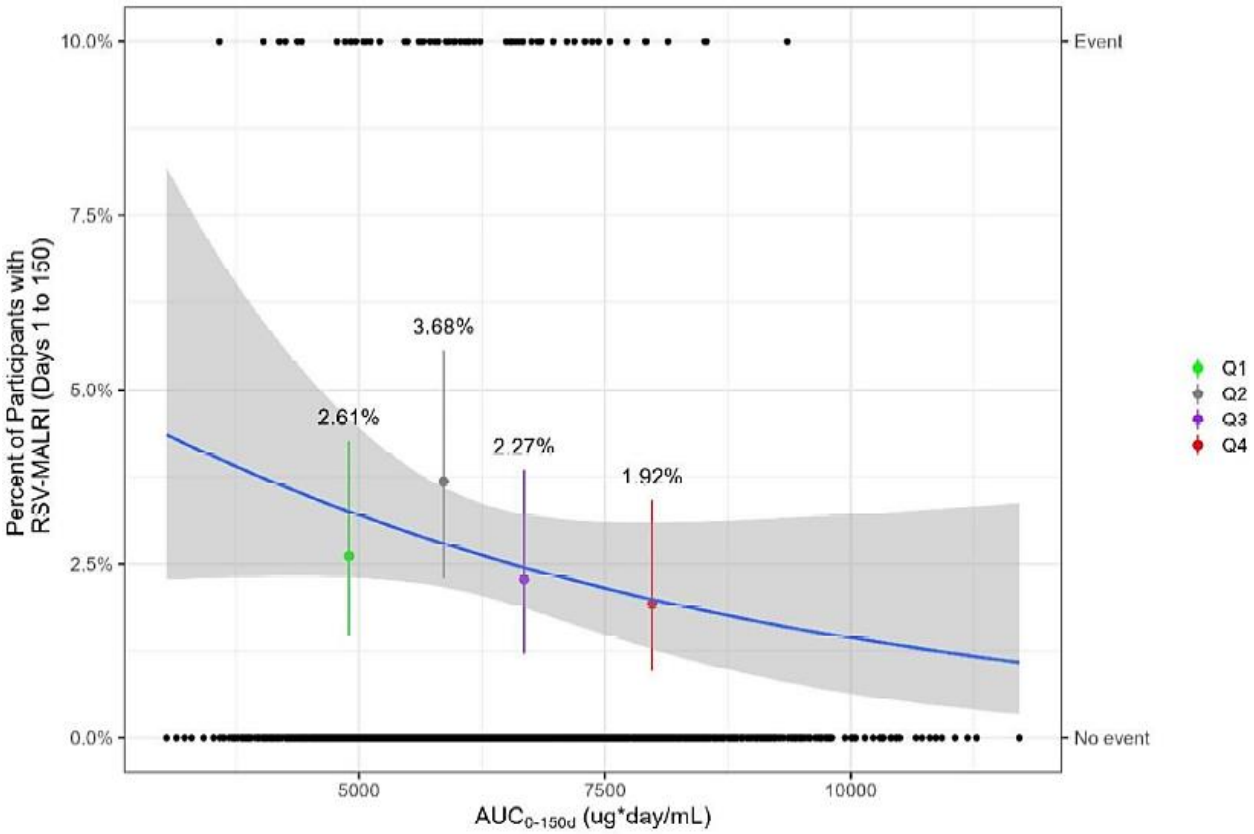
14.5.2.1. Exposure-Response for RSV-Associated MALRI, Days 1 to 150

The exposure-response relationship (without placebo) for the primary endpoint RSV-associated MALRI (Days 1 to 150) versus $AUC_{0\text{-}150d}$ (Figure 18) was relatively flat across the exposure range associated with a single 105 mg IM dose of clesrovimab in Season 1, and the estimated trend of the exposure-response relationship, using a logistic regression, was not found to be statistically significant.

Similar flat and not statistically significant relationship was estimated between clesrovimab exposure for the endpoint associated with RSV subtypes A and B.

Table 89 summarizes the estimated parameters for the different exposure-response relationships using logistic regression.

Figure 18. Observed Proportion and Predicted Probability of RSV-Associated MALRI, Days 1 to 150, vs. $AUC_{0\text{-}150d}$



Source: Applicant's Modeling and Simulation Report (08khnc), Figure 5-2, page 26
Black dots: $AUC_{0\text{-}150d}$ from individual participants. Closed circles (error bars) show the observed proportion of participants with an event (95% CI based on the Pearson-Klopper method) by exposure quartile, plotted at the median exposure of each quartile of $AUC_{0\text{-}150d}$. Solid (blue line and gray area) curves are the model-predicted probability of the event (95% CI). Median (range) of $AUC_{0\text{-}150d}$ (ug*day/mL) for each quartile is 4900 [3050, 5430) for Q1 (n=575 participants), 5860 [5430, 6270) for Q2 (n=571), 6680 [6270, 7240) for Q3 (n=573), and 7980 [7240, 11700] for Q4 (n=572).
The y axis for the percentage of participants with RSV-associated MALRI (Day 1 to 150) is capped at 10% (instead of 100%) for clarity and to better observe the relationship.
Abbreviations: $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; CI, confidence interval; MALRI, medically attended lower respiratory infection; n, number of participants with given characteristic; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; RSV, respiratory syncytial virus

Table 89. Parameter Estimates of Logistic Regression for Exposure-Primary Efficacy Endpoints Analyses

Endpoint	Parameter	Estimate (SE)	Odds Ratio (95% CI)	p-Value
RSV-associated MALRI (Days 1 to 150)	Intercept	-2.59 (0.644)	N/A (N/A-N/A)	0.0000579
	$AUC_{0\text{-}150d}$ (mg*day/mL)	-0.164 (0.103)	0.849 (0.694-1.04)	0.111
RSV subtype A-MALRI (Days 1 to 150)	Intercept	-2.98 (0.926)	N/A (N/A – N/A)	0.00131
	$AUC_{0\text{-}150d}$ (mg*day/mL)	-0.222 (0.150)	0.801 (0.596-1.07)	0.139
RSV subtype B-MALRI (Days 1 to 150)	Intercept	-3.19 (0.863)	N//A (N/A – N/A)	0.000219
	$AUC_{0\text{-}150d}$ (mg*day/mL)	-0.165 (0.138)	0.848 (0.647-1.11)	0.231

Source: Adapted from Applicant's Pharmacometric Report (08khnc), Tables 5-6 and 5-8, pages 26 and 33
Abbreviations: $AUC_{0\text{-}150d}$, area under the concentration-time curve from Day 1 to Day 150; CI, confidence interval; MALRI, medically attended lower respiratory infection; N/A, not applicable; RSV, respiratory syncytial virus; SE, standard error

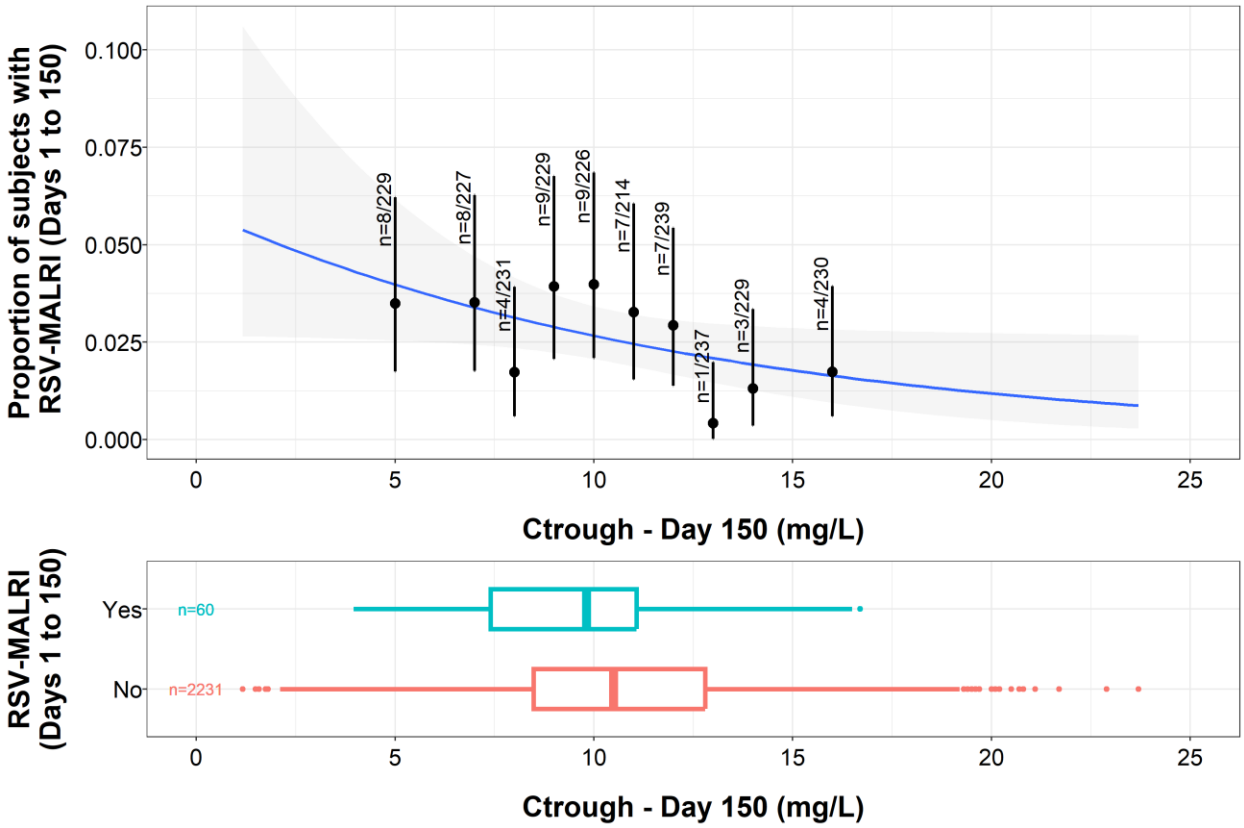
FDA's Assessment of the Exposure-Response for RSV-Associated MALRI (Days 1 to 150)

FDA was able to replicate the Applicant's findings. The absence of a significant exposure-efficacy relationship for the primary endpoint across the range of $AUC_{0\text{-}150d}$ (associated with a single 105-mg IM dose of clesrovimab in Season 1) suggests the efficacy response most likely reached a plateau at the studied and proposed single dose of 105 mg IM for clesrovimab.

FDA's assessment of the exposure-efficacy relationship for the primary endpoint, with C_{trough} on Day 150 as the exposure metric (Figure 19 and Table 90), found a statistically significant relationship (p-value of 0.04 for the slope coefficient parameter) between C_{trough} and RSV-associated MALRI (Days 1 to 150). Even though there was a trend towards statistical significance for C_{trough}, the slope coefficient parameter was estimated with high uncertainty (relative standard error of 49%), and the relationship was not considered clinically meaningful to suggest that other doses higher than 105 mg would offer meaningful improvement in efficacy. Rather, the observations suggest that the 105-mg dose produces exposure in the plateau of response. This is supported in particular by the largely overlapping C_{trough} values between participants with and without RSV-associated MALRI (Days 1 to 150) event, and the flat relationship when considering the proportion of participants with RSV-associated MALRI (Days 1 to 150) across most of the quantiles of C_{trough} (representing more than 75% of C_{trough} observations), except for eight participants at the highest three quantiles of C_{trough} driving the trend towards statistical significance.

Given the trend of lower exposure in older participants or participants with higher body weight, the reviewer evaluated the exposure-response relationship for RSV-associated MALRI (Days 1 to 150), after adjustment for weight subgroups (Figure 22) or chronological age subgroups (Figure 23).

Figure 19. Observed Proportion and Predicted Probability of RSV-Associated MALRI, Days 1 to 150, vs. C_{trough} on Day 150



Source: FDA reviewer
Upper panel: Closed circles (error bars) show the observed proportion of participants with an event (95% CI based on the Pearson-Klopper method) by exposure decile and are plotted at the median exposure of each decile of C_{trough} on Day 150. Solid (blue line and gray area) curves are the model-predicted (logistic regression) probability of the event (95% CI). Lower panel: boxplot of C_{trough} on Day 150 in participants with or without RSV-associated MALRI (Days 1 to 150) event.
Abbreviations: CI, confidence interval; C_{trough}, trough concentration; MALRI, medically attended lower respiratory infection; n, number of participants with a given event; RSV, respiratory syncytial virus

Table 90. Parameter Estimates of Logistic Regression for C_{trough}-RSV-Associated MALRI, Days 1 to 150 Analyses

Endpoint	Parameter	Estimate (SE)	Odds Ratio (95% CI)	p-Value
RSV-associated MALRI (Days 1 to 150)	Intercept	-2.77 (0.42)	N/A (N/A – N/A)	<0.00001
	C_{trough}-Day 150 (mg/L)	-0.083 (0.041)	0.92 (0.849-0.996)	0.0419

Source: Adapted from Applicant's Pharmacometric Report (08khnc), Tables 5-6 and 5-8, pages 26 and 33
Abbreviations: CI, confidence interval; C_{trough}, trough concentration; MALRI, medically attended lower respiratory infection; RSV, respiratory syncytial virus

The relationship between RSV-associated MALRI from Days 1 to 150 and clesrovimab exposure ($AUC_{0\text{-}150d}$), using a logistic regression analysis adjusted by weight subgroups, did not find baseline weight subgroups as significant predictors of the exposure-response relationship. Figure 4 shows an inverse relationship with weight subgroups, with heavier subgroups have lower or comparable proportion of events compared to participants in the <5 kg weight subgroup. In addition, participants in the ≥8 kg weight subgroup have lower or comparable proportion and probability of RSV-associated MALRI across the entire lower range of exposure compared to the

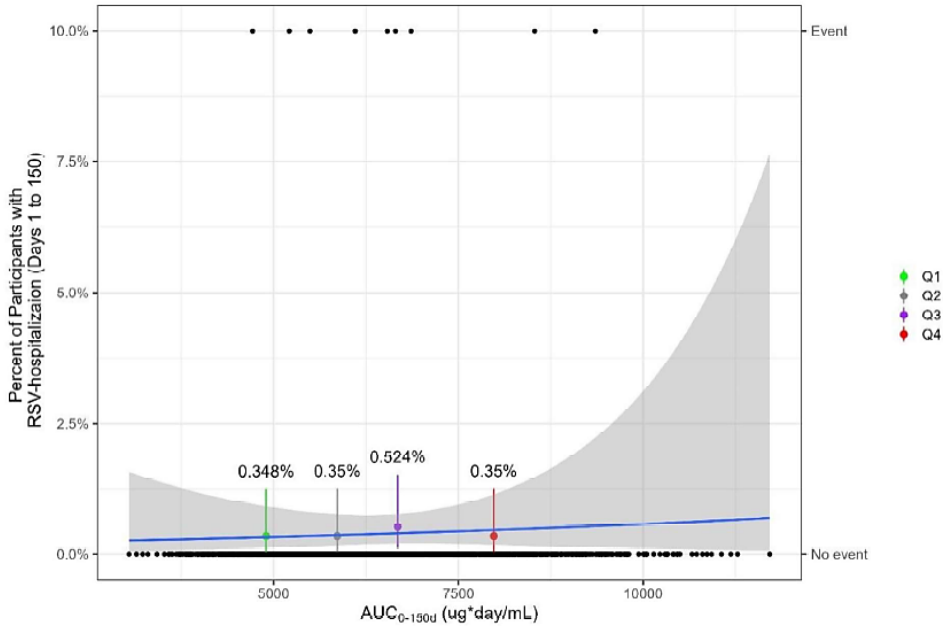
other weight groups. No difference was observed between RSV-associated MALRI and C_{trough} at Day 150, stratified by baseline weight subgroups.

The relationship between RSV-associated MALRI from Days 1 to 150 and clesrovimab exposure ($AUC_{0\text{-}150d}$), using a logistic regression analysis adjusted by baseline postnatal age subgroups, did not find baseline postnatal age subgroups as significant predictors of the exposure-response relationship. Figure 5 shows no significant difference in the proportion and probability of RSV-associated MALRI (Day 1 to 150) across the clesrovimab exposure ranges in the different baseline postnatal age subgroups. No difference was observed between RSV-associated MALRI and C_{trough} at Day 150, stratified by baseline postnatal age subgroups.

14.5.2.2. Exposure-Response for Secondary Efficacy Endpoints

Nine participants experienced RSV-associated hospitalization (Days 1 to 150). The observed exposure-response relationship (without placebo) between $AUC_{0\text{-}150d}$ and RSV-hospitalization (Days 1 to 150) is presented in Figure 20. There was no statistically significant relationship between $AUC_{0\text{-}150d}$ and response of RSV-associated hospitalization (Days 1 to 150).

Figure 20. Observed Proportion and Predicted Probability of RSV-Hospitalization, Days 1 to 150, vs. $AUC_{0\text{-}150d}$



Source: Applicant's Modeling and Simulation Report (08khnc, Figure 5-6, page 31
Black dots: $AUC_{0\text{-}150d}$ from individual participants. Closed circles (error bars) show the observed proportion of participants with an event (95% CI based on the Pearson-Klopper method) by exposure quartile, plotted at the median exposure of each quartile of $AUC_{0\text{-}150d}$. Solid (blue line and gray area) curves are the model-predicted probability of the event (95% CI). Median (range) of $AUC_{0\text{-}150d}$ (ug*day/mL) for each quartile is 4900 [3050, 5430) for Q1 (n=575 participants), 5860 [5430, 6270) for Q2 (n=571), 6680 [6270, 7240) for Q3 (n=573), and 7980 [7240, 11700] for Q4 (n=572).
Reviewer's note: the y axis for the percentage of participants with RSV-associated MALRI (Day 1 to 150) is capped at 10% (instead of 100%) for clarity and to better observe the relationship.
Abbreviations: $AUC_{0\text{-}150d}$ area under the concentration-time curve from Day 1 to Day 150; CI, confidence interval; MALRI, medically attended lower respiratory infection; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; RSV, respiratory syncytial virus

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Protocol Synopsis, Trial MK-1654-004

Title

A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study To Evaluate the Efficacy and Safety of MK-1654 in Healthy Preterm and Full-Term Infants

Hypotheses, Objectives, and Endpoints

This is an adequate and well-controlled trial with hypotheses. The primary and secondary objectives and endpoints are shown in Table 91.

Table 91. Primary and Secondary Objectives and Endpoints, Trial MK-1654-004

Objectives	Endpoints
Primary	

• To evaluate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose.
Hypothesis: Administration of MK-1654 reduces the incidence of RSV-associated MALRI from Days 1 through 150 postdose compared to placebo (The statistical criterion for success requires the lower limit of the 95% CI for efficacy to be greater than 25%).
	• RSV-associated MALRI (outpatient and inpatient), defined as the following seen in an outpatient or inpatient clinical setting:
	  • Cough or difficulty breathing; and
	  • One or more of the following: wheezing, chest wall indrawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms; and
	  • RSV-positive RT-PCR NP sample

• To evaluate the safety and tolerability of MK-1654 compared to placebo as assessed by the proportion of participants experiencing AEs.	• Solicited injection site AEs from Days 1 through 5 postdose. • Solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C), from Days 1 through 5 postdose. • Solicited systemic AEs from Days 1 through 5 postdose. • Anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose. • Rash AESI from Days 1 through 42 postdose. • Nonserious AEs from Days 1 through 42 postdose. • SAEs through the duration of trial participation.

Objectives	Endpoints
Secondary	

• To evaluate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated hospitalization from Days 1 through 150 postdose.
Hypothesis: Administration of MK-1654 reduces the incidence of RSV-associated hospitalization from Days 1 through 150 postdose compared to placebo (The statistical criterion for success requires the lower limit of the 95% CI for efficacy to be greater than 0%).
	• RSV-associated hospitalization, defined as the following:
	  • Hospital admission for respiratory illness; and
	  • RSV-positive RT-PCR NP sample

• To estimate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose.	• RSV-associated MALRI (outpatient and inpatient), defined as above

Source: Clesrovimab Clinical Protocol Amendment MK-1654-004-05
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; MALRI, medically attended lower respiratory infection; NP, nasopharyngeal; RSV, respiratory syncytial virus; RT-PCR, reverse transcription–polymerase chain reaction; SAE, serious adverse event

Trial Design

Trial MK-1654-004 is a double-blind, randomized, placebo-controlled, multisite Phase 2b/3 study to evaluate the efficacy and safety of clesrovimab for the prevention of RSV-associated MALRI in healthy preterm and term infants. Approximately 3300 healthy male and female infants, from birth up to 1 year of age, born during or entering their first RSV season, were randomized to receive a single dose of clesrovimab or placebo (2:1 ratio).

Randomization was stratified according to the following factors: regions (Northern and Southern Hemisphere), gestational age (early and moderate preterm infants [≥29 to <35 weeks gestational age] and late preterm and term infants [≥35 weeks gestational age]), and chronological age at the time of consent (<6 and ≥6 months of age). Infants who were eligible or recommended to receive palivizumab, per national or local guidelines or professional society recommendations, were not enrolled. A minimum of 600 early and moderate preterm infants were expected to be enrolled into the trial. A minimum of 90% of enrolled infants were expected to be 0 through 8 months of age.

Clinical investigator study sites are located in 24 countries: Argentina, Belgium, Canada, Chile, China, Colombia, Denmark, Finland, France, Israel, Italy, Japan, Malaysia, Mexico, Peru, Philippines, Poland, Romania, South Africa, South Korea, Thailand, Turkey, United Kingdom, and United States. Sites in Israel and Romania did not screen participants.

Enrollment was planned to begin during the 4 weeks before the estimated onset of the RSV season and ended before the estimated peak of the RSV season in each country. Special considerations, including epidemiological monitoring of RSV circulation at each site, were made for disrupted RSV seasonality (due to the coronavirus disease 2019 [COVID-19] pandemic) and RSV season determination in tropical and subtropical regions.

Two cohorts of participants were planned: 300 participants for Phase 2b (aged >2 weeks to 1-year-old), and approximately 3000 participants for Phase 3 (aged from birth to 1-year-old). All

participants were to receive the assigned study intervention (clesrovimab or placebo [0.9% sodium chloride, sterile saline]) administered via IM injection on Day 1.

All participants will be followed for at least 365 days after receiving study intervention. Efficacy surveillance for respiratory infection symptoms was conducted for up to 180 days postdose. Safety monitoring includes solicited AEs (eDiary) through Day 5 postdose, AESI (anaphylaxis/hypersensitivity, rash) and nonserious AEs through Day 42 postdose, and SAEs throughout trial participation (at least 365 days). Solicited AEs (through Day 5 postdose) included the following:

- Injection site AEs: redness/erythema, swelling, pain/tenderness
- Daily body temperature (fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C)
- Solicited systemic AEs: irritability, drowsiness, appetite loss

The first approximately 1500 participants enrolled were planned to be followed from Days 365 through 515 postdose without additional study intervention. Weekly surveillance to monitor the incidence of RSV-associated MALRI and hospitalization was conducted between Days 365 and 515, and SAEs were collected for the duration of trial participation.

For PK, ADA, and SNA data, all participants were also randomized to one of two blood sampling groups (Group 1 or 2) that differed with respect to the schedule of serum pharmacokinetics, ADA, and SNA sampling. Participants were then assigned to one of the two testing subgroups (a or b) that differed in the types of tests to be performed.

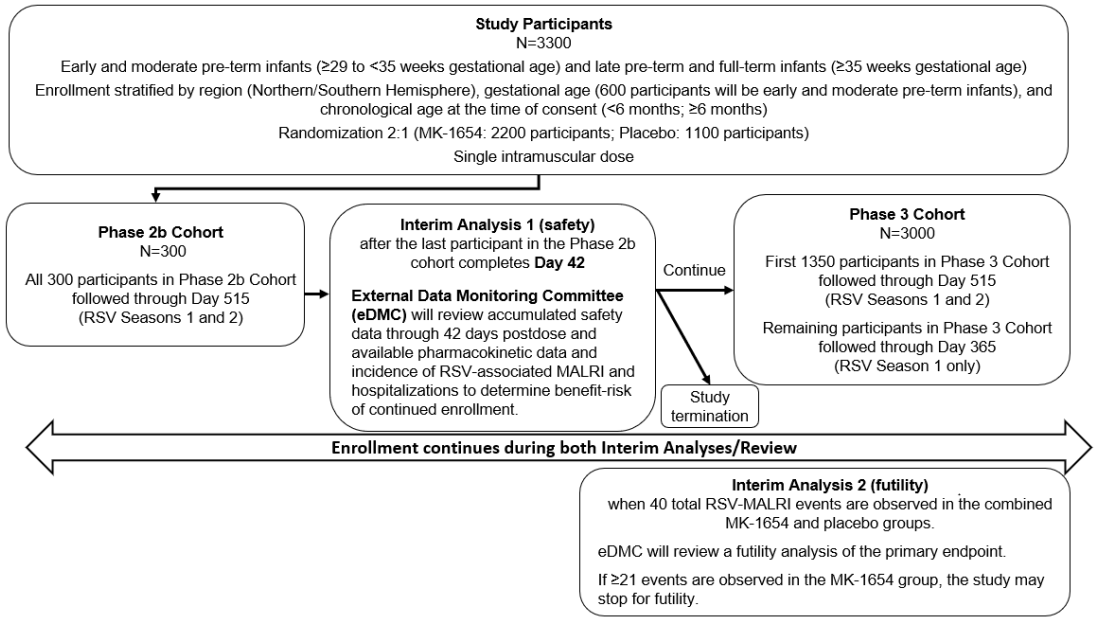
Two IAs (IA#1 and IA#2) were planned and conducted by an external unblinded statistician and reviewed by an eDMC. IA#1 was conducted after the last participant randomized in the Phase 2b cohort completed the Day 42 visit and the safety data was available. The eDMC reviewed safety data and all available PK data as well as efficacy estimates for the endpoints of RSV-associated MALRI and RSV-associated hospitalization to determine the benefit-risk of continued enrollment. During the eDMC review, participant screening and randomization continued. IA#2 was conducted in the Phase 3 cohort to assess futility, but not efficacy. IA#2 occurred after the first 40 total RSV+MALRI cases were observed in the pooled treatment groups. If ≥21 cases were observed in the MK-1654 group, then the trial could stop for futility.

After all participants have completed 180 days postdose follow-up, the database will be locked, and the Applicant will be unblinded.

Schema

The trial design is depicted in Figure 21.

Figure 21. Trial Design, Trial MK-1654-004



Source: MK-1654-004-05 Final Protocol
Abbreviations: eDMC, external data monitoring committee; MALRI, medically attended lower respiratory infection; MK-1654, clesrovimab; N, number of participants; RSV, respiratory syncytial virus

Eligibility Criteria

Inclusion Criteria

- Healthy, defined as the absence of medical conditions or acute illnesses (beyond mild symptoms requiring no more than minimal medical intervention). Any congenital or chronic medical conditions should be stable.
- Early or moderate preterm infant (≥29 to 34 weeks and 6 days gestational age) or a late preterm or full-term infant (≥35 weeks gestational age).
- For the Phase 2b cohort only: Has a chronological age >2 weeks of age up to 1 year and is entering their first RSV season.
- For the Phase 3 cohort only: Has a chronological age from birth up to 1 year and is entering their first RSV season.
- For South Korea only: Participant weighs ≥2 kg.

Key Exclusion Criteria

- Eligible or recommended to receive palivizumab per national or local (e.g., state or provincial) guidelines or professional society recommendations.
- Has known hypersensitivity to any component of MK-1654.

- Has a bleeding disorder contraindicating intramuscular administration.
- Has 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.
- Has received any vaccine or mAb for the prevention of RSV, including receipt of maternal RSV vaccination during the mother's pregnancy.

Weekly phone calls will be used to assess for the presence of respiratory symptoms. In addition, caregivers will be instructed to call the site to report respiratory symptoms. If respiratory infection symptoms are reported, the participant will be assessed at the site. If a participant was assessed for respiratory symptoms in an outpatient or inpatient clinical setting, the participant should also be assessed by site personnel.

Statistical Analysis Plan

Statistical Analyses

Efficacy for the primary endpoint of RSV-associated MALRI through Day 150 postdose is defined as RRR, efficacy =1-(Rt/Rp), where Rt and Rp are the incidence rates of RSV-associated MALRI in the MK-1654 and placebo groups, respectively. The incidence rate Rt is defined as Rt = Ct/Tt, where Ct = the count of RSV-associated MALRI cases in the MK-1654 group and Tt = total person-time of follow-up for efficacy in the MK-1654 group. The incidence rate Rp is defined similarly. The statistical criterion for success with respect to the primary hypothesis will be met if the two-sided 95% lower confidence bound is greater than 25%. The p-value is based on testing the primary hypothesis that efficacy is >25%.

Every participant is counted a single time for each applicable endpoint. A participant may have multiple cases. For each participant, only the first occurrence of the case for each endpoint is counted for the analysis. The analyses were based on the data cutoff of March 4, 2024.

Analyses of the Primary and Secondary Endpoints

A modified Poisson regression approach with robust variance (Zou 2004) was used for the efficacy analyses. The mean and 95% CI of relative risk, Rt/Rp, were obtained from the model, and was used to estimate the mean and 95% CI of relative risk reduction. The modified Poisson regression model included treatment group, and stratification variables of region (Southern Hemisphere and Northern Hemisphere), gestational age (early and moderate preterm infants [≥29 to <35 weeks gestational age] and late preterm and full-term infants [≥35 weeks gestational age]), and chronological age at the time of consent (<6 months; ≥6 months) as covariates. To allow for differences in follow-up times among participants, log (follow-up time) as the offset term was added in the modified Poisson regression.

If the number of participants in any stratum is too small and/or convergence cannot be achieved for either of the primary and secondary efficacy endpoints, the covariate will be excluded from the model for the final analysis of all primary and secondary efficacy endpoints. If convergence issues persist, additional covariates will be excluded from the model in the following order: region, chronological age, and gestational age, until the model converges for all primary and secondary efficacy endpoints. Therefore, the same set of covariates will be used in the models for all the primary and secondary efficacy endpoints in the final analyses.

For the primary efficacy hypothesis, cases of both RSV A and RSV B associated MALRI will be analyzed as exploratory endpoints. The efficacy of MK-1654 against RSV A and RSV B associated MALRI will also be estimated separately.

For the secondary efficacy hypothesis of RSV-associated hospitalization from Day 1 through Day 150 postdose, the statistical criterion for success will be met if the lower bound of the 95% CI was >0%. For the secondary efficacy endpoint of RSV-associated outpatient and inpatient MALRI occurring from Day 1 through Day 180 postdose, the estimate of efficacy and corresponding 95% CI would be provided.

For an episode of respiratory infection to be considered for evaluation of an efficacy endpoint, a RT-PCR result from the study central laboratory must be available for a nasopharyngeal sample that is collected no more than 12 days after symptom onset or symptom worsening, or after symptom onset and no more than 7 days before symptom worsening. A sensitivity analysis will be conducted, which will include RT-PCR results from nasopharyngeal samples collected within the timeframe mentioned above, but not tested at the study central laboratory. Also, if a participant with symptoms of respiratory infection prior to dosing has a nasopharyngeal sample collected predose on Day 1 that is RT-PCR positive for RSV, this episode will not be counted as a case toward the efficacy endpoints.

Prespecified Hypothesis Testing Order, Type-I Error Control, and Interim Analysis

Testing multiplicity is controlled at an overall one-sided Type-1 error of 2.5% using a gatekeeping procedure. The primary efficacy hypothesis will be tested at an overall one-sided Type-1 error of 2.5%. The secondary efficacy hypothesis regarding RSV hospitalization from Days 1 through 150 postdose will be tested at one-sided Type-1 error of 2.5% only if the primary efficacy hypothesis is successfully demonstrated.

Of note, the statistical analysis plan outlined a plan for two interim analyses. The interim analyses were conducted for futility assessment. No Type-1 error adjustment is needed for the futility analyses.

For the safety parameters, estimates and 95% CIs for between-treatment differences in the percentage of participants with events will be calculated using the Miettinen and Nurminen method (Miettinen and Nurminen 1985).

Sample Size

The sample size of 3300 (2200 MK-1654 and 1100 placebo) participants was selected to ensure collection of adequate safety information on the use of MK-1654 in this otherwise healthy population of preterm and term infants. A total of approximately 167 cases of RSV-associated MALRI in the MK-1654 and placebo groups are expected to accrue by the end of the trial, under the following assumptions: 1) incidence of RSV-associated MALRI in the placebo group is 10% per season; 2) efficacy =70%, so that the incidence of RSV-associated MALRI in the MK-1654 group is 3% per season; and 3) attrition rate is 5%. Under these assumptions, a sample size of 2200 infants in the MK-1654 group and 1100 infants in the placebo group results in >95% power to demonstrate that the efficacy of MK-1654 compared to placebo to prevent RSV-associated MALRI is >25% if the underlying efficacy is 70% at an overall one-sided Type-1 error of 2.5%. The calculations are based on a simulation study for the modified Poisson regression and carried out using the SAS software.

Analysis Populations

FAS Population

The protocol-defined efficacy population was the FAS population (as defined in the SAP), which consisted of all randomized participants who receive one dose of study treatment. The FAS population served as the primary population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. Participants were included in the treatment group based on the study treatment they were randomized to for the efficacy analyses. Of note, even though the FAS population was defined as above, participants with protocol violations were excluded from the FAS population as well as from the efficacy analyses presented in this review. However, the Prescribing Information presents the results from the protocol-defined FAS population (i.e., participants with protocol violations were not excluded from the efficacy results in the Prescribing Information). Notably, the efficacy results were not impacted by the inclusion or exclusion of these participants.

PPE Population

To be eligible for inclusion in the PPE population, trial participants must satisfy the following criteria:

- Receive one dose of the correct clinical material corresponding to the treatment group the participants were randomized into.
- Have at least one follow-up visit/phone call for assessment of RSV disease.
- At any time during dosing or efficacy follow-up, do not experience a protocol deviation that may interfere with the assessment of protection against RSV infection conferred by clesrovimab.

The PPE population serves as a supportive analysis population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. Participants were included in the treatment group based on their randomization.

APaT Population

The protocol-defined safety population was the APaT population (as defined in the SAP), which consisted of all randomized participants who received a dose of study treatment. Participants were included in the treatment group based on the study treatment they actually received for the analysis of safety data using the APaT population. Of note, even though the safety analysis population was defined as above, participants with protocol violations were excluded from the APaT population as well as from the safety analyses presented in this review. However, the Prescribing Information presents the results from the protocol-defined APaT population.

Subgroup Analyses

The relative risk reduction for the primary efficacy endpoint and secondary efficacy endpoints were examined among the following subgroups: RSV subtype (RSV A and RSV B), gestational age (early and moderate preterm infant [≥29 to <35 weeks] and late preterm and full-term infant [≥35 weeks]), age (≤6 months, 6 to 9 months, and ≥9 months), baseline body weight (≤5 kg, 5 to 8 kg, and ≥8 kg), sex (male and female), race (American Indian or Alaska Native, Asian, Black

or African American, Multiple, Native Hawaiian or Other Pacific Islander, White, and missing), hemisphere (Northern Hemisphere and Southern Hemisphere), and climate (temperate and tropical/subtropical).

For the analyses by RSV subtype, the RSV A and RSV B subgroups are not mutually exclusive. The efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate.

For the other subgroup analyses, the efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate, or an exact binomial method if convergence issues exist with the Poisson approach.

Missing Data (To Evaluate the Impact of Missing Data)

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, they are trial dropouts. Missing data will not be imputed for any of the efficacy analyses.

Safety Monitoring

Clesrovimab was administered on Day 1 and participants were observed for at least 30 minutes postdose for any signs/symptoms of: an immediate anaphylaxis/hypersensitivity AE, an immediate rash AE, injection site AEs including redness/erythema, swelling, and tenderness/pain, and any other AEs. Because clesrovimab is administered as a single dose (per RSV season), all participants received the entire course of clesrovimab (for Season 1). Participants were monitored for 30 minutes postdose for all clesrovimab and placebo doses.

The safety of clesrovimab was primarily assessed by the occurrence of treatment-emergent AEs, SAEs, and AESI reported during the trial. Severity of adverse events was graded according to an adaption of NCI-CTCAE version 5.0 as applicable for pediatric/infant assessments. Safety monitoring occurred for solicited AEs (eDiary) through Day 5 postdose, AESI (anaphylaxis/hypersensitivity, rash) and nonserious AEs through Day 42 postdose, SAEs throughout trial participation (at least 365 days).

An eDMC reviewed accumulated safety data through 42 days postdose, available PK data, and RSV-associated disease incidences to determine benefit-risk of continued enrollment.

15.2. Protocol Synopsis, Trial MK-1654-007

Title

A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab-Controlled Study To Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease

Hypotheses, Objectives, and Endpoints

This is an estimation trial without hypotheses. The primary and secondary objectives and endpoints are shown in Table 92.

Table 92. Primary and Secondary Objectives and Endpoints, Trial MK-1654-007

Objectives	Endpoints
Primary	
RSV Season 1: To evaluate the safety and tolerability of MK-1654 compared to palivizumab in RSV Season 1 as assessed by the proportion of participants experiencing AEs.	• Solicited injection site AEs from Days 1 through 5 after each dose • Solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C) from Days 1 through 5 after each dose • Solicited systemic AEs from Days 1 through 5 after each dose • Anaphylaxis/hypersensitivity AESI from Days 1 through 42 Postdose 1 • Rash AESI from Days 1 through 42 Postdose 1 • Nonserious AEs from Days 1 through 42 Postdose 1 and 14 days after each subsequent dose • SAEs through the duration of participation in RSV Season 1
Secondary	
RSV Season 1: To estimate the efficacy of MK-1654 compared to palivizumab as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 Postdose 1 in RSV Season 1.	RSV-associated MALRI (outpatient and inpatient), defined as the following seen in an outpatient or inpatient clinical setting: • Cough or difficulty breathing • One or more of the following: wheezing, chest wall indrawing/retractions, rales/crackles, hypoxemia, tachypnea • Dehydration due to respiratory symptoms • RSV-positive RT-PCR NP sample
RSV Season 1: To estimate the incidence of RSV-associated hospitalizations from Days 1 through 150 Postdose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.	RSV-associated hospitalization, defined as the following: • Hospital admission for respiratory illness • RSV-positive RT-PCR NP sample
RSV Season 1: To describe the serum PK concentration of MK-1654 at Days 7, 150, and 240 after the dose of MK-1654 in RSV Season 1.	MK-1654 PK concentration
RSV Season 2: To describe the safety of MK-1654 administered in RSV Season 2 as assessed by the proportion of participants experiencing AEs.	• Solicited injection site AEs from Days 1 through 5 postdose • Solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (39.0°C) or axillary temperature ≥101.7°F (38.7°C) from Days 1 through 5 postdose • Solicited systemic AEs from Days 1 through 5 postdose • Anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose • Rash AESI from Days 1 through 42 postdose • Nonserious AEs from Days 1 through 42 postdose • SAEs from Days 1 through 180 postdose

Objectives	Endpoints
RSV Season 2: To describe the serum PK concentration of MK-1654 at Days 7 and 150 postdose in RSV Season 2.	MK-1654 PK concentration

Source: Clesrovimab Clinical Protocol Amendment MK-1654-007-02
Abbreviations: AE, adverse event; AESI, adverse event of special interest; MALRI, medically attended lower respiratory infection; MK-1654, clesrovimab; NP, nasopharyngeal; PK, pharmacokinetic; RSV, respiratory syncytial virus; RT-PCR, reverse transcription–polymerase chain reaction; SAE, serious adverse event

Trial Design

Trial MK-1654-007 is an ongoing Phase 3, partially blinded, randomized, active-controlled, multisite study to evaluate the safety, tolerability, and efficacy of clesrovimab versus palivizumab and the pharmacokinetics of clesrovimab in infants who are at increased risk for severe RSV disease, born during or entering their first RSV season (RSV Season 1), and recommended to receive palivizumab. Part 1 of the trial (Day 1 to Day 60 visit in RSV Season 1) is double-blind, and Part 2 (Day 60 visit through trial completion) is open-label. The primary objective/endpoint for Trial MK-1654-007 is evaluation of safety; efficacy and pharmacokinetics are assessed as secondary endpoints. Efficacy is extrapolated from healthy preterm and term infants (Trial MK-1654-004) to infants at increased risk for severe RSV disease (Trial MK-1654-007) based on comparable pharmacokinetics. A secondary purpose of the trial is to evaluate the safety, efficacy, and pharmacokinetics of an additional dose of clesrovimab administered at the start of the second RSV season (RSV Season 2) for eligible participants in either treatment group who continue to be at increased risk of severe RSV disease and who are entering their second RSV season.

Approximately 1000 infants who 1) had either CLD of prematurity (gestational age ≤32 weeks) or hemodynamically significant CHD (regardless of gestational age), or were ≤35 weeks gestational age, and 2) had a chronological age from birth up to one year and were entering their first RSV season, were planned to be randomized in a 1:1 ratio to receive either a single dose of clesrovimab (105 mg IM) or palivizumab (three to five monthly doses of 15 mg/kg). Randomization was stratified according to region (Northern and Southern Hemispheres) and participant condition (CLD, CHD, neither CLD nor CHD <29 weeks gestational age, and neither CLD nor CHD ≥29 weeks gestational age). Eligible participants with CLD and CHD or in the early or moderate preterm group were consented for inclusion in two RSV seasons. Enrollment was planned to begin during the 4 weeks before the estimated onset of the RSV season and to end before or soon after the estimated peak of the RSV season in each country. Special considerations, including epidemiological monitoring of RSV circulation at each site throughout the trial, were made for disrupted RSV seasonality (e.g., due to the COVID-19 pandemic) and RSV season determination in tropical and subtropical regions.

In Part 1 of the trial (double-blind), participants in the clesrovimab arm received a single dose of clesrovimab for Dose 1 (Day 1) followed by placebo for Dose 2 (Day 28 [+4]). Participants in the palivizumab arm received palivizumab for Dose 1 (Day 1) and Dose 2 (Day 28 [+4]).

In Part 2 (open-label), participants are unblinded, and participants in the palivizumab group continue to receive palivizumab open-label for a total of three to five doses administered monthly (Dose 3 on Day 60, Dose 4 on Day 90, Dose 5 on Day 120). Participants in the clesrovimab group received no additional study drug in Part 2, with rare exceptions where an

additional dose was administered following ECMO or cardiac surgery requiring CPB. RSV Season 1 safety follow-up is continued through 365 days Postdose 1.

Safety monitoring includes solicited AEs (eDiary) through Day 5 postdose; AESI (anaphylaxis/hypersensitivity, rash) through Day 42 Postdose 1 (through Day 14 Postdose 2), and for 42 days after an additional postsurgery dose of clesrovimab); SAEs throughout the duration of participation in RSV Season 1; all other AEs through Day 42 Postdose 1 (Day 14 Postdose 2), for 14 Days after each dose of palivizumab, and for 42 days after an additional postsurgery dose of clesrovimab (when applicable). Solicited AEs (through Day 5 postdose) included the following:

- Injection site AEs: redness/erythema, swelling, pain/tenderness
- Daily body temperature (fever defined as rectal temperature ≥102.2°F [≥39.0°C] or axillary temperature ≥101.7°F [≥38.7°C])
- Systemic AEs: irritability, drowsiness, appetite loss

Eligible participants in either treatment group who continue to be at increased risk of RSV and are entering their second RSV season (approximately 300 infants/children) will be administered clesrovimab at the start of the second RSV season (RSV Season 2).

RSV Season 1 Administrations and Assessments

Part 1 (double-blind): Trial participants were to receive two blinded doses (as follows) before being unblinded at the Day 60 visit:

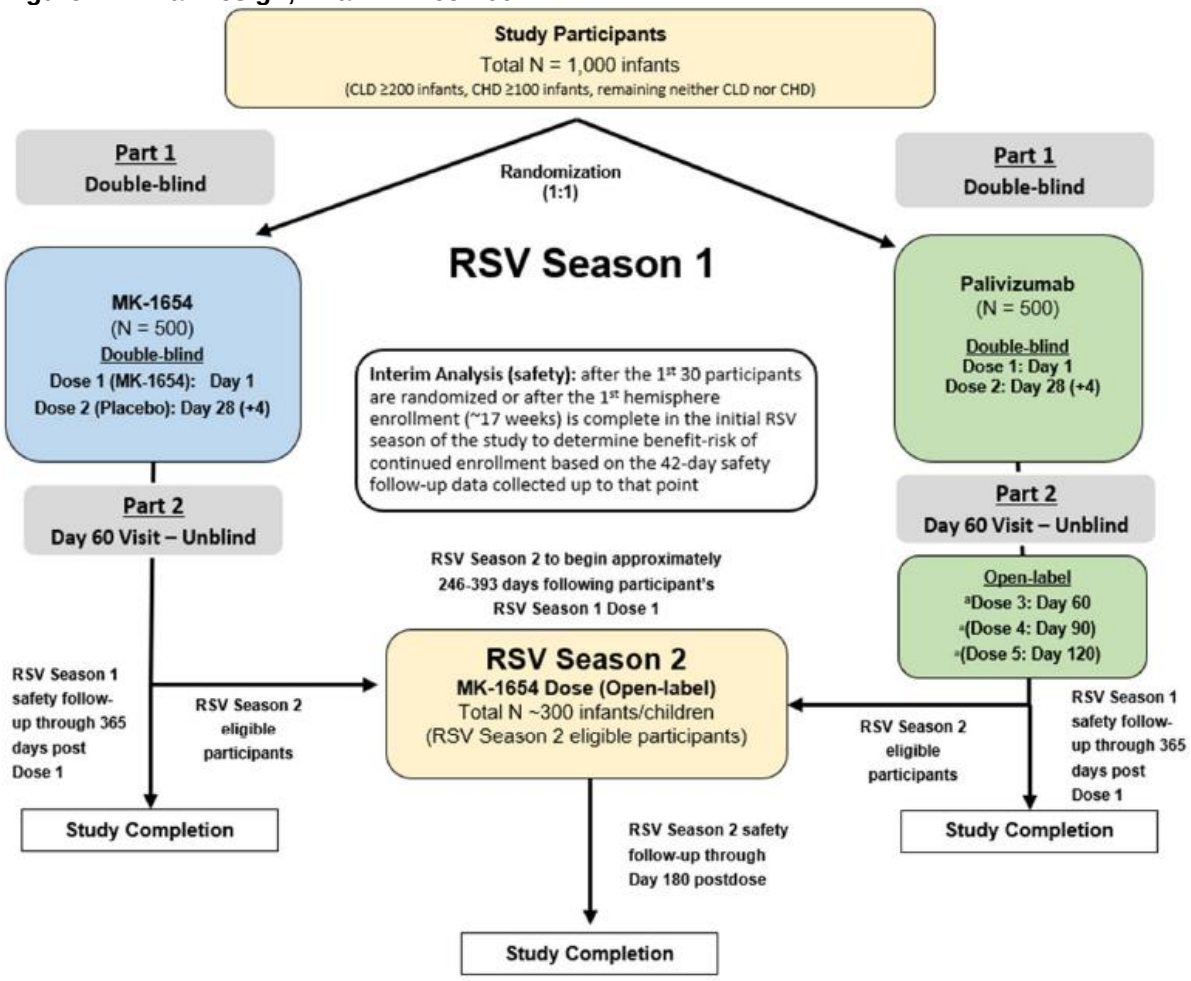
- MK-1654 group: clesrovimab 105 mg (Dose 1) and placebo (Dose 2)
- Palivizumab group: palivizumab (Dose 1 and Dose 2)

Part 2 (open-label): Participants in the palivizumab group received at least three and up to five single doses of palivizumab in RSV Season 1 depending on the timing of enrollment relative to the RSV season.

Schema

The planned trial design is depicted in Figure 22.

Figure 22. Trial Design, Trial MK-1654-007



Source: MK-1654-007-02 Final Protocol
All doses administered intramuscularly.
[a] Each subsequent dose must be administered between 28-32 days after the previous dose. Receipt of palivizumab Doses 4 and 5 depend on enrollment date relative to RSV season.
Note: If during the RSV season a participant undergoes 1) ECMO or 2) surgical intervention for CHD and requires cardiopulmonary bypass during the surgical procedure, additional study intervention may be administered postsurgery based on the Applicant consultation.
Abbreviations: CHD, congenital heart disease; CLD, chronic lung disease; ECMO, extracorporeal membrane oxygenation; MK-1654, clesrovimab; N, number of randomized participants; RSV, respiratory syncytial virus

Eligibility Criteria

Inclusion Criteria

Male or female infants who had a chronological age from birth up to 1 year and entering their first RSV season were enrolled if they were recommended to receive palivizumab and met 1 or more of the following criteria:

- Early or moderate preterm group (excluding participants with CLD or hemodynamically significant CHD): ≤35 weeks, 0 days gestational age
- CLD/CHD group:
  - CLD participants: had CLD of prematurity (also known as bronchopulmonary dysplasia), as defined by:
    - American Academy of Pediatrics [16.1.12.9]: ≤32 weeks, 0 days gestational age and require medical intervention/management (i.e., supplemental oxygen, bronchodilators, or chronic systemic corticosteroids) for at least 28 days after birth.
    - Other national or local guidelines or professional society recommendations.
  - CHD participants: have hemodynamically significant CHD, as defined by:
    - American Academy of Pediatrics: Uncorrected or palliated cyanotic or acyanotic disease associated with documented pulmonary hypertension (e.g., systolic pulmonary arterial pressure ≥40 mm Hg or ≥1/2 systolic blood pressure) or a requirement for daily medication to manage congestive heart failure, or as diagnosed by a pediatric cardiologist
    - Other national or local guidelines or professional society recommendations

Additional Inclusion Criteria for Participation in RSV Season 2

CLD and CHD participants and participants in the early or moderate preterm group who met the additional inclusion criteria for RSV Season 2 were consented for inclusion in two RSV seasons, and continued into RSV Season 2 if they still met the following inclusion criteria at the RSV Season 1 Day 240 and RSV Season 2 Day 1 visits:

- Participants enrolled in the CLD/CHD group as defined in #2 above. Participants with CHD were required to meet the following additional criteria:
  - Have hemodynamically significant CHD at the beginning of RSV Season 2.
  - If the participant had surgically repaired hemodynamically significant CHD that did not include ECMO or cardiopulmonary bypass:
    - Continued to require medications to manage CHD.
    - Any additional medical intervention related to their CHD.
- Participants enrolled in the early or moderate preterm group (#1 above) with the following:
  - Neuromuscular disease or congenital pulmonary anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough.
  - Down syndrome (trisomy of chromosome 21).

- Cystic fibrosis with nutritional compromise (e.g., weight <10th percentile at time of enrollment).
- Native Americans and Alaskan Indians or other indigenous populations at high risk for severe RSV disease.

Key Exclusion Criteria

- Required mechanical ventilation at time of enrollment.
- Had a life expectancy <6 months.
- Had known hepatic or renal dysfunction, or chronic seizure disorder.
- Was hospitalized at the time of randomization unless discharge was expected within 7 days after randomization.
- Had severe immunodeficiency or was severely immunocompromised, 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 trial
  - Status post solid-organ or bone marrow transplantation and on a systemic immunosuppressive regimen

OR

  - Severe combined immunodeficiency

- Was anticipated to have either of the following within 60 days after randomization:
  - Surgical correction resulting in hemodynamically insignificant CHD.
  - Cardiac surgical procedure that required cardiopulmonary bypass.
  - Required ECMO or continuous positive airway pressure at the time of enrollment or anticipated within 60 days after randomization.
- Had an anticipated or planned cardiac transplantation to occur during the course of this trial.
- Had received any vaccine or mAb for the prevention of RSV, including receipt of maternal RSV vaccination during the mother's pregnancy.

If a previously eligible and consented RSV Season 2 participant had 1) ECMO or 2) surgical intervention during the RSV season for CHD and required cardiopulmonary bypass during the procedure in RSV Season 1, they were excluded from participating in RSV Season 2.

Statistical Analysis Plan

Statistical Analyses

No formal hypothesis testing was planned for this trial and the goal of the efficacy analyses was to estimate incidence rates. Efficacy for the secondary efficacy endpoints of RSV-associated MALRI (inpatient and outpatient) through Day 150 Postdose 1 in RSV Season 1 and RSV-associated hospitalization through Day 150 Postdose 1 in RSV Season 1 is defined as RRR, efficacy % =100*{1-(Rt/Rp)}, where Rt and Rp are the incidence rates of RSV-associated

MALRI in the MK-1654 and palivizumab groups, respectively. The incidence rate Rt is defined as Rt = Ct/Tt, where Ct = the count of RSV-associated MALRI cases in the MK-1654 group and Tt = total person-time of follow-up for efficacy in the MK-1654 group. The incidence rate Rp is defined similarly. Efficacy for RSV-associated hospitalization through Day 150 Postdose 1 in RSV Season 1 is defined similarly.

Every participant is counted a single time for each applicable endpoint. A participant may have multiple cases. For each participant, only the first occurrence of the case for each endpoint is counted for the analysis. The analyses were based on the data cutoff of March 4, 2024.

Analyses of the Primary and Secondary Endpoints

For the safety parameters, estimates and 95% CIs for between-treatment differences in the percentage of participants with events will be calculated using the Miettinen and Nurminen method (Miettinen and Nurminen 1985). Comparisons between treatment groups will be conducted only for RSV Season 1. The primary comparison of safety endpoints in RSV Season 1 will be after the first two doses in each group, i.e., after the MK-1654 and placebo doses versus after the first two palivizumab doses. A supplemental comparison of safety endpoints in RSV Season 1 will be after the MK-1654 and placebo doses versus after all doses in the palivizumab group.

A modified Poisson regression approach with robust variance (Zou 2004) was used for both the RSV-associated MALRI through Day 150 Postdose 1 in RSV Season 1 analysis and the RSV-associated MALRI through the end of RSV Season 1. The mean and 95% CI of relative risk, Rt/Rp, were obtained from the model, and was used to estimate the mean and 95% CI of relative risk reduction. The modified Poisson regression model included treatment group, and stratification variables of region (Southern Hemisphere and Northern Hemisphere) and participant condition (CLD, CHD, neither CLD nor CHD ≥29 weeks gestational age, and neither CLD nor CHD <29 weeks gestational age) as covariates. If the number of participants in any stratum is too small and/or convergence cannot be achieved, the covariate may be excluded from the model. To allow for differences in follow-up times among the participants, log (follow-up time) as the offset term was added in the modified Poisson regression. If the number of participants in any stratum is too small and/or convergence cannot be achieved, the covariate may be excluded from the model.

The incidence of RSV-associated hospitalization occurring from Days 1 through 150 Postdose 1 in the MK-1654 and palivizumab groups in RSV Season 1 will be estimated and the exact 95% CIs will be provided using the Chi-square distribution for Poisson variable method (Ulm 1990).

An additional analysis to estimate the efficacy of MK-1654 compared to palivizumab against RSV-associated MALRI through the end of the first RSV season will be performed. In this analysis, only infants who develop RSV-associated MALRI through the end of their RSV season will be defined as cases. In other words, the efficacy follow-up duration to be included in the analysis will be until either the date of the end of the RSV season or the Day 150 date, whichever occurs first, thereby only including the relevant period of risk of RSV disease for each infant. A similar analysis will be performed for the endpoint of RSV-associated hospitalization and the incidence of this endpoint along with the CI will be estimated for each treatment group.

For the efficacy analyses, cases of both RSV A and RSV B associated MALRI (or hospitalization) will be counted as endpoints. The efficacy of MK-1654 relative to palivizumab

in RSV Season 1 against RSV A associated MALRI and RSV B associated MALRI will also be estimated separately. Similarly, the incidence of RSV A-associated hospitalization and RSV B-associated hospitalization in each treatment group will be estimated separately.

The incidence of RSV-associated MALRI and RSV-associated hospitalization through Day 180 postdose MK-1654 in RSV Season 2 and the corresponding 95% CIs will be computed:

- Separately by treatment group to which participants were randomized to in RSV Season 1.
- Both treatment groups combined.

For an episode of respiratory infection to be considered for evaluation of an efficacy endpoint, a RT-PCR result from the study central laboratory must be available for a nasopharyngeal sample that is collected no more than 12 days after symptom onset or symptom worsening, or after symptom onset and no more than 7 days before symptom worsening. A sensitivity analysis will be conducted, which will include RT-PCR results from nasopharyngeal samples collected within the timeframe mentioned above, but not tested at the study central laboratory. Also, if a participant with symptoms of respiratory infection prior to dosing has a nasopharyngeal sample collected predose on Day 1 that is RT-PCR positive for RSV, this episode will not be counted as a case toward the efficacy endpoints.

Sample Size

There is no formal sample size calculation. The Applicant chosen sample size of 1000 participants took into account the difficulty in recruiting this population and the estimated precision for the efficacy estimates. Based on literature and assuming an RSV-associated MALRI incidence of 15%, an attrition rate of 10%, and the expected range of efficacy of MK-1654 versus palivizumab of 25% to 40%. Based on these assumptions, the Applicant decided that 1000 participants in this trial would provide a reasonable level of precision for the efficacy estimates.

Analysis Populations

FAS Population

The protocol-defined FAS population (as defined in the SAP) consists of all randomized participants who received at least one dose of study treatment and is intended to serve as the primary population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. Participants were included in the treatment group based on the study treatment they were randomized to for the efficacy analyses. Of note, even though the FAS was defined as above, participants with protocol violations were excluded from the FAS used for the efficacy analyses presented in this review. However, the Prescribing Information presents the results from the protocol-defined FAS population (i.e., participants with protocol violations were not excluded from the efficacy results in the Prescribing Information). Notably, the efficacy results were not impacted by the inclusion or exclusion of these participants.

PPE Population

To be eligible for inclusion in the PPE population, trial participants must satisfy the following criteria:

- Receive a complete regimen of the correct clinical material corresponding to the treatment group the participants were randomized into (i.e., one dose of clesrovimab for participants randomized to the clesrovimab group and three to five doses of palivizumab within the protocol-specified windows for participants randomized to the palivizumab group based on the date of enrollment and the predefined RSV season end date at each site).
- Have at least one follow-up visit/contact for assessment of RSV disease.
- Do not undergo 1) ECMO or 2) surgical intervention for CHD requiring cardiopulmonary bypass during the efficacy follow-up period (Day 150 or Day 180).
- At any time during dosing or efficacy follow-up, do not experience a protocol deviation that may interfere with the assessment of protection against RSV infection conferred by clesrovimab.

APaT Population

The protocol-specified safety population was the APaT population (as defined in the SAP), which consisted of all randomized/allocated participants who received at least one dose of study treatment. Participants were included in the treatment group based on the study treatment they actually received for the analysis of safety data using the APaT population. Of note, even though the safety analysis population was defined as above, participants with protocol violations were excluded from the APaT population as well for the safety analyses presented in this review. However, the Prescribing Information presents the results from the protocol-defined APaT population.

Missing Data (To Evaluate the Impact of Missing Data)

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, they were trial dropouts. Missing data will not be imputed for any of the efficacy analyses.

Safety Monitoring

In Trial MK-1654-007, clesrovimab was administered on Day 1 and participants were observed for at least 30 minutes postdose for any signs/symptoms of: an immediate anaphylaxis/hypersensitivity AE, an immediate rash AE, injection site AEs including redness/erythema, swelling, and tenderness/pain, and any other AEs. Because clesrovimab is administered as a single dose (per RSV season), all participants received the entire course of clesrovimab (for Season 1). Participants were monitored for 30 minutes postdose for all clesrovimab, placebo, and palivizumab doses.

The safety of clesrovimab will primarily be assessed by the occurrence of treatment-emergent AEs, SAEs, and AESI reported during the trial. Severity of adverse events will be graded according to an adaption of NCI-CTCAE version 5.0 as applicable for pediatric/infant assessments.

The eDMC will review available safety, pharmacokinetics, and RSV disease incidence data from Trial MK-1654-007 approximately every 6 months.

Protocol MK-1654-007-00 and amendments MK-1654-007-01, MK-1654-007-02, which were submitted to BLA 761432 on October 10, 2024, were reviewed and are referenced in this BLA review. Of note, the most recent version of this protocol, MK-1654-007-03, was submitted to IND 130097 on October 29, 2024, but was not submitted the BLA. In this protocol amendment, the most substantive update was that the reporting period for SAEs after the protocol-specified follow-up period only includes reporting of drug-related SAEs.

16. Efficacy

16.1.1. Trial MK-1654-004

Demographics

In the following demographics summary (Table 93), we added ethnicity and length at randomization to the baseline demographics and clinical characteristics table presented earlier in Section 6. Among participants who received clesrovimab or placebo, 28% were Hispanic or Latino and 69% were Not Hispanic or Latino; and the median length of infants was 59.5 cm (range: 37.8 to 80.5 cm). The ethnicity and length at randomization were balanced between clesrovimab group and placebo group.

Table 93. Baseline Demographics and Clinical Characteristics, Full Analysis Set, Trial MK-1654-004

Characteristic	Clesrovimab (N=2411)	Placebo (N=1203)	Total (N=3614)
Sex, n (%)			
Male	1228 (50.9)	617 (51.3)	1845 (51.1)
Female	1183 (49.1)	586 (48.7)	1769 (48.9)
Age at randomization (months)[1], n (%)			
<6	1918 (79.6)	960 (79.8)	2878 (79.6)
≥6 to <9	388 (16.1)	196 (16.3)	584 (16.2)
≥9	105 (4.4)	47 (3.9)	152 (4.2)
Mean	3.7	3.7	3.7
SD	2.6	2.6	2.6
Median	3.0	3.1	3.1
Range	0.1 to 11.9	0.1 to 11.7	0.1 to 11.9
Race, n (%)			
American Indian or Alaska Native	50 (2.1)	18 (1.5)	68 (1.9)
Asian	641 (26.6)	320 (26.6)	961 (26.6)
Black or African American	326 (13.5)	171 (14.2)	497 (13.8)
Multiple	302 (12.5)	138 (11.5)	440 (12.2)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	2 (<1)
White	1082 (44.9)	550 (45.7)	1632 (45.2)
Missing	9 (<1)	5 (<1)	14 (<1)
Ethnicity, n (%)			
Hispanic or Latino	682 (28.3)	335 (27.8)	1017 (28.1)
Not Hispanic or Latino	1660 (68.9)	834 (69.3)	2494 (69.0)
Unknown or missing	69 (2.9)	34 (2.8)	103 (2.9)

Characteristic	Clesrovimab (N=2411)	Placebo (N=1203)	Total (N=3614)
Gestational age, n (%)			
Early and moderate preterm infant (≥29 to <35 weeks)	422 (17.5)	209 (17.4)	631 (17.5)
Late preterm and full-term infant (≥35 weeks)	1989 (82.5)	994 (82.6)	2983 (82.5)
Hemisphere at randomization, n (%)			
Northern hemisphere	1650 (68.4)	814 (67.7)	2464 (68.2)
Southern hemisphere	761 (31.6)	389 (32.3)	1150 (31.8)
Climate at randomization, n (%)			
Temperate	1952 (81.0)	970 (80.6)	2922 (80.9)
Tropical/subtropical	459 (19.0)	233 (19.4)	692 (19.1)
Body weight at randomization (kg)			
Mean	5.8	5.9	5.8
SD	2.0	2.0	2.0
Median	5.8	5.8	5.8
Range	1.6 to 11.9	1.6 to 11.6	1.6 to 11.9
Length at randomization (cm)			
Mean	59.2	59.3	59.2
SD	7.6	7.5	7.5
Median	59.5	59.5	59.5
Range	37.8 to 80.0	39.7 to 80.5	37.8 to 80.5

Source: FDA statistical reviewer; Tool: SAS
Data source: adsl.xpt.
[1] For age categories, the statistical reviewer used the natural calendar to decide the age in months and then categorized participants into age groups. The primary endpoint also uses the natural calendar to convert age in months. The Applicant used the average number of days (30.4 days/month) to determine the age in months. The different ways to convert age in months can result in a small difference in the demographics table.
Abbreviations: N, number of participants in treatment arm; n, number of participants with given characteristic; SAS, statistical analysis system; SD, standard deviation

Discrepancy in Age-Group Categorization

We identified an inconsistency in the Applicant's approaches for categorizing participants into age groups. Two distinct approaches were employed: natural calendar-based categorization and average days per month (30.4 days) based categorization. This discrepancy in methods can lead to conflicting age group assignments. For instance, a participant born on February 16, 2023, would be classified as older than 6 months on August 16, 2023, using the natural calendar method, but less than 6 months old using the average days per month conversion.

The Applicant applied these two methods inconsistently across analyses:

- Primary and secondary endpoint analyses utilized the natural calendar-based categorization.
- Demographic tables and subgroup analyses employed the average days per month conversion.

The following table illustrates that 10 participants categorized as older than 6 months based on the natural calendar were classified as less than 6 months old using the average days method; and one participant categorized as less than 6 months old based on the natural calendar was classified as 6 months or older using the average days method.

Table 94. Discrepancy in Age-Group Classification, Full Analysis Set, Trial MK-1654-004

	Average Days per Month-Based Categorization		
Natural Calendar-Based Categorization	**<6 Months**	**≥6 Months**	**Total**
<6 months	2877	1	2878
≥6 months	10	726	736

Source: FDA statistical reviewer; Tool: SAS. Data source: adeff.xpt, adsl.xpt
Abbreviation: SAS, statistical analysis system

To address this inconsistency and ensure methodological coherence, we decided to standardize the age group categorization. We aligned all analyses with the primary endpoint methodology, adopting the natural calendar-based approach throughout the trial.

Sensitivity Analyses

Section 6.2.2.4 outlines the sensitivity analyses using various settings or assumptions. All those analyses employed the Poisson regression model with robust variance. An additional sensitivity analysis, not listed in Section 6.2.2.4, was conducted as described below.

The Agency implemented a negative binomial model as an alternative to the Poisson regression. The rationale for this change is that negative binomial regression is a generalization of Poisson regression, which relaxes the restrictive assumption of equal variance and mean, which is inherent in the Poisson model.

The Agency noted that the results from the Poisson regression model (without robust variance) showed a scaled Pearson Chi-Square value of 8 (>1), indicating overdispersion and suggesting that the mean and variance are not equal, which is an assumption of the model.

To evaluate the effect of the possible overdispersion, Table 95 presents the sensitivity analysis results from a negative binomial model with robust variance, maintaining other settings identical to the Poisson regression model. The relative risk reduction is 77.6% (95% CI: 67.7%, 84.5%; p<0.001), which is higher than the primary endpoint analysis of 60.4% (95% CI: 44.1%, 71.9%; p<0.001) using the Poisson regression.

To compare the goodness of fit, the quasi-information criterion was used. The quasi-information criterion values are 394 and 191 for the negative binomial model and the Poisson model, respectively. This suggests that the Poisson model provides a better fit to the data.

Table 95. Sensitivity Analyses on RSV-Associated MALRI (Outpatient and Inpatient) From Days 1 Through 150 Postdose, Full Analysis Set, Trial MK-1654-004

Clesrovimab (N=2411)				Placebo (N=1203)				Relative Risk Reduction (%)	
No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Estimate (95% CI)[3]	p-Value (1-Sided)[3]
2398	62	11680.0	0.027	1201	77	5699.0	0.068	77.6 (67.7, 84.5)	<0.001

Source: FDA statistical reviewer; Tool: SASData source: adeff.xpt, adsl.xpt.
[1] One month is defined as 30 days for the total follow-up time calculation.
[2] Five months is defined as 150 days.
[3] Estimate and 95% CI of efficacy were estimated from the negative binomial regression model with robust variance method. For the RSV-associated MALRI endpoint, the model included the following covariates: hemisphere at randomization, gestational age group, and age group at randomization. One-sided p-value was estimated by an exact binomial method.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus; SAS, statistical analysis system

Subgroup Analyses

Subgroup analyses were conducted on the primary efficacy endpoint: RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose.

The detail for Figure 3 is shown in Table 95.

Table 96. Subgroup Analyses on RSV-Associated MALRI (Outpatient and Inpatient) From Days 1 Through 150 Postdose, Full Analysis Set, Trial MK-1654-004

	Clesrovimab (N=2411)				Placebo (N=1203)				
Subgroups	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	No. of Participants	No. of Cases	Total Follow-Up Time in Months[1]	Incidence Rate Over 5 Months[2]	Relative Risk Reduction (%) Estimate (95% CI)[3]
Overall	2398	60	11685.6	0.026	1201	74	5710.5	0.065	60.4 (44.1, 71.9)
RSV subtype									
RSV A	2398	29	11780.2	0.012	1201	26	5868.9	0.022	44.4 (5.5, 67.3)
RSV B	2398	33	11786.1	0.014	1201	48	5797.4	0.041	66.2 (47.2, 78.3)

	Clesrovimab (N=2411)				Placebo (N=1203)				
Subgroups	**No. of Participants**	**No. of Cases**	**Total Follow-Up Time in Months[1]**	**Incidence Rate Over 5 Months[2]**	**No. of Participants**	**No. of Cases**	**Total Follow-Up Time in Months[1]**	**Incidence Rate Over 5 Months[2]**	**Relative Risk Reduction (%) Estimate (95% CI)[3]**
Gestational age									
Early and moderate preterm	417	9	2027.3	0.022	208	21	957.6	0.11	79.8 (55.5, 90.8)
Late preterm and full-term	1981	51	9658.3	0.026	993	53	4752.9	0.056	52.6 (30.3, 67.8)
Age									
<6 months	1910	47	9323.9	0.025	959	66	4537.4	0.073	65.3 (49.6, 76.5)
≥6 to <9 months	384	10	1856.1	0.027	195	6	944.6	0.032	15.2 (-140.5, 70.3)
≥9 months	104	3	505.6	0.03	47	2	228.6	0.044	32.2 (-446.2, 89.4)
Body weight									
<5 kg	860	23	4181.4	0.028	428	36	2012.1	0.089	69.3 (47.9, 81.8))
≥5 to <8 kg	1150	25	5622.5	0.022	577	25	2770.6	0.045	50.7 (13.9, 71.8)
≥8 kg	388	12	1881.7	0.032	196	13	927.9	0.070	54.5 (-0.6, 79.4)
Sex									
Female	1176	18	5766	0.016	586	32	2803.4	0.057	72.7 (51.2, 84.7)
Male	1222	42	5919.6	0.035	615	42	2907.1	0.072	50.9 (24.4, 68.1)
Race									
American Indian or Alaska Native	48	0	237.1	0	18	0	88.3	0	N/A
Asian	638	9	3145.3	0.014	320	12	1565.7	0.038	62.7 (11.1, 84.3)
Black or African American	325	9	1544.9	0.029	171	13	785.8	0.083	64.8 (17.1, 85.0)
Multiple	302	18	1421.2	0.063	138	12	639.9	0.094	32.5 (-42.1, 67.9)
White	1075	24	5290.9	0.023	548	37	2603.5	0.071	68.1 (46.5, 81.0)

	Clesrovimab (N=2411)				Placebo (N=1203)				
Subgroups	**No. of Participants**	**No. of Cases**	**Total Follow-Up Time in Months[1]**	**Incidence Rate Over 5 Months[2]**	**No. of Participants**	**No. of Cases**	**Total Follow-Up Time in Months[1]**	**Incidence Rate Over 5 Months[2]**	**Relative Risk Reduction (%) Estimate (95% CI)[3]**
Hemisphere									]
Northern hemisphere	1637	26	8063	0.016	812	35	3926.2	0.045	63.8 (39.8, 78.3)
Southern hemisphere	761	34	3622.6	0.047	389	39	1784.3	0.109	57.1 (31.6, 73.1)
Climate									
Subtropical or tropical regions	456	21	2189.4	0.048	233	15	1098.3	0.068	29.8 (-37.5, 64.1)
Temperate regions	1942	39	9496.3	0.021	968	59	4612.2	0.064	67.9 (51.8, 78.6)
United States vs. non-U.S. region									
United States	313	10	1507.4	0.033	155	3	758.6	0.020	-67.7 (-515.1, 54.3)
Non-U.S. region	2085	50	10178.2	0.025	1046	71	4952.0	0.072	65.7 (50.7, 76.2)
North America and Western Europe vs. other countries									
North America and Western Europe	623	15	3048.7	0.025	315	16	1509.4	0.053	53.6 (5.6, 77.2)
Other countries	1775	45	8637.0	0.026	886	58	4201.1	0.069	62.3 (44.1, 74.5)

Source: FDA statistical reviewer; Tool: R.
Data source: adeff.xpt, adsl.xpt.
The point estimate sizes are reflective of their value.
For the analyses by RSV subtype, the RSV A and RSV B are not mutually exclusive. The efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate.
For the other subgroup efficacy analyses, the efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, or an exact binomial method if convergence issues exist with the Poisson approach.
Abbreviations: CI, confidence interval; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; No., number; RSV, respiratory syncytial virus; U.S., United States

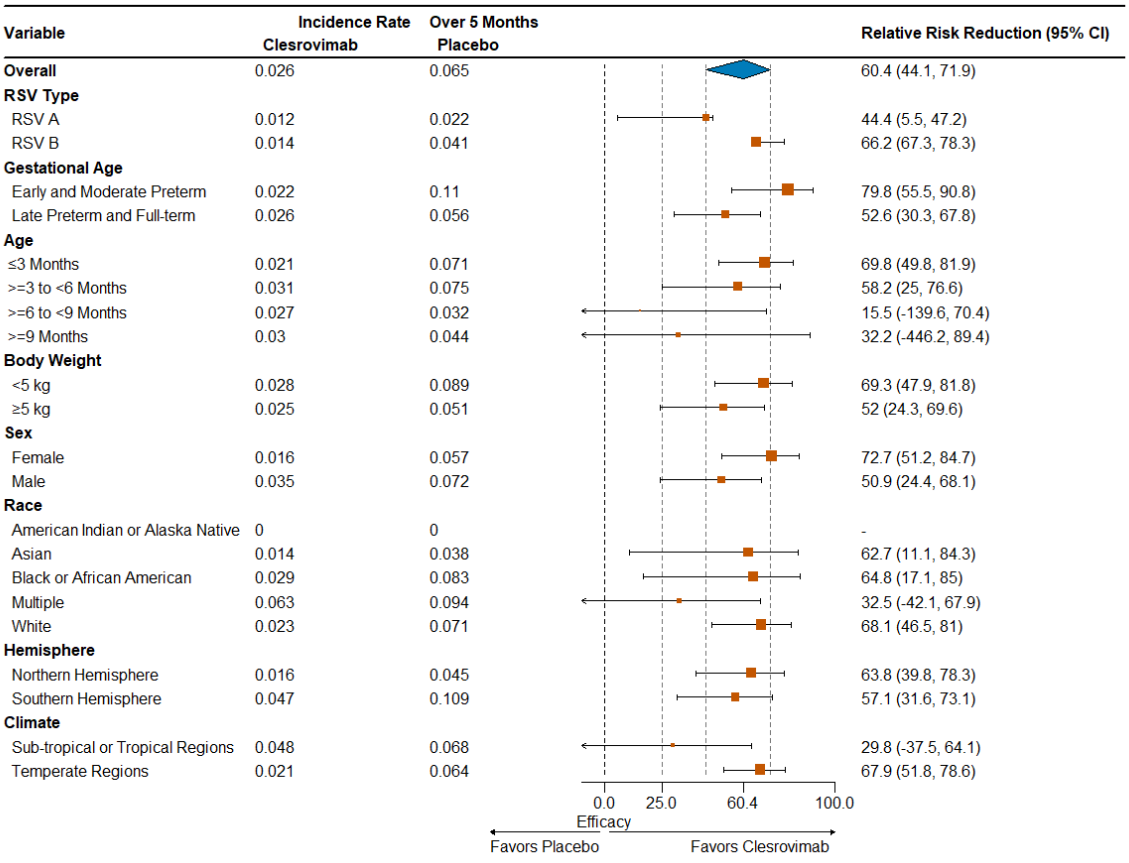
Since the results of subgroup analyses can depend on the categorization of a baseline factor, we explored different categorizations of age and weight in the subgroup analyses. Additional subgroup analyses, not listed in Section 6.2.2.4, were conducted as described below.

Setting

Age groups were categorized as <3 months, 3 to 6 months, 6 to 9 months, and ≥9 months, as well as weight groups were categorized as <5 kg and ≥5 kg.

As shown in Figure 23, the estimated RRR for the ≤3 months and 3 to 6 months age subgroups were similar to the observed in the overall primary efficacy results, while the RRR estimates for the age subgroups of 6 to 9 months and ≥9 months were lower than observed in the overall primary efficacy results. The subgroup analyses by weight (<5 kg and ≥5 kg) appeared consistent. Given that age and weight are highly correlated, we would expect to observe similar trends in both age and weight subgroups. However, the weight categorization (<5 kg and ≥5 kg) does not reflect the trend observed in age groups.

Figure 23. Subgroup Analyses, Trial MK-1654-004



Source: FDA statistical reviewer; Tool: R. Data source: adeff.xpt, adsl.xpt.
The point estimate sizes are reflective of their value.
For the analyses by RSV subtype, the RSV A and RSV B are not mutually exclusive. The efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, which included only the term of treatment group as a covariate.
For the other subgroup efficacy analyses, the efficacy and 95% CI were estimated from the Poisson regression model with robust variance method, or an exact binomial method if convergence issues exist with the Poisson approach.
Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus

Reasons for Participants Who Were Excluded From FAS

A total of 3614 participants were randomized and dosed, and of these, the Applicant excluded 15 participants from the FAS due to protocol violations (13 participants from the clesrovimab group and 2 participants from the placebo group). These 15 participants are also excluded from the primary statistical analyses presented in this review. However, sensitivity analyses in which these 15 participants are included in the efficacy population are presented in Section 6.2.2.4 and analyses using the protocol-specified efficacy population (i.e., including these participants with protocol violations) is presented in Patient Labeling.

The exclusion reasons for the 15 participants are listed in Table 97. Regarding the 5 participants who were excluded for "suspected misconduct", they were all excluded from Site 0057 in Ontario, Canada, United States. According to the Applicant "Blinded study staff completed protocol-specific forms intended to be completed only by the unblinded Study Coordinator. The information was given from unblinded Study Coordinator to the blinded Study Coordinator using post-it notes that were not maintained as an original source document. The post-it notes were discarded. Although there is no unequivocal evidence that unblinding occurred, this cannot be ruled out based on conflicting explanations provided by the site." The review team concluded that it was appropriate to include these 5 participants as well as the other 10 participants with protocol deviations in the efficacy analyses presented in Patient Labeling, consistent with the protocol-defined efficacy/FAS population.

Table 97. Participants Excluded From Efficacy Analyses For the Full Analysis Set Population, Trial MK-1654-004

Unique Subject ID[1]	Arm	Excluded From Safety (Y/N)	Excluded From Efficacy (Y/N)	Reason for Exclusion	Completed Day 150 Visit (Y/N)[2]
(b) (6)	Clesrovimab	N	Y	Improper storage of study treatment	Y
	Clesrovimab	N	Y	Improper storage of study treatment	Y
	Clesrovimab	N	Y	Improper storage of study treatment	Y
	Clesrovimab	N	Y	Improper storage of study treatment	Y
	Clesrovimab	N	Y	Suspected misconduct	Y
	Clesrovimab	N	Y	Suspected misconduct	Y
	Clesrovimab	N	Y	Suspected misconduct	Y
	Clesrovimab	N	Y	Suspected misconduct	Y
	Clesrovimab	N	Y	Suspected misconduct	Y
	Clesrovimab	N	Y	Improper storage of study treatment	Y
	Clesrovimab	Y	Y	Enrolled in the trial more than once[3]	Y
	Clesrovimab	Y	Y	Enrolled in the trial more than once[3]	Y

Unique Subject ID[1]	Arm	Excluded From Safety (Y/N)	Excluded From Efficacy (Y/N)	Reason for Exclusion	Completed Day 150 Visit (Y/N)[2]
(b) (6)	Clesrovimab	Y	Y	Enrolled in the trial more than once[3]	Y
	Placebo	N	Y	Improper storage of study treatment	Y
	Placebo	N	Y	Improper storage of study treatment	Y

Source: Response to FDA IR Received on May 28, 2025, Biostatistics and Clinical Information, Table 1. MK-1654-004 Participants Excluded From Analyses
[1] This is not the unique subject ID used in the ADaM datasets. This ID includes the site ID and subject ID only
[2] N/A= participants who were randomized but not treated and discontinued from the study before completing any follow-up visits.
[3] Of the 3 participants enrolled in the trial more than once, 1 participant received 2 doses of clesrovimab. The other 2 participants received 1 dose of clesrovimab and 1 dose of placebo.
Abbreviations: ID, identification; IR, information request; N, no; Y, yes

16.1.2. Trial MK-1654-007

Demographics

In the following demographics summary (Table 98), we added ethnicity and length at randomization to the demographics and baseline characteristics table presented earlier in Section 6. Among participants who received clesrovimab or placebo, 32% were Hispanic or Latino and 66% were Not Hispanic or Latino; the median length of infants was 50.0 cm (range: 35.0 to 74.5 cm). The ethnicity and length were balanced between the clesrovimab and placebo groups.

Table 98. Demographics and Baseline Characteristics, Full Analysis Set, Trial MK-1654-007

Characteristic	Clesrovimab (N=446)	Palivizumab (N=450)	Total (N=896)
Sex, n (%)			
M	225 (50.4)	221 (49.1)	446 (49.8)
F	221 (49.6)	229 (50.9)	450 (50.2)
Age at randomization (months), n (%)			
<6	409 (91.7)	390 (86.7)	799 (89.2)
≥6 to <9	33 (7.4)	51 (11.3)	84 (9.4)
≥9	4 (<1)	9 (2.0)	13 (1.5)
Race, n (%)			
American Indian or Alaska Native	5 (1.1)	7 (1.6)	12 (1.3)
Asian	82 (18.4)	80 (17.8)	162 (18.1)
Black or African American	67 (15.0)	71 (15.8)	138 (15.4)
Multiple	56 (12.6)	53 (11.8)	109 (12.2)
Native Hawaiian or Other Pacific Islander	5 (1.1)	2 (<1)	7 (<1)
White	231 (51.8)	237 (52.7)	468 (52.2)
Ethnicity, n (%)			
Hispanic or Latino	138 (30.9)	146 (32.4)	284 (31.7)
Non-Hispanic or Latino	296 (66.4)	296 (65.8)	592 (66.1)
Unknown or missing	12 (2.7)	8 (1.8)	20 (2.2)
Gestational age, n (%)			
<29 weeks	98 (22.0)	108 (24.0)	206 (23.0)
≥29 to <35 weeks	299 (67.0)	290 (64.4)	589 (65.7)
≥35 weeks	49 (11.0)	52 (11.6)	101 (11.3)

Characteristic	Clesrovimab (N=446)	Palivizumab (N=450)	Total (N=896)
Participants condition, n (%)			
CHD	52 (11.7)	49 (10.9)	101 (11.3)
CLD	124 (27.8)	126 (28.0)	250 (27.9)
Neither CLD nor CHD greater than or equal to 29 weeks gestational age	244 (54.7)	251 (55.8)	495 (55.2)
Neither CLD nor CHD less than 29 weeks gestational age	26 (5.8)	24 (5.3)	50 (5.6)
Region at randomization, n (%)			
Northern hemisphere	318 (71.3)	323 (71.8)	641 (71.5)
Southern hemisphere	128 (28.7)	127 (28.2)	255 (28.5)
Climate at randomization, n (%)			
Temperate	367 (82.3)	369 (82.0)	736 (82.1)
Tropical/subtropical	79 (17.7)	81 (18.0)	160 (17.9)
Body weight at randomization (kg)			
Mean	3.8	3.6	3.7
SD	1.47	1.49	1.48
Median	3.5	3.2	3.3
Min, max	1.1, 9.6	1.5, 9.1	1.1, 9.6
Length at randomization (cm)			
Mean	51.3	50.9	51.1
SD	6.43	6.72	6.58
Median	50.0	49.4	50.0
Min, max	35.0, 71.0	35.0, 74.5	35.0, 74.5
Missing	3	0	3

Source: FDA Statistical Reviewer. Tool: SAS. Data source: adsl.xpt
Abbreviations: CHD, congenital heart disease; CLD, chronic lung disease; FAS, full analysis set; F, female; M, male; max, maximum; min, minimum; N, number of participants in treatment arm; n, number of participants with given characteristic; SD, standard deviation

Reasons for Participants Who Were Excluded From FAS

A total of 896 participants were randomized and dosed, and of these, 16 participants were excluded from the FAS due to protocol violations, with 3 participants from the clesrovimab group and 13 participants from the palivizumab group excluded by the Applicant and from the analyses presented in this review. The exclusion reasons for the 16 participants are listed in Table 99.

Table 99. Participants Excluded From Efficacy Analyses For the Full Analysis Set Population, Trial MK-1654-007

Unique Subject ID[1]	Arm	Excluded From Safety (Y/N)	Excluded From Efficacy (Y/N)	Reason for Exclusion	Completed Day 150 Visit (Y/N)[2]
(b) (6)	Clesrovimab	N	Y	Improper storage of study treatment	N
	Clesrovimab	N	Y	Improper storage of study treatment	Y
	Clesrovimab	N	Y	Improper storage of study treatment	Y
	Clesrovimab	Y	N	Mis-dosed; received palivizumab at Dose 2 instead of placebo	Y

Unique Subject ID[1]	Arm	Excluded From Safety (Y/N)	Excluded From Efficacy (Y/N)	Reason for Exclusion	Completed Day 150 Visit (Y/N)[2]
(b) (6)	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	No consent[4]	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	N
	Palivizumab	N	Y	Improper storage of study treatment	Y
	Palivizumab	N	Y	Improper storage of study treatment	Y

Source: Response to FDA IR Received on May 28, 2025, Biostatistics and Clinical Information, Table 2. MK-1654-007 Participants Excluded From Analyses in RSV Season 1
[1] This is not the unique subject ID used in the ADaM datasets. This ID includes the site ID and subject ID only.
[2] N/A= participants who were randomized but not treated and discontinued from the study before completing any follow-up visits.
[3] The participant (Unique Subject ID: (b) (6)) was excluded from safety analysis but included in the efficacy analysis.
[4] Initial consent (IC) form missing date; therefore, IC considered incomplete.
Abbreviations: ID, identification; IR, information request; N, no; RSV, respiratory syncytial virus; Y, yes

17. Clinical Safety

17.1. Safety Results

17.1.1. Trial MK-1654-001

Trial MK-1654-001 was a Phase 1 single-ascending dose study evaluating the safety and pharmacokinetics of clesrovimab in 152 healthy adult participants who were randomized 3:1 to receive a single dose of clesrovimab or placebo. Single doses of clesrovimab (administered at 100 mg and 300 mg IM; and 300 mg, 1,000 mg, and 3,000 mg IV) were generally well tolerated in healthy adult participants. No deaths were reported, there were no dose-limiting tolerability issues, the trial pause criteria were not met, and no participants discontinued from the trial due to an AE. No dose-dependent pattern of intervention-related AEs was observed. Two participants developed rashes (generalized urticaria and nonspecific maculo-papular rash), which were both

attributed to study intervention, mild in severity, and self-resolved. One SAE was reported in the placebo group; this was a tibial fracture that was assessed as not related to study intervention by the Investigator. No SAEs were reported in the clesrovimab group.

17.1.2. Trial MK-1654-003

Trial MK-1654-003 was a Phase 1 single-ascending dose study evaluating the safety and pharmacokinetics of a single dose of clesrovimab in 44 healthy Japanese male adult participants who were randomized 3:1 to receive a single dose of clesrovimab or placebo. Single doses of clesrovimab (administered at 100 mg and 300 mg IM; and 300 mg and 1,000 mg IV) were generally well tolerated in healthy Japanese male participants in the trial. No deaths were reported, there were no dose-limiting tolerability issues, the trial pause rules were not met, and no participants discontinued from the trial due to an AE. No dose-dependent pattern of intervention-related AEs was observed. One SAE of tendon rupture was reported in a participant in the clesrovimab 300 mg IV group which occurred 250 days after dosing while the participant was playing soccer. The SAE was assessed as not related to study intervention by the Investigator and resolved.

17.1.3. Trial MK-1654-005

Trial MK-1654-005 was a Phase 2 double-blind, randomized, placebo-controlled, challenge study to evaluate the efficacy and safety of clesrovimab in healthy adult participants 18 to 55 years of age who were inoculated with experimental RSV. Single IV doses of MK-1654 (100 mg, 200 mg, 300 mg, and 900 mg) were generally well tolerated in healthy male and female trial participants and there was no apparent increase in safety events in participants that received clesrovimab after RSV challenge. No deaths or SAEs were reported, and no participants discontinued from the trial due to an AE. No dose-dependent pattern of drug-related AEs were observed.

17.1.4. Trial MK-1654-002

Trial MK-1654-002 was a Phase 1/2 single ascending-dose (dose-finding) study to evaluate the safety and pharmacokinetics of clesrovimab in healthy male and female infants 2 weeks to 8 months of age who were preterm (born at 29 to 35 weeks gestational age) or full-term (born at greater than 35 weeks gestational age). In this trial, 143 infant participants received clesrovimab at any dose, of which 64 participants (enrolled in Panels D and E) received clesrovimab at a dose of 100 mg, which is comparable to the to-be-marketed dose of 105 mg. The proportions of participants with solicited injection site AEs, solicited systemic AEs, and SAEs were generally comparable across all clesrovimab dose groups and placebo groups. No acute hypersensitivity/allergic reactions related to any study intervention were reported 2 hours postdose. Solicited allergic reactions of difficulty breathing (one participant in the MK-1654 75-mg group) and wheezing (one participant in each of the placebo, MK-1654 50-mg, and 75-mg groups) were reported through Day 30. All solicited allergic reactions to MK-1654 were of mild intensity and were assessed as not related to study intervention by the Investigator. No deaths were reported, and no participant discontinued the trial due to an AE. No SAEs were assessed as related to study intervention by the Investigator.

17.1.5. Trial MK-1654-008

Trial MK-1654-008 was a single arm, open-label Phase 1 study in China to evaluate the safety and tolerability of MK-16544 in 75 Chinese participants, of which 25 infants ≤1 year of age received a single 105-mg dose of clesrovimab. Healthy Chinese male adults (age ≥18 to ≤55 years), children (age ≥2 to ≤8 years), and infants (full-term with ≥35 weeks gestational age and preterm with ≥29 to <35 weeks gestational age) with a chronological age of ≥2 weeks to ≤1 year were enrolled. This trial enrolled 25 healthy infant participants aged ≥2 weeks (14 days) to ≤1 year (365 days), including three to five preterm infants born at ≥29 to <35 weeks gestational age and 20 to 22 full-term infants born at ≥35 weeks gestational age. Safety data through 42 days postdose were reviewed for all participants by the eDMC, after which the eDMC recommended these participants enroll in Trial MK-1654-004. One (4.0%) participant in Panel A (adults 20 to 54 years of age) reported an anaphylaxis/hypersensitivity AESI which was assessed as not related by the Investigator. This event occurred on Day 24 postdose due to cefazolin sodium (IV) received for "contusion of finger" on Day 23, was reported as moderate in severity, and resolved 9 days after the cefazolin sodium stopped on Day 24 postdose. No rash AESI was reported from Day 1 through Day 42 postdose. Two SAEs were reported by two (8.0%) participants in Panel B (children 2 to 8 years of age) during the trial. Both of these SAEs were reported after Day 42 postdose and were assessed as not related to study drug by the Investigator. No deaths were reported in Trial MK-1654-008.

17.2. Subgroup Analyses

17.2.1. Subgroup Analyses by Baseline Characteristics, Trial MK-1654-004

In Trial MK-1654-004, participants of American Indian or Alaska Native, Black or African American, or multiple race experienced AEs more frequently in the clesrovimab group than the placebo group compared with White or Asian participants; with AEs reported in 68.0% versus 61.1% of American Indian or Alaska Native participants, 73.1% versus 67.6% of Black or African American participants, and 80.1% versus 74.6% of multiple race participants in the clesrovimab versus placebo groups, respectively.

By the subgroup of age, in children ≥9 months of age, AEs were observed at a higher frequency in the clesrovimab group (86.7%) than the placebo group (76.6%).

Many of these subgroups were small and the differences in rates of AEs by treatment group across the subgroups is of unclear clinical significance.

Table 100. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial MK-1654-004

Characteristic	MK-1654 (N=2409) n/N_s (%)	Placebo (N=1202) n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	865/1180 (73.3)	442/586 (75.4)	-2.1 (-6.3, 2.3)
Male	951/1229 (77.4)	476/616 (77.3)	0.1 (-3.9, 4.2)
Age group, months			
<6	1412/1921 (73.5)	730/963 (75.8)	-2.3 (-5.6, 1.1)
≥6 to <9	313/383 (81.7)	152/192 (79.2)	2.6 (-4.1, 9.8)
≥9	91/105 (86.7)	36/47 (76.6)	10.1 (-2.5, 25.1)
Race			
American Indian or Alaska Native	34/50 (68.0)	11/18 (61.1)	6.9 (-17.0, 32.9)
Asian	447/638 (70.1)	227/320 (70.9)	-0.9 (-6.9, 5.4)
Black or African American	239/327 (73.1)	115/170 (67.6)	5.4 (-2.9, 14.1)
Multiple	242/302 (80.1)	103/138 (74.6)	5.5 (-2.7, 14.4)
Native Hawaiian or Other Pacific Islander	1/1 (100)	1/1 (100)	0.0 (-88.5, 88.5)
White	845/1082 (78.1)	456/550 (82.9)	-4.8 (-8.7, -0.7)*
Missing	8/9 (88.9)	5/5 (100)	-11.1 (-44.8, 36.6)
Ethnicity			
Hispanic or Latino	474/682 (69.5)	238/335 (71.0)	-1.5 (-7.4, 4.5)
Not Hispanic or Latino	1290/1658 (77.8)	657/833 (78.9)	-1.1 (-4.4, 2.4)
Not reported	14/17 (82.4)	8/10 (80.0)	2.4 (-27.1, 37.4)
Unknown	36/49 (73.5)	14/23 (60.9)	12.6 (-9.7, 36.0)
Missing	2/3 (66.7)	1/1 (100)	-33.3 (-82.7, 66.9)
Is in United States			
United States	267/322 (82.9)	137/156 (87.8)	-4.9 (-11.2, 2.2)
Not United States	1549/2087 (74.2)	781/1046 (74.7)	-0.4 (-3.6, 2.8)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; N_s, total number of participants for each specific subgroup and were assigned to that specific arm

17.2.2. Subgroup Analyses by Baseline Characteristics, RSV Season 1, Postdose 1, Days 1 Through 42, Trial MK-1654-007

In Trial MK-1654-007, in female participants, AEs were reported at a higher frequency in the clesrovimab group compared with the palivizumab group, with 72.9% of female clesrovimab recipients and 63.3% of female palivizumab recipients reporting an AE.

Participants of Black or African American, White, or Asian race experienced an AE at a higher percentage in the clesrovimab group than the palivizumab group.

Table 101. Overview of Adverse Events by Demographic Subgroup, Safety Population, RSV Season 1, Postdose 1 Days 1 Through 42, Trial MK-1654-007

Characteristic	MK-1654 (N=445) n/N_s (%)	Palivizumab (N=450) n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	161/221 (72.9)	145/229 (63.3)	9.5 (0.9, 18.0) *
Male	152/224 (67.9)	154/221 (69.7)	-1.8 (-10.4, 6.8)
Age group, months			
<6	282/408 (69.1)	253/390 (64.9)	4.2 (-2.3, 10.8)
≥6 to <9	28/33 (84.8)	41/51 (80.4)	4.5 (-13.8, 20.5)
≥9	3/4 (75.0)	5/9 (55.6)	19.4 (-37.8, 61.0)
Race			
American Indian or Alaska Native	2/5 (40.0)	3/7 (42.9)	-2.9 (-52.3, 49.4)
Asian	53/82 (64.6)	50/80 (62.5)	2.1 (-12.6, 16.8)
Black or African American	58/67 (86.6)	56/71 (78.9)	7.7 (-5.2, 20.5)
White	161/231 (69.7)	155/237 (65.4)	4.3 (-4.2, 12.7)
Native Hawaiian or Other Pacific Islander	5/5 (100)	1/2 (50.0)	50.0 (-15.0, 91.6)
Multiple	34/55 (61.8)	34/53 (64.2)	-2.3 (-20.3, 15.8)
Ethnicity			
Hispanic or Latino	91/137 (66.4)	97/146 (66.4)	-0.0 (-11.0, 10.9)
Not Hispanic or Latino	212/296 (71.6)	195/296 (65.9)	5.7 (-1.7, 13.2)
Not reported	5/7 (71.4)	4/5 (80.0)	-8.6 (-53.3, 44.1)
Unknown	5/5 (100)	3/3 (100)	0.0 (-46.8, 59.4)
Is in United States			
United States	12/16 (75.0)	19/24 (79.2)	-4.2 (-32.6, 21.7)
Not United States	301/429 (70.2)	280/426 (65.7)	4.4 (-1.8, 10.7)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; N_s, total number of participants for each specific subgroup and were assigned to that specific arm; RSV, respiratory syncytial virus

17.3. Safety Analyses of Key Safety Events Pooled Across Infant Trials and Across Adult Trials

Pooled safety analyses were conducted across the infant trials (MK-1654-004; MK-1654-007; MK-1654-002 Panels D and E and placebo pooled across panels; MK-1654-008 Panel C) and across the adult trials (MK-1654-001, MK-1654-003, and MK-1654-008 Panel A) for key safety endpoints of interest. Results from additional analyses of hypersensitivity reactions/anaphylaxis AEs within 42 days postdose, rash AEs with 14 days postdose, injection site reactions within 5 days postdose, and fever within various cut points are shown below.

17.3.1. Safety Analyses of Key Safety Events Pooled Across Infant Populations

Key safety analyses conducted in the pooled infant population are shown in the following tables.

Hypersensitivity

Table 102. Adverse Events Assessment of Hypersensitivity OCMQ Medical Query (Narrow), Within 42 Days Postdose, Safety Population, Trial MK-1654-ISS Infant

OCMQ (Narrow) Preferred Term	Trial MK-1654-004 MK-1654 (N=2409) n (%)	Trial MK-1654-004 Placebo (N=1202) n (%)	Trial MK-1654-007 MK-1654 (N=445) n (%)	Trial MK-1654-002 MK-1654 (N=64) n (%)	Trial MK-1654-002 Placebo (N=38) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=2943) n (%)	Pooled Placebo (N=1240) n (%)
Hypersensitivity (OCMQ)	4 (0.2)	3 (0.2)	1 (0.2)	0	0	0	5 (0.2)	3 (0.2)
Allergic gastroenteritis	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Drug eruption	4 (0.2)	2 (0.2)	1 (0.2)	0	0	0	5 (0.2)	2 (0.2)
Maximum severity								
Death	0	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Mild	4 (0.2)	3 (0.2)	1 (0.2)	0	0	0	5 (0.2)	3 (0.2)
Serious	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0	0	0
Relatedness	2 (0.1)	2 (0.2)	1 (0.2)	0	0	0	3 (0.1)	2 (0.2)

Source: adae.xpt; Software: R
Relatedness is determined by the Investigator.
Abbreviations: ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Rash

Table 103. Adverse Events Assessment of Rash FDA Medical Query (Narrow), Within 14 Days Postdose, Safety Population, Trial MK-1654-ISS Infant

OCMQ (Narrow) Preferred Term	Trial MK-1654-004 MK-1654 (N=2409) n (%)	Trial MK-1654-004 Placebo (N=1202) n (%)	Trial MK-1654-007 MK-1654 (N=445) n (%)	Trial MK-1654-002 MK-1654 (N=64) n (%)	Trial MK-1654-002 Placebo (N=38) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=2943) n (%)	Pooled Placebo (N=1240) n (%)
Rash (OCMQ)	84 (3.5)	37 (3.1)	4 (0.9)	5 (7.8)	3 (7.9)	1 (4.0)	94 (3.2)	40 (3.2)
Acne	4 (0.2)	0	0	0	0	0	4 (0.1)	0
Acne infantile	6 (0.2)	2 (0.2)	0	0	1 (2.6)	0	6 (0.2)	3 (0.2)
Candida nappy rash	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Dermatitis	9 (0.4)	5 (0.4)	0	0	0	0	9 (0.3)	5 (0.4)
Dermatitis allergic	2 (0.1)	4 (0.3)	0	0	0	0	2 (0.1)	4 (0.3)
Dermatitis contact	2 (0.1)	3 (0.2)	0	2 (3.1)	0	0	4 (0.1)	3 (0.2)
Erythema multiforme	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Exfoliative rash	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Injection site rash	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Rash	41 (1.7)	11 (0.9)	2 (0.4)	0	0	0	43 (1.5)	11 (0.9)
Rash erythematous	2 (0.1)	1 (0.1)	0	0	0	0	2 (0.1)	1 (0.1)
Rash macular	0	2 (0.2)	0	0	0	0	0	2 (0.2)
Rash maculo-papular	2 (0.1)	1 (0.1)	0	0	2 (5.3)	1 (4.0)	3 (0.1)	3 (0.2)
Rash papular	6 (0.2)	2 (0.2)	0	2 (3.1)	0	0	8 (0.3)	2 (0.2)
Rash pustular	2 (0.1)	0	0	0	0	0	2 (0.1)	0
Rash vesicular	1 (0.0)	0	0	1 (1.6)	0	0	2 (0.1)	0
Skin exfoliation	1 (0.0)	0	0	0	0	0	1 (0.0)	0
Toxic skin eruption	0	1 (0.1)	1 (0.2)	0	0	0	1 (0.0)	1 (0.1)
Urticaria	4 (0.2)	1 (0.1)	1 (0.2)	0	0	0	5 (0.2)	1 (0.1)
Vaccination site rash	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Viral rash	4 (0.2)	2 (0.2)	0	0	0	0	4 (0.1)	2 (0.2)

OCMQ (Narrow) Preferred Term	Trial MK-1654-004 MK-1654 (N=2409) n (%)	Trial MK-1654-004 Placebo (N=1202) n (%)	Trial MK-1654-007 MK-1654 (N=445) n (%)	Trial MK-1654-002 MK-1654 (N=64) n (%)	Trial MK-1654-002 Placebo (N=38) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=2943) n (%)	Pooled Placebo (N=1240) n (%)
Maximum severity								
Death	0	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Severe	1 (0.0)	0	0	0	0	0	1 (0.0)	0
Moderate	5 (0.2)	6 (0.5)	0	0	0	0	5 (0.2)	6 (0.5)
Mild	78 (3.2)	31 (2.6)	4 (0.9)	0	0	0	82 (2.8)	31 (2.5)
Serious	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0	0	0
Relatedness	7 (0.3)	3 (0.2)	0	2 (3.1)	2 (5.3)	1 (4.0)	10 (0.3)	5 (0.4)

Source: adae.xpt; Software: R
Relatedness is determined by the Investigator.
Abbreviations: ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Injection Site Reactions

Table 104. Adverse Events Assessment of Local Administration Reaction OCMQ Medical Query (Narrow), Within 5 Days Postdose, Safety Population, Trial MK-1654-ISS Infant

OCMQ (Narrow) Preferred Term	Trial MK-1654-004 MK-1654 (N=2409) n (%)	Trial MK-1654-004 Placebo (N=1202) n (%)	Trial MK-1654-007 MK-1654 (N=445) n (%)	Trial MK-1654-002 MK-1654 (N=64) n (%)	Trial MK-1654-002 Placebo (N=38) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=2943) n (%)	Pooled Placebo (N=1240) n (%)
Local administration reaction (OCMQ)	235 (9.8)	121 (10.1)	43 (9.7)	4 (6.2)	2 (5.3)	2 (8.0)	284 (9.7)	123 (9.9)
Injection site bruising	4 (0.2)	2 (0.2)	0	0	0	0	4 (0.1)	2 (0.2)
Injection site erythema	90 (3.7)	40 (3.3)	20 (4.5)	2 (3.1)	1 (2.6)	2 (8.0)	114 (3.9)	41 (3.3)
Injection site haematoma	1 (0.0)	0	0	0	0	0	1 (0.0)	0
Injection site haemorrhage	1 (0.0)	1 (0.1)	0	0	0	0	1 (0.0)	1 (0.1)
Injection site induration	1 (0.0)	2 (0.2)	0	0	0	0	1 (0.0)	2 (0.2)
Injection site inflammation	0	0	1 (0.2)	0	0	0	1 (0.0)	0
Injection site irritation	0	0	1 (0.2)	0	0	0	1 (0.0)	0
Injection site macule	1 (0.0)	0	0	0	0	0	1 (0.0)	0
Injection site mass	1 (0.0)	0	0	0	0	0	1 (0.0)	0
Injection site pain	122 (5.1)	77 (6.4)	19 (4.3)	2 (3.1)	1 (2.6)	0	143 (4.9)	78 (6.3)
Injection site rash	0	1 (0.1)	0	0	0	0	0	1 (0.1)
Injection site reaction	1 (0.0)	0	0	0	0	0	1 (0.0)	0
Injection site swelling	65 (2.7)	31 (2.6)	21 (4.7)	1 (1.6)	1 (2.6)	0	87 (3.0)	32 (2.6)
Injection site warmth	1 (0.0)	0	0	0	0	0	1 (0.0)	0
Vaccination site pain	3 (0.1)	1 (0.1)	0	0	0	0	3 (0.1)	1 (0.1)
Vessel puncture site pain	1 (0.0)	0	0	0	0	0	1 (0.0)	0

OCMQ (Narrow) Preferred Term	Trial MK-1654-004 MK-1654 (N=2409) n (%)	Trial MK-1654-004 Placebo (N=1202) n (%)	Trial MK-1654-007 MK-1654 (N=445) n (%)	Trial MK-1654-002 MK-1654 (N=64) n (%)	Trial MK-1654-002 Placebo (N=38) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=2943) n (%)	Pooled Placebo (N=1240) n (%)
Maximum severity								
Death	0	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Severe	2 (0.1)	2 (0.2)	2 (0.4)	0	0	0	4 (0.1)	2 (0.2)
Moderate	43 (1.8)	22 (1.8)	7 (1.6)	0	0	0	50 (1.7)	22 (1.8)
Mild	190 (7.9)	97 (8.1)	34 (7.6)	0	0	0	224 (7.6)	97 (7.8)
Serious	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0	0	0
Relatedness	231 (9.6)	120 (10.0)	43 (9.7)	4 (6.2)	2 (5.3)	2 (8.0)	280 (9.5)	122 (9.8)

Source: adae.xpt; Software: R
Relatedness is determined by the Investigator.
Abbreviations: ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Fever: Protocol-Defined

Table 105. Participants With One or More Elevated Temperature Values Defined by the Protocol as Rectal Temperature ≥102.2°F or Axillary Temperature ≥101.7°F, Safety Population, Trial MK-1654-ISS Infant

Timepoint	Trial MK-1654-004 MK-1654 (N=2409 n (%)	Trial MK-1654-004 Placebo (N=1202) n (%)	Trial MK-1654-007 MK-1654 (N=445) n (%)	Trial MK-1654-002 MK-1654 (N=64) n (%)	Trial MK-1654-002 Placebo (N=38) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=2943) n (%)	Pooled Placebo (N=1240) n (%)
2 days	7 (0.3)	5 (0.4)	1 (0.2)	0 (0)	0 (0)	0 (0)	8 (0.3)	5 (0.4)
5 days	16 (0.7)	15 (1.2)	4 (0.9)	1 (1.6)	1 (2.6)	0 (0)	21 (0.7)	16 (1.3)
7 days	18 (0.7)	15 (1.2)	4 (0.9)	1 (1.6)	1 (2.6)	0 (0)	23 (0.8)	16 (1.3)

Source: advs.xpt; vs.xpt for trial 002; Software: R
Abbreviations: ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with given characteristic

Fever: AAP-Defined

Table 106. Participants With One or More Elevated Temperature Values Defined by the AAP as Rectal Temperature ≥100.4°F or Axillary Temperature ≥98.4°F, Safety Population, Trial MK-1654-ISS Infant

Timepoint	Trial MK-1654-004 MK-1654 (N=2409) n (%)	Trial MK-1654-004 Placebo (N=1202) n (%)	Trial MK-1654-007 MK-1654 (N=445) n (%)	Trial MK-1654-002 MK-1654 (N=64) n (%)	Trial MK-1654-002 Placebo (N=38) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=2943) n (%)	Pooled Placebo (N=1240) n (%)
2 days	538 (22.3)	280 (23.3)	125 (28.1)	9 (14.1)	8 (21.1)	20 (80)	692 (23.5)	288 (23.2)
5 days	741 (30.8)	384 (31.9)	171 (38.4)	13 (20.3)	11 (28.9)	22 (88)	947 (32.2)	395 (31.9)
7 days	760 (31.5)	389 (32.4)	175 (39.3)	13 (20.3)	11 (28.9)	22 (88)	970 (33.0)	400 (32.3)

Source: advs.xpt; vs.xpt for Trial MK-1654-002; Software: R
Abbreviations: AAP, American Academy of Pediatrics; ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with given characteristic

Conclusion

Analyses of hypersensitivity reactions, rash, injection site reactions, and fever among the pooled pediatric population reveal no notable imbalances between the clesrovimab and placebo arms.

17.3.2. Safety Analyses of Key Safety Events Pooled Across Adult Populations

Key safety analyses conducted in the pooled adult population are shown in the following tables.

Hypersensitivity

Table 107. Adverse Events Assessment of Hypersensitivity OND Medical Query (Narrow), Within 42 Days Postdose, Safety Population, Trial MK-1654-ISS Adult

OCMQ (Narrow) Preferred Term	Trial MK-1654-001 MK-1654 (N=114) n (%)	Trial MK-1654-001 Placebo (N=38) n (%)	Trial MK-1654-003 MK-1654 (N=33) n (%)	Trial MK-1654-003 Placebo (N=11) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=172) n (%)	Pooled Placebo (N=49) n (%)
Hypersensitivity (OCMQ)	0	0	0	0	1 (4.0)	1 (0.6)	0
Drug hypersensitivity	0	0	0	0	1 (4.0)	1 (0.6)	0
Maximum severity							
Death	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0
Mild	0	0	0	0	0	0	0
Serious	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0	0

Source: adae.xpt; Software: R
Relatedness is determined by the Investigator.
Abbreviations: ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Rash

Table 108. Adverse Events Assessment of Rash OND Medical Query (Narrow), Within 14 Days Postdose, Safety Population, Trial MK-1654-ISS Adult

OCMQ (Narrow) Preferred Term	Trial MK-1654-001 MK-1654 (N=114) n (%)	Trial MK-1654-001 Placebo (N=38) n (%)	Trial MK-1654-003 MK-1654 (N=33) n (%)	Trial MK-1654-003 Placebo (N=11) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=172) n (%)	Pooled Placebo (N=49) n (%)
Rash (OCMQ)	1 (0.9)	0	1 (3.0)	0	0	2 (1.2)	0
Acne	0	0	1 (3.0)	0	0	1 (0.6)	0
Urticaria	1 (0.9)	0	0	0	0	1 (0.6)	0

OCMQ (Narrow) Preferred Term	Trial MK-1654-001 MK-1654 (N=114) n (%)	Trial MK-1654-001 Placebo (N=38) n (%)	Trial MK-1654-003 MK-1654 (N=33) n (%)	Trial MK-1654-003 Placebo (N=11) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=172) n (%)	Pooled Placebo (N=49) n (%)
Maximum severity							
Death	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0
Mild	0	0	0	0	0	0	0
Serious	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0	0
Relatedness	1 (0.9)	0	0	0	0	1 (0.6)	0

Source: adae.xpt; Software: R
Relatedness is determined by the Investigator.
Abbreviations: ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Injection Site Reactions

Table 109. Adverse Events Assessment of Local Administration Reaction OND Medical Query (Narrow), Within 5 Days Postdose, Safety Population, Trial MK-1654-ISS Adult

OCMQ (Narrow) Preferred Term	Trial MK-1654-001 MK-1654 (N=114) n (%)	Trial MK-1654-001 Placebo (N=38) n (%)	Trial MK-1654-003 MK-1654 (N=33) n (%)	Trial MK-1654-003 Placebo (N=11) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=172) n (%)	Pooled Placebo (N=49) n (%)
Local administration reaction (OCMQ)	6 (5.3)	4 (10.5)	0	0	2 (8.0)	8 (4.7)	4 (8.2)
Application site dermatitis	1 (0.9)	0	0	0	0	1 (0.6)	0
Infusion site haemorrhage	1 (0.9)	1 (2.6)	0	0	0	1 (0.6)	1 (2.0)
Injection site erythema	0	0	0	0	1 (4.0)	1 (0.6)	0
Injection site haemorrhage	1 (0.9)	0	0	0	0	1 (0.6)	0
Injection site pain	2 (1.8)	1 (2.6)	0	0	2 (8.0)	4 (2.3)	1 (2.0)
Injection site swelling	0	0	0	0	1 (4.0)	1 (0.6)	0
Vessel puncture site pain	1 (0.9)	2 (5.3)	0	0	0	1 (0.6)	2 (4.1)

OCMQ (Narrow) Preferred Term	Trial MK-1654-001 MK-1654 (N=114) n (%)	Trial MK-1654-001 Placebo (N=38) n (%)	Trial MK-1654-003 MK-1654 (N=33) n (%)	Trial MK-1654-003 Placebo (N=11) n (%)	Trial MK-1654-008 MK-1654 (N=25) n (%)	Pooled MK-1654 (N=172) n (%)	Pooled Placebo (N=49) n (%)
Maximum severity							
Death	0	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0
Mild	0	0	0	0	0	0	0
Serious	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	0	0	0	0
Relatedness	2 (1.8)	1 (2.6)	0	0	2 (8.0)	4 (2.3)	1 (2.0)

Source: adae.xpt; Software: R
Relatedness is determined by the Investigator.
Abbreviations: ISS, integrated summary of safety; MK-1654, clesrovimab; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND Custom Medical Query; OND, Office of New Drugs

Conclusion

Analysis of select AEs among the pooled adult population reveal some imbalances between the clesrovimab and placebo arms which are of uncertain clinical significance and unclear relevance to the pediatric population. Overall, these safety data in adults did not reveal any new safety signals.

18. Clinical Virology

18.1. RSV Surveillance Studies

Like other respiratory viruses, RSV is continually evolving, particularly in genomic regions expressing envelope and fusion proteins which are exposed on the virion surface and therefore key targets of immune surveillance. Amino acid substitutions in the F protein may alter specific epitopes, or the overall structure of the protein, potentially impacting the binding and neutralization by monoclonal antibodies targeting this protein. As an example, suptavumab, which targets antigenic site V of prefusion F protein, failed to meet the primary endpoint of prevention of hospitalization or medically attended LRTI in a Phase 3 clinical trial. The loss of efficacy was attributed mainly to the emergence in 2015 and subsequent predominance of L172Q+S173L substitutions in RSV B strains, which are still predominant in currently circulating strains, and caused loss of binding and neutralization activity (Simoes et al. 2021). Hence, it is important to establish whether RSV variants and F protein substitutions maintain susceptibility to mAbs targeting the F protein by conducting surveillance studies, including genotypic and phenotypic characterization of contemporary and geographically diverse isolates.

The Applicant conducted surveillance studies by analyzing RSV sequences from a public database (i.e., GenBank®), and through collection and sequencing of contemporary clinical RSV isolates from global locations. These studies were in addition to the phenotypic assessment of historical and contemporary isolates described in Section 20.4. There are also published sources of RSV surveillance data which are referenced in this review, in particular, literature describing programs conducted in the United States and internationally (Ruzin et al. 2018; Bin et al. 2019; Langedijk et al. 2020; Tabor et al. 2020; Wilkins et al. 2023).

18.1.1. Assessment of RSV F Protein Diversity From Sequences Reported in GenBank®, Study Report PD004-MK-1654

The objective of the analysis of sequence data from GenBank® was to determine the RSV sequence diversity at the clesrovimab epitope and identify amino acid polymorphisms which may cause reduced susceptibility to clesrovimab.

Methodology

Analyses of RSV Sequences

For analyses of RSV sequences, 15,527 complete RSV F protein sequences from clinical isolates were obtained from GenBank® (NCBI 2022). Most isolates were collected in the United States (42%), followed by China (8%), Kenya (7%), and Australia (5%). A total of 55% of isolates were collected in the years 2017 through 2020, and 13% from recent years (2021 through 2024). A modified Seq2Logo program (Thomsen and Nielsen 2012) was used to align the RSV sequences, and percent identity subsequently determined. Additional sequence data from 46 clinical isolates used in neutralization assays (Section 20.4) were included as part of this analysis.

Dendrogram Analysis of RSV F Protein Extracellular Domain Sequences

A dendrogram analysis was conducted for a smaller panel of 3,058 RSV F protein sequences which were derived from GenBank® in March 2020; an attempt to increase the number of sequences for this analysis to include the ones from the more recent GenBank® download was not successful. The 3,058 isolates had a similar geographic distribution as the larger panel of 15,527 isolates, with most isolates from the United States (33%), followed by China (19%), Kenya (13%) and Australia (5%). However, the majority of isolates were collected in earlier years, with 52% from 2010, 2012, 2013, and 2015 combined, and none more recent than 2018.

From the 3,058 complete RSV F protein sequences, and the sequences from the panel of 46 clinical isolates, a total of 391 unique extracellular domain sequences (amino acids 27 through 529, according to UniProt annotation (The°UniProt°Consortium 2025)) were clustered using the clustalW algorithm (Chenna et al. 2003; Conway°Institute°UCD°Dublin 2012). The resulting clustered data were visualized using FigTree version 1.4.3 (Rambaut°lab 2016).

Results

From the 15,527 complete RSV F protein sequences obtained from GenBank®, an analysis was conducted of the extracellular domains (amino acids 27 through 529) with respect to the clesrovimab epitope (nonlinear, amino acids 426 to 429, 432, 433, 440, 441, 443, 445 to 447; see Section 20.1). The clesrovimab binding site (antigenic site IV) was 99.8% conserved by identity in 15,495 of the 15,527 sequences. From the sequences in which the binding site was not conserved, a total of 13 variants were identified (Table 110).

The most frequently observed variant included an I432T polymorphism, which was identified in five RSV A samples and one RSV B sample (0.04%). The samples were isolated from different geographic locations and years, including two from the widely sampled United States in 2018 and 2019, respectively. The I432T polymorphism reduces clesrovimab binding to the F protein (2-fold increase in half-maximal inhibitory concentration [IC_{50}] value), and neutralization of both RSV A and RSV B subtypes (4-fold and 1.6-fold increase in EC_{50} values, respectively; see Section 20.6.2).

Other epitope polymorphisms were also observed at low frequency, including several seen in more than one sample: K433R (0.03%), D440N (0.01%), S443T (0.02%), K445R (0.03%), G446E (0.02%), and V447M (0.03%). Most samples were from different geographic locations and years indicating independent events, although three of four samples with a V447M

polymorphism were isolated in Kuwait in 2021. Of these polymorphisms, G446E was identified in cell culture resistance selection experiments, and causes a >3,800-fold reduction in susceptibility to clesrovimab in a neutralization assay (see Section 20.6.1). Also, substitution at position S443 was observed in cell culture passage: RSV A S443P causes a >3,800-fold reduction in susceptibility to clesrovimab, and against RSV B with this substitution, clesrovimab activity was not observed up to the highest concentration tested, 67nM (10,000 µg/mL) (360-fold-change; see Section 20.6.1). The K445R polymorphism does not confer reduced susceptibility (<5-fold change) to clesrovimab (see Section 20.6.3).

Another epitope position important to clesrovimab binding based on an alanine scanning mutagenesis, R429 (see Section 20.2), was seen rarely in the GenBank® database (no polymorphisms observed), although 2/555 (0.4%) clinical isolates were seen with R429 polymorphisms in surveillance studies (see Section 18.1.2).

Table 110. Sequence Diversity at the RSV F Protein Binding Site of MK-1654

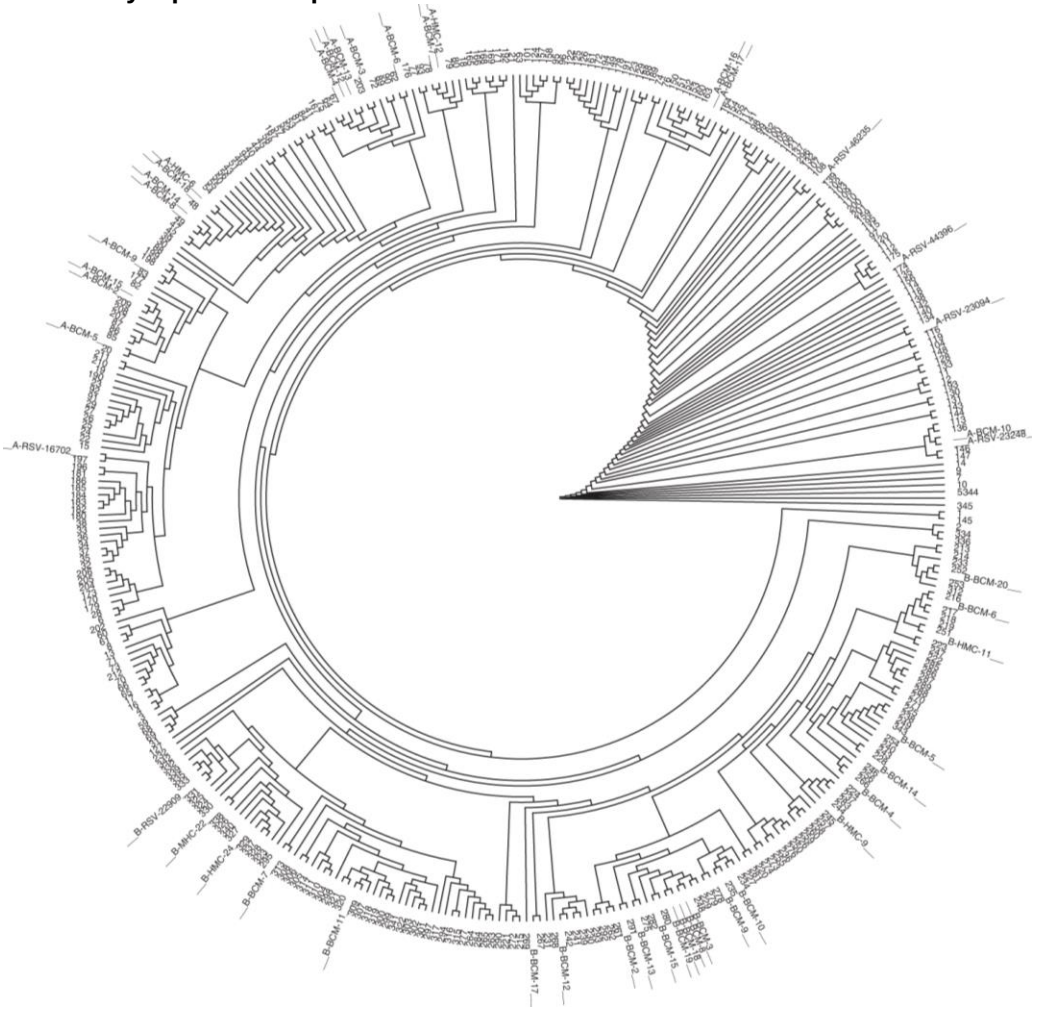
Subtype	No.[a]	Frequency	Polymorphism[b]	Sample ID	Sample Country	Sample Year
Consensus RSV A, RSV B	15,495	99.8%	-	Consensus AHY21375	United States	1984
RSV A	6	0.04%	I432T	WDV36368	United States	2019
RSV B				WDV37672	Spain	2019
RSV A				WDV34740	Brazil	2019
RSV A				WWM07732	Brazil	2019
RSV A				WDV36046	United States	2018
RSV A				BBB35153	Japan	2001
RSV B	4	0.03%	K445R	WDV38995	United States	2018
RSV A				WDV35614	United States	2016
RSV A				WCO06581	Argentina	2022
RSV A				AMA67163	United States	1987
RSV A	4	0.03%	V447M	WVD50424	Kuwait	2021
				WVD50798	Kuwait	2021
				WVD51040	Kuwait	2021
				AAB59858	No data	1985
RSV B	4	0.03%	K433R	WWM15501	Australia	2018
				UDL08986	Australia	2018
				QJC61625	Kenya	2019
				WLG19809	Australia	2016
RSV A	3	0.02%	S443T	WDV35317	S. Africa	2021
RSV A				WDV35326	S. Africa	2021
RSV B				WDV38324	United States	2017
RSV A	3	0.02%	G446E	WPW24250	United States	2022
				WDV35972	United States	2016
				AHY21320	United States	1982

Subtype	No.[a]	Frequency	Polymorphism[b]	Sample ID	Sample Country	Sample Year
RSV B	2	0.01%	D440N	WDV38151 AVQ93607	United States China	2016 2016
RSV B	1	0.01%	V447L	ASU44563	China	2011
RSV A	1	0.01%	N428D	BAA00105	No data	1987
RSV B	1	0.01%	G446V	WDV37946	United States	2016
RSV A	1	0.01%	I432V	WDV37124	United States	2020
RSV B	1	0.01%	K433Q	ASU44576	China	2012
RSV B	1	0.01%	N426T	ASU44575	China	2012

Source: Table 8, page 33 (Merck 2024h)
[a] Number of sequences out of 15,527 total sequences from GenBank®, accessed April 15, 2024.
[b] The epitope for MK-1654 on RSV F protein is nonlinear and includes amino acid positions 426, 427, 428, 429, 432, 433, 440, 441, 443, 445, 446, and 447. The two amino acid positions identified as important to clesrovimab binding in alanine scanning experiments are R429 and I432.
Abbreviations: F, fusion protein; ID, identifier; No., number; RSV, respiratory syncytial virus

The extracellular domains of the sequences from 46 clinical isolates which were evaluated phenotypically (see Section 20.4) were compared with an earlier (2020) download of 3058 sequences from GenBank®, which included 345 unique extracellular domain sequences. The extracellular domain sequences were clustered and visualized as a dendrogram (Figure 24). The 46 clinical isolate sequences were distributed throughout the dendrogram rather than being clustered in any particular region, indicative that they were a diverse panel of isolates.

Figure 24. Panel of 46 Clinical Isolate Sequences Overlaid on a Representative Sample of 3,058 Fusion Glycoprotein Sequences From GenBank®



Source: Figure 1, page 43 (Merck 2024h)
A panel of sequences from 46 clinical isolates was overlaid on a representative sample of 3,058 F protein sequences from GenBank®. Neutralization data for clesrovimab for the 46 isolates, and one additional isolate for which sequence data were not determined, are presented in Section 20.4. This figure depicts the phylogenetic tree for extracellular domain F protein sequences, with the 3,058 F protein sequences and their phylogenetic trees represented in the inner part of the circle, and the sequences of the 46 RSV A and B clinical isolates marked as spokes on the outside of the circle.
Abbreviations: F, fusion protein; RSV, respiratory syncytial virus

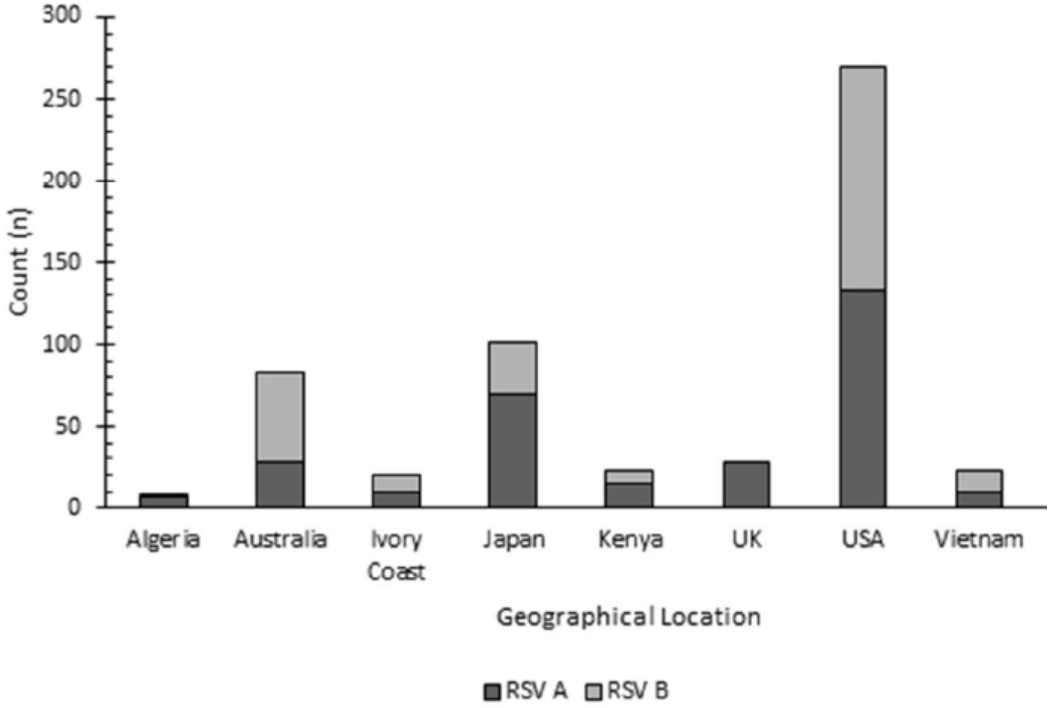
Conclusion

Analysis of 15,527 RSV F protein sequences from GenBank® (accessed April 15, 2024) indicated that amino acid polymorphisms in the clesrovimab epitope were rarely observed (≤0.4%). Of the polymorphisms seen, G446E is known to be resistance-associated, and was seen in three isolates. Other epitope polymorphisms may also impact susceptibility to clesrovimab, in particular at position 443 where an S443P substitution was observed in cell culture resistance selection with RSV A and RSV B. The most frequent polymorphism, I432T, caused reduced susceptibility to clesrovimab of 4-fold reduction for RSV A, and 1.6-fold for RSV B; however, it is not known what fold-change may confer reduced clinical efficacy. It is also possible that polymorphisms outside the binding site may impact susceptibility to clesrovimab, for example through allosteric effects. It will be important for the Applicant to continue monitoring RSV variants as they arise and assess for susceptibility in cell culture neutralization assays.

18.1.2. Evaluation of RSV F Gene Sequences in RSV-Positive Clinical Samples From Global Locations Collected Between 2019 and 2023, RSV Surveillance and Clinical Virology Report

The Applicant conducted additional surveillance of RSV F protein sequence diversity of RSV-positive clinical samples which were collected from eight countries (in Northern and Southern Hemispheres) between 2019 and 2023 (Figure 25). Samples were from individuals who were male or female of any age and were not enrolled in clinical trials.

Figure 25. RSV Subtype by Geographical Location



Source: Figure 2, page 15, RSV Surveillance and Clinical Virology report (Merck 2024e)
Abbreviations: n, number; RSV, respiratory syncytial virus

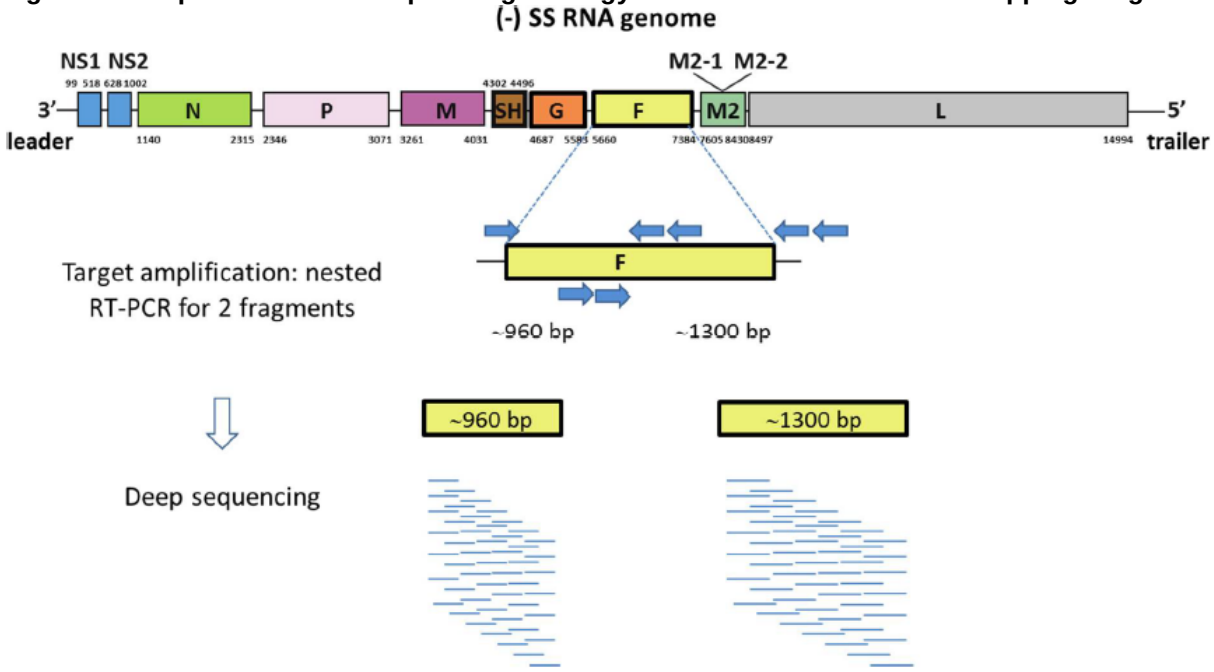
Methodology

Samples from RSV infected individuals were assessed by amplification of the 1,724 bases F gene followed by next-generation sequencing. Assays were developed and conducted by (b) (4) RSV subtyping used a duplex one-step real-time quantitative RT-PCR assay targeting the N-gene of RSV A and RSV B [validation report VV-QUAL-09801, provided in Section 7.2, page 122 of the RSV Surveillance and Clinical Virology report (Merck 2024e)].

RSV RNA was extracted from samples using the MagNA Pure 96 DNA and Viral NA Large Volume Kit (Roche). A one-step quantitative RT-PCR method was used to determine the RSV subtype through amplification of the nucleocapsid gene region with SuperScript® III One-step RT-PCR System and Platinum®Taq DNA Polymerase (Invitrogen). The assay was duplexed, with specific primer-probe sets for each RSV subtype (A and B).

Nested RT-PCR was used to amplify the complete F gene as two overlapping fragments, with specific primer sets depending on the RSV subtype (Figure 26). Nested amplification of the initial PCR product utilized the Expand High Fidelity PCR system (Roche).

Figure 26. Amplification and Sequencing Strategy of RSV F Gene in Two Overlapping Fragments



Source: Figure 1, page 13, RSV Surveillance and Clinical Virology report (Merck 2024e)
RSV F gene positions are numbered according to RSV-A strain (GenBank® accession AY911262 (NCBI 2005)
Abbreviations: F, fusion protein; RNA, ribonucleic acid; RSV, respiratory syncytial virus; RT-PCR, reverse transcription–polymerase chain reaction

Deep sequencing was conducted on amplified F gene products using the Illumina MiSeq platform ([redacted] (b) (4) RSV Surveillance and Clinical Virology report (Merck 2024e)). Sequence alignment was performed against RSV A Long (NCBI 2005) or RSV B 9320 (NCBI 2004) reference strains using a 1% VAF cutoff for variant calling and a 3% cutoff for eliminating the majority of sequence errors. Variant reporting used a 10% VAF cutoff.

Amino acid substitutions were assessed in the F protein binding sites for clesrovimab (Site IV, amino acids 426 to 447), and nirsevimab (site Ø, amino acids 62 to 69 and 196 to 212). For reporting variants, prespecified criteria were used for prevalence of >5% across all samples assessed (i.e., >27/555 samples), and ≥10% VAF within individual samples. As an exploratory criterion, a ≥5% VAF was also used, regardless of the prevalence threshold.

Results

F protein sequences were successfully analyzed from a total of 555 samples collected from global locations between 2019 and 2023. These included 300 (54%) samples with RSV A and 255 (46%) with RSV B subtypes. The number of samples tested for each year from 2019 to 2023 were 111, 137, 137, 80, and 38, respectively, with 52 samples having no collection year reported. The distribution of samples according to subtype, age and gender is shown in Table 111. Most

samples were from the United States, followed by Japan and Australia, and lower representation from other countries (Figure 25**)**. The relative proportion of RSV subtypes by year is shown in Table 112; published surveillance studies for years 2015 to 2021 showed similar proportions of RSV A and RSV B for 2019, but a predominance of RSV A in 2020 and 2021 (Wilkins et al. 2023), although data are likely confounded by the SARS-CoV-2 pandemic for 2020 and 2021.

Table 111. Distribution of RSV A and RSV B Samples by Gender and Age

		Gender			Age				
RSV Subtype	Total (%)	Female n (%)	Male n (%)	Not Reported n (%)	<1 Yr n (%)	1-2 Yr n (%)	3-5 Yr n (%)	6-59 Yr n (%)	60+ Yr n (%)
Total[a]	555	230 (41%)	302 (54%)	23 (4%)	135 (24%)	222 (40%)	63 (11%)	94 (17%)	41 (7%)
RSV-A[b]	300 (54%)	125 (54%)	165 (55%)	10 (43%)	91 (67%)	113 (51%)	32 (51%)	46 (49%)	18 (44%)
RSV-B[b]	255 (46%)	105 (46%)	137 (45%)	13 (57%)	44 (33%)	109 (49%)	31 (49%)	48 (51%)	23 (56%)

Source: Table 1, page 14, RSV Surveillance and Clinical Virology report (Merck 2024e)
[a] Percentages are the proportion of total samples (n=555)
[b] Percentages are the subtype proportion within each gender or age category
Abbreviations: n, number of participants in a given category; RSV, respiratory syncytial virus; yr, year(s)

Table 112. RSV A and RSV B Sequences by Year of Collection

	Samples Collected		
Year	Total	RSV A	RSV B
2019	111	70	41
2020	137	67	70
2021	137	47	90
2022	80	57	23
2023	38	20	18
2024	--	--	--
Year not reported[a]	52	39	13
Total	555	300	255

Source: Response to FDA IR (Merck 2024j)
[a] Only collection months were reported for these 52 samples.
Abbreviations: IR, Information Request; RSV, respiratory syncytial virus

Table 113 summarizes the F protein amino acid variants identified in the clesrovimab and nirsevimab binding sites across the 555 sequences analyzed. For the clesrovimab binding site, using the prespecified criteria of >5% prevalence and ≥10% VAF, there were no changes seen, but three changes were identified using the lower exploratory VAF threshold of ≥5%. For the nirsevimab binding site, four changes were seen at >5% prevalence and ≥10% VAF, and 15 using the lower VAF threshold.

Of the three variants for clesrovimab, two were at position R429, known to be important for clesrovimab binding from an alanine scanning mutagenesis (see Section 20.2), and at the other position, K445N was selected concurrently with S443P in cell culture passage of RSV A, but has not been assessed phenotypically on its own (see Section 20.6).

Table 113. Amino Acid Changes Seen in the RSV F Protein Clesrovimab and Nirsevimab Binding Sites Across 555 Clinical Isolates

Reporting Criteria	Variant	VAF (%)[a]	Prevalence (%)[b]	Subtype	Location	Assay Date
Clesrovimab binding site, amino acids 426-447						
>5% prevalence, ≥10% VAF	None					
≥5% VAF	R429C	13.06	0.2	RSV B	Kenya	2024
	R429H	6.06	0.2	RSV A	United States	2020
	K445R	69.7	0.2	RSV B	Vietnam	2020
Nirsevimab binding site, amino acids 62-69, 196-212						
>5% prevalence, ≥10% VAF	S197N	99.8	46	RSV B	Ivory Coast, Japan, Kenya, United States, Vietnam	2020-2024
	I206M[c]	99.5	41	RSV B	Algeria, Australia, Ivory Coast, Japan, Kenya, United States, Vietnam	2020-2024
	Q209R[c]	99.5	41	RSV B	Algeria, Australia, Ivory Coast, Japan, Kenya, United States, Vietnam	2020-2024
	S211N	99.9	13	RSV B	Australia, United States	2021-2024

Reporting Criteria	Variant	VAF (%)[a]	Prevalence (%)[b]	Subtype	Location	Assay Date
≥5% VAF	S62G	13.66	0.2	RSV A	United States	2023
	N63D	10.86	0.4	RSV B	United States	2020
	I64V	99.6, 7.43	0.4	RSV B	Australia, Vietnam	2020, 2021
	K65E	11.74	0.2	RSV A	United States	2023
	K65R	99.46	0.2	RSV A	United States	2023
	E66K	11.74	0.2	RSV A	Australia	2022
	T67A	24.13	0.2	RSV B	Ivory Coast	2021
	T67N	99.63	0.6	RSV B	United States	2022
	N67S	99.7	0.4	RSV A	Australia	2022
	T67S	99.7	0.4	RSV B	United States	2022
	K68N	99.6	0.4	RSV B	United States	2020
	N200D	99.8	1	RSV B	United States	2022
	N201K	99.7	1	RSV B	United States	2022
	Q209K	99.7	1	RSV B	United States	2022
	Q210H	VAF <5% in 6 samples and 7% in 1 sample	ND	RSV-B	Japan, United States, Vietnam	2020, 2021

Source: Tables 3 and 4, pages 16-17, RSV Surveillance and Clinical Virology report; response to FDA IR (Merck 2024e; Merck 2024k)
[a] VAF % values shown represent the mean of all samples with each variant if there are at least instances
[b] Prevalence percentage refers to the frequency of variants within the 555 samples meeting the reporting criteria; hence, a prevalence of 0.2% indicates 1/555 variants.
[c] I206M is rarely seen without Q209R substitution, and together they do not confer reduced susceptibility to nirsevimab. I206M on its own confers a 5-fold reduced susceptibility to nirsevimab (ASTRAZENECA°AB 2023).
Abbreviations: IR, Information Request; ND, not determined; RSV, respiratory syncytial virus; USPI, United States Prescribing Information; VAF, variant allele frequency

Table 114 shows the polymorphisms outside the clesrovimab binding site, at highly conserved positions (>99% based on GenBank® data) compared with RSV A Long (NCBI 2005) or RSV B 9320 (NCBI 2004) reference strains. For this analysis, a prevalence threshold of ≥1.0% and max VAF% of ≥10% were used. Only two changes, RSV A V457H and RSV B V452E, were identified within the linear region 426 to 470, which encompasses the clesrovimab epitope and amino acids residing within 5Å of the epitope. Both of these changes were seen at low mean VAF% (<10%).

Table 114. F Protein Amino Acid Changes, Max. VAF ≥10%, Compared With Reference Strains Observed at Highly Conserved (≥99%) Positions Based on GenBank® Data

Change	Position	Prevalence N	Prevalence %	Min. VAF%	Mean VAF%	Max. VAF%
RSV A						
A16T	16	3	1.00%	99.8	99.8	99.9
F22L	22	6	2.00%	5.4	21.2	98.9
N80K [a]	80	300	100.00%	98.4	99.8	100
T101P [a]	101	300	100.00%	96.2	99.5	99.9
L111I	111	4	1.30%	99.5	99.6	99.6
Y117H	117	7	2.30%	99.5	99.8	99.8
R135K	135	3	1.00%	99.7	99.8	99.9
R213S [a]	213	300	100.00%	98.8	99.6	99.7
T337I	337	4	1.30%	99.8	99.8	99.9
S362L	362	8	2.70%	53.3	92.8	99.8
Y457H	457	19	6.30%	5.6	8	14.3
H515N [a]	515	300	100.00%	99.3	99.8	99.9
A543V	543	3	1.00%	99.7	99.8	99.8
D562N	562	5	1.70%	99.6	99.7	99.8
RSV B						
T23A	23	3	1.20%	99.8	99.8	99.9
T67N	67	3	1.20%	99.5	99.6	99.8
T74A	74	5	2.00%	99.8	99.8	99.9
T97M [a]	97	255	100.00%	99.3	99.7	99.9
N99S	99	5	2.00%	99.6	99.7	99.8
N105S	105	5	2.00%	99.7	99.8	99.9
A111L	111	4	1.60%	99.9	99.9	99.9
P112L	112	8	3.10%	99.9	99.9	99.9
Q113R	113	3	1.20%	99.7	99.8	99.9
Y114F	114	5	2.00%	99.6	99.9	100
I119L	119	5	2.00%	98.8	99.4	99.8
T121N	121	5	2.00%	97.5	99	99.7
S128T	128	5	2.00%	99.3	99.6	99.7
I129L	129	6	2.40%	99.9	99.9	99.9
H159N	159	30	11.80%	99.8	99.8	99.9
N169S	169	5	2.00%	99.5	99.7	99.8
S197N [a]	197	255	100.00%	99.2	99.9	100
N200D	200	5	2.00%	99.8	99.9	99.9
N201K	201	5	2.00%	99.6	99.7	99.8
R213S	213	5	2.00%	99.5	99.6	99.7
S228N	228	6	2.40%	7.1	84.1	99.6
L247V	247	5	2.00%	99.9	99.9	99.9
K327N	327	4	1.60%	99.7	99.8	99.8
S380N	380	3	1.20%	99.7	99.8	99.8
V452E	452	9	3.50%	5	6.6	10
E472K	472	3	1.20%	96.6	98.5	99.4
N517S	517	4	1.60%	95.7	98.7	99.8
V537I	537	3	1.20%	99.7	99.8	99.8

Source: Response to FDA IR (Merck 2025c)
Bold amino acid changes: occur at positions within linear region 426 to 470, encompassing clesrovimab epitope and amino acids ≤5Å of epitope.
[a] Amino acid change resulting from mismatch between GenBank® consensus sequence and reference strains
Abbreviations: F, fusion protein; IR, Information Request; max, maximum; min, minimum; N, number of items in each category; RSV, respiratory syncytial virus; VAF, variant allele frequency

In the 2017-2018 INFORM-RSV surveillance program (Tabor et al. 2020), one instance of RSV B K433R in the clesrovimab epitope was observed, and other polymorphisms were seen that reside in antigenic Site IV, but not at clesrovimab contact residues, including RSV A (n=127): S435T (0.8%), S466N (2.4%), L467I (4.7%), and RSV B (n=283): L462Q (0.4%), E463D (8.5%). Positions 463, 466 and 467 are located adjacent to amino acids which reside within 5Å of the clesrovimab binding site. S466N substitution was also seen in clinical trials of clesrovimab (see Section 18.4).

For substitutions identified in the nirsevimab binding site, in general, the observed frequencies are consistent with published data (Wilkins et al. 2023), although RSV B N197 was observed at 99.6% frequency in epidemiological studies between 2015 and 2021 and serine at this position was seen in 0.04% of isolates (aspartic acid was seen in 0.39% of isolates).

Conclusion

Sequence analysis of 555 RSV clinical isolates collected from 2019 to 2023 from global locations showed that the clesrovimab binding site was well conserved, with only three amino acid changes identified in one isolate each compared with reference sequences, two of which were detected at a low VAF (13% and 6%, respectively). Only two other amino acid changes occurred at conserved residues (>99%) in the linear region 426-470, and outside the clesrovimab epitope. Both of these changes were seen at low mean VAF% (<10%).

Published surveillance studies have reported polymorphisms at positions adjacent to amino acids which reside within 5Å of the clesrovimab binding site, and at ≥1% frequency. It will be important for the Applicant to assess these polymorphisms phenotypically. It will also be important to continue surveillance activities of the RSV F protein, with a focus on changes in antigenic Site IV, and prioritizing for phenotyping any polymorphisms seen in this region.

18.2. Impact of Clesrovimab on RSV Diagnostic Assays, RSV Surveillance, and Clinical Virology Report

Rapid antigen testing is frequently used in the clinic for diagnosis of RSV infection. Because these assays use antibodies targeting the F protein for detection, there is potential for interference by clesrovimab in individuals who have received this product. This is particularly the case for assays using an antibody targeting the same or overlapping epitope as the immunoprophylaxis mAb, as was seen with palivizumab, leading to false negative or equivocal results (Deming et al. 2013). In this study, the Applicant assessed commonly used rapid antigen tests for interference by clesrovimab. These data were also reviewed by a CDRH reviewer; a summary of the consult is provided after the results section.

Methodology

Four commonly used RSV rapid antigen tests kits were evaluated for detection of RSV in the presence or absence of clesrovimab, including BinaxNOW™ RSV (Abbott, Green Oaks, IL), TRU RSV® (Meridian Bioscience, Cincinnati, OH), Remel™ Xpect® RSV (Remel, Lenexa, KS), and BD Veritor™ System (BD, Franklin Lakes, NJ). Each kit includes a positive control, which was used as the RSV positive control in this assessment.

The positive controls from each RSV kit were spiked with clesrovimab to final concentrations of 1 and 5 µg/mL, the higher concentration having been selected based on nasal concentrations determined in Phase 1 adult studies and expected pharmacokinetics at the 105-mg dose in infants.

The clesrovimab-spiked samples were tested according to the respective manufacturer's protocol. Additional samples were prepared with RSV A (American-type culture collection [ATCC] cat. # VR-1540) at a range of titers from 10^6 to 10^2 PFU/mL.

Results

Initial experiments were conducted with the BinaxNOW™ RSV and TRU RSV® kits. Using the positive control in the BinaxNOW™ RSV kit, interference was seen for both kits in the presence of 5 µg/mL clesrovimab; however, it was not observed when the positive control from the TRU RSV® kit was used. Based on the assumption that the TRU RSV® kit control had a higher titer of RSV, and that interference only occurred at lower titers, a range of known titers of RSV A were assessed in a similar manner.

As shown in Table 115, all the rapid antigen tests had a sensitivity detection limit between 10^4 to 10^5 PFU/mL RSV. In the absence of clesrovimab (0 µg/mL), the BinaxNOW™ RSV and BD Veritor™ System assays detected RSV A down to titers of 10^4 PFU/mL, and the TRU RSV® and Remel™ Xpect® RSV assays down to titers of 10^5 PFU/mL. Assay interference was seen in the BinaxNOW™ RSV assay with 1 and 5 µg/mL of clesrovimab at an RSV titer of 10^4 PFU/mL, and in the Remel™ Xpect® RSV assay at 5 µg/mL of clesrovimab at an RSV titer of 10^5 PFU/mL. It was also observed that the lateral flow test band intensity was lower for the BinaxNOW™ RSV and TRU RSV® kits in the presence of clesrovimab.

Table 115. Rapid Antigen Test Kit Detection of RSV A (10^2 to 10^6 PFU/mL) in the Presence or Absence of Clesrovimab

	Virus Titer (PFU/mL)					
Clesrovimab (µg/mL)	**10^6**	**10^5**	**10^4**	**10^3**	**10^2**	**No Virus**
BinaxNOW™ RSV						
5	Pos	Pos	Neg	Neg	Neg	Neg
1	Pos	Pos	Neg	Neg	Neg	Neg
0	Pos	Pos	Pos	Neg	Neg	Neg
TRU RSV®						
5	Pos	Pos	Neg	Neg	Neg	Neg
1	Pos	Pos	Neg	Neg	Neg	Neg
0	Pos	Pos	Neg	Neg	Neg	Neg
Remel™ Xpect® RSV						
5	Pos	Neg	Neg	Neg	ND	Neg
1	Pos	Pos	Neg	Neg	ND	Neg
0	Pos	Pos	Neg	Neg	ND	Neg
BD Veritor™ system						
5	Pos	Pos	Pos	Neg	ND	Neg
1	Pos	Pos	Pos	Neg	ND	Neg
0	Pos	Pos	Pos	Neg	ND	Neg

Source: Table 11, page 34, RSV Surveillance and Clinical Virology report (Merck 2024e)
Abbreviations: ND, not determined; neg, negative; PFU, plaque-forming units; pos, positive; RSV, respiratory syncytial virus

Summary of CDRH Consult

A consult was requested of CDRH to provide an opinion on the validity and robustness of the Applicant's data showing interference by clesrovimab with commonly used rapid antigen diagnostic tests (RADT**s**) used for RSV detection, including whether additional testing may be needed and how the findings should be presented in the product Prescribing Information. The following paragraphs summarize the consult.

The Applicant evaluated similar RADTs to those previously assessed by AstraZeneca and MedImmune in the presence or absence of nirsevimab or palivizumab (with 10^5 PFU/mL RSV A or B, and mAb at final concentrations of 1 and 10 μg/mL), respectively, as part of their analytical studies for product validation. The tests considered as the most commonly used according to the College of American Pathologists at that time included: the BinaxNOW RSV (Binax°Inc. 2003), the TRU RSV (MERIDIAN°BIOSCIENCE 2007), the Remel Xpect RSV (Remel°Inc. 2005) , the BD Directigen EZ RSV test kit (Becton°Dickinson°and°Company 2002), and the Quidel QuickVue RSV test kit (QUIDEL°CORP 2007). The BD Directigen EZ RSV kit has been discontinued by the manufacturer and could not be procured for testing by the Applicant, instead the BD Veritor System (Becton°Dickinson°and°Company 2012)was used; the QuickVue RSV test was not evaluated.

Lateral-flow immunoassays for the detection of RSV typically target fusion (F) protein and/or a nucleoprotein (N) in human nasal wash, nasopharyngeal aspirate, or nasal/nasopharyngeal swab samples. The Applicant described using lateral flow tests for their interference studies that can identify one or both proteins (e.g., TRU RSV kit). Other examples of lateral flow tests that describe targeting the F protein, and/or the nucleoprotein antigen from RSV include the NanoCheck RSV (Nano-Ditech°Corporation 2024) and the Sofia RSV fluorescent immunoassay test (QUIDEL°CORP 2013).

The results provided by the Applicant show that clesrovimab could compete with antibodies that bind the same or overlapping epitopes, including those that are critical components of some RSV diagnostic assays (Landry 2009). Clesrovimab interference with these immunoassays might lead to false-negative results and contribute to inappropriate use of antibiotics and unnecessary laboratory testing, prolonged hospitalizations and delay actions to limit nosocomial infections (Byington et al. 2002; Mills et al. 2011).

The CDRH reviewer agreed with the Applicant's conclusion from the data, that "for rapid antigen diagnostic kit results, which are negative when clinical observations are consistent with RSV infection, it is recommended to confirm using an RT-PCR-based assay." The demonstration of interference with commonly used assays (Binax NOW RSV and Remel Xpect RSV kits) are probably enough to consider appropriate safety mitigations as limitations and Prescribing Information provisions where individuals who have received clesrovimab prophylaxis to consider that a negative result does not preclude RSV infection, that these tests should be interpreted with caution, and that all negative test results should be confirmed by nucleic acid amplification tests, such as RT-PCR. Nucleic acid amplification tests cleared under regulations 21 CFR 866.3980 and 866.3981 may be better alternatives to RSV Ag tests if no interference from this is observed with preventative RSV mAb. The CDRH reviewer did not recommend a particular RADT over the others for further interference studies, although noted that it may be of value to conduct interference studies with commonly used direct or indirect immunofluorescence assays.

Whether clesrovimab interference is specific for RADTs which target antigenic Site IV is not clear because lateral flow immunoassay kits do not disclose the specific antigenic target site(s) of their antibody composition. Hence, reactivity to specific mAbs has not been tested in many of the antigenic tests. Regarding whether the Applicant should also evaluate clesrovimab interference with RSV B, in general, RSV assays are validated to identify either subtype, and do not necessarily differentiate between RSV A and RSV B. Given the high degree of conservation of antigenic Site IV between subtypes, the CDRH reviewer did not see value in assessing RSV B in additional interference studies.

For product Prescribing Information, the CDRH reviewer noted that because RSV RADTs do not preclude RSV infection, these kits carry disclaimers in the Prescribing Information to advise that these tests are not to be used as the sole basis for treatment or other management decisions (Onwuchekwa et al. 2023). It is recommended that negative test results be confirmed by viral cell culture or an alternative method, such as an FDA-cleared molecular assessment. Recently cleared assays also includes a limitation statement reporting that therapeutic anti-RSV monoclonal antibodies may interfere with the RSV test; monoclonal antibodies may fail to detect, or detect with less sensitivity, RSV viruses that have undergone minor amino acid changes in the target epitope region, (e.g., the Nanocheck RSV kit).

CDRH recognized the potential for clesrovimab to interfere with diagnostic assays should be a consideration for the diagnostician and recommended that the interference of RSV diagnostic assays by clesrovimab to be disclosed in the Prescribing Information to use caution when interpreting negative immunological assay results when clinical observations are consistent with RSV infection. An RT-PCR assay, if is not inhibited by clesrovimab, may prove useful for laboratory confirmation of RSV infection.

Conclusion

Four commonly used rapid antigen tests were able to detect RSV A at titers as low as 10^4 or 10^5 PFU/mL. In the presence of clesrovimab, the sensitivity of the assay was reduced for the BinaxNOW™ RSV and Remel™ Xpect® RSV kits, and there was a qualitative impact on the readout for BinaxNOW™ RSV and TRU RSV® kits. In the presence of clesrovimab, the sensitivity of the BinaxNOW™ RSV, TRU RSV® and Remel™ Xpect® RSV kits was $\geq 10^5$ PFU/mL compared to the BD Veritor™ System which was 10^4 PFU/mL. Data on the impact of clesrovimab on RSV B detection by these rapid antigen tests were provided late in the review cycle and showed that interference by clesrovimab was only observed for the TRU RSV® kit at 10^4 PFU/mL and 5 μg/mL clesrovimab. In patients who have received clesrovimab, confirmation using a RT-PCR assay is recommended when rapid antigen assay results are negative and clinical observations are consistent with RSV infection (RT-PCR assays are not affected by the presence of clesrovimab).

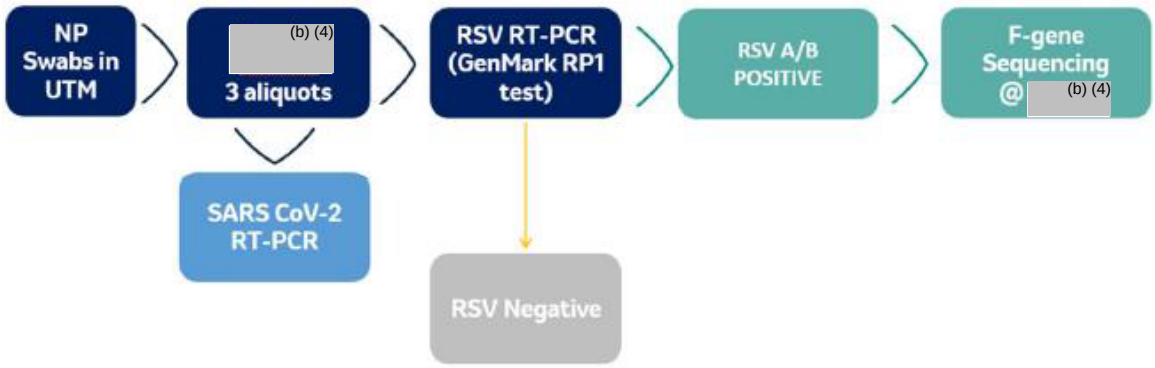
18.3. Clinical Virology Assays and Bioanalytical Reports

For diagnosis of RSV infection in clinical trials of clesrovimab, NP swabs were collected from participants who presented with respiratory symptoms, and an RT-PCR-based multiplex assay used for detection of RSV and several other respiratory pathogens. SARS-CoV-2 infection was determined using a separate assay. Positive RSV samples were sequenced to determine F protein changes compared with reference sequences. The following sections detail the collection and processing of clinical samples.

18.3.1. Sample Collection

NP swabs were collected in Universal Transport Medium from participants who presented with signs and symptoms of respiratory infection in clinical Trials MK-1654-004 and MK-1654-007. Three aliquots of each sample were processed at (b) (4), and assessed for respiratory viruses using the GenMark respiratory panel 1 (RP1) test, described in the following section. This test also distinguishes RSV A and RSV B. Samples which tested positive for RSV were shipped to (b) (4) for RSV sequencing of the F gene. Figure 27 shows the workflow for sample processing.

Figure 27. Workflow for MK-1654-004 and MK-1654-007 Clinical Trial Sample Testing



Source: Figure 10, page 38, RSV Surveillance and Clinical Virology report (Merck 2024e)
Abbreviations: F, fusion protein; NP, nasopharyngeal; RSV, respiratory syncytial virus; RT-PCR, reverse transcription–polymerase chain reaction; SARS CoV-2, severe acute respiratory syndrome coronavirus 2; UTM, Universal Transport Medium

18.3.2. Diagnostic Testing for RSV and Other Respiratory Pathogens

The identification of respiratory infections in NP samples collected from participants in Trials MK-1654-004 and MK-1654-007 was determined using the GenMark Dx ePlex RP1 in vitro diagnostic test (GENMARK°DIAGNOSTICS 2017), and Conformité Européene marked. This assay distinguishes the following respiratory viral and bacterial pathogens:

- Human adenovirus type 3
- Human coronavirus (NL63, 229E, OC43 and HKU-1)

- Human metapneumovirus
- Human rhinovirus/enterovirus
- Influenza A virus (H1, H3), influenza B virus
- Parainfluenza (types 1, 2, 3, and 4A)
- Respiratory syncytial virus A, B
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

The GenMark eSensor RP1 is a RT-PCR-based assay and is comparable in specificity and sensitivity to real-time RT-PCR for individual viruses (Pierce and Hodinka 2012). For the clesrovimab clinical program, this assay was used to qualitatively detect and distinguish RSV A and RSV B. Assay performance was initially verified for use with the XT-8 molecular diagnostic system. Following discontinuation of the XT-8 instrument by GenMark approximately 1 year into the clinical study, the ePlex system was adopted, which includes automated nucleic acid extraction and concentration, target amplification, and detection. For clinical studies in China, the ePlex system was transferred to (b) (4). The (b) (4) verification report for the ePlex system, including interlaboratory concordance between (b) (4), was provided by the Applicant (Merck (b) (4)). The limit of detection of the RP1 assay using the ePlex system, based on the concentration at which each target was detected at least 95% of the time, was $1.5x10^{0}$ tissue culture infectious dose $(TCID)_{50}$/mL using an RSV A reference isolate, and $2x10^{-1}$ $TCID_{50}$/mL using an RSV B reference isolate.

18.3.3. SARS-CoV-2 Qualitative Detection

The GenMark RP1 assay does not detect SARS-CoV-2, so a separate assay was utilized for qualitative detection of SARS-CoV-2 RNA in NP samples from clinical trials of clesrovimab. The SARS-CoV-2 test was a real-time RT-PCR-based assay developed by Virocor Eurofins, BioPharma Services clinical laboratory, intended for use under the FDA emergency use authorization program. The assay detects two independent regions of the SARS-CoV-2 nucleocapsid gene, and could detect all strains of SARS-CoV-2 at the time of development, with no expected cross-reactivity with other respiratory pathogens (Merck 2024a).

18.3.4. Genotypic Resistance Characterization

F gene amplicons were generated from RSV RNA extracted from clinical samples and subjected to next-generation sequencing (NGS) on the Illumina MiSeq platform, and quality based variant detection was performed with DDL's Athena pipeline (version 3.1.2) using 1% cutoff threshold for minor variant detection. Like the surveillance studies, sequence alignment was performed against RSV-A Long (NCBI 2005) or RSV B 9320 (NCBI 2004) reference strains using a 1% VAF cutoff for variant calling and a 3% cutoff for eliminating the majority of sequence errors. The Applicant used a 10% VAF cutoff for variant reporting. For the FDA review, a more stringent VAF of 3% was used, based on the validation report for the NGS assay.

18.4. Clinical Virology Genotypic and Phenotypic Analyses

Genotypic analysis was conducted of the RSV F gene from NP samples collected in clinical trials of clesrovimab, MK-1654-004 and MK-1654-007. The Applicant provided a study report which described the sequence data for each trial and identified F protein amino acid changes compared with reference strains RSV A Long (NCBI 2005) or RSV B 9320 (NCBI 2004), with a focus on substitutions identified in antigenic Site IV/clesrovimab binding site (Merck 2024e). Limited phenotypic data for substitutions were reported, but the Applicant generated a list for evaluation based on the clinical trial data.

To support the clinical study report, clinical resistance datasets and raw NGS data as FASTQ files were submitted, which were reviewed independently by the FDA. The resistance datasets included F protein amino acids seen at ≥1% VAF which differed from reference sequences, from all samples which were successfully sequenced, along with the VAF%, day of collection, and other relevant information. In addition, the prevalence (%) in GenBank® of each F protein substitution seen in clinical trial data was reported. Sequence data integrity was assessed independently by the FDA (see Section 18.4.2).

The main objectives of the FDA analyses on the sequence data were to determine if there was any association of clesrovimab treatment with increased incidence of substitutions in antigenic Site IV/clesrovimab binding site, which may be resistance-associated, or if there was an association of these substitutions with increased incidence of RSV-associated MALRI or RSV-associated hospitalization.

18.4.1. Assessment of Sequence Data Quality

Analyses were conducted by the FDA to assess sequence data quality for Trials MK-1654-004 and MK-1654-007. These analyses included confirmation of RSV subtype for participants identified as having coinfections with RSV A and RSV B, and a phylogenetic analysis of sequence data to determine if there were identical nucleotide sequences, which may indicate data integrity issues. F nucleotide consensus sequence alignment was used to determine the level of sequence identity with sequences from other participants infected with the same RSV subtype in the trial(s). Genetic variation and variant percentages based on NGS data of samples of identical F consensus sequences were compared using the Frequency tables provided by the Applicant.

In Trial MK-1654-004, RSV A and RSV B infections in the same participant over the course of the trial were uncommon and were identified in 16/544 (3%) participants. Of these, six were coinfections identified on the same Visit/Day. For many of the infections seen in the same participant, no sequence data were provided for both subtypes for further analysis.

No large clusters of identical F nucleotide consensus sequences were identified from study sites with small numbers of participants. There were a few instances of clusters of identical consensus F sequences from participants in different countries. However, analysis of VAF percentages of different variants in these sequences indicated that the sequence populations were not identical, and therefore it was unlikely that there were issues with data integrity.

Two pairs of identical F sequences were identified which harbored substitutions at or near binding-site epitopes, from participants who were likely twins based on demographic data. In one pair from Trial MK-1654-004, there was an amino acid substitution (S466N) in the vicinity of the clesrovimab epitope in both participants, and in the other from Trial MK-1654-007, there was a known palivizumab resistance-associated substitution (S275F) in both participants. It is most probable that in these cases, participants were infected from the same index case at the same time, or from each other.

Overall, these analyses did not indicate that there were issues of concern with sequence data integrity across Trials MK-1654-004 and MK-1654-007 that might impact study results.

18.4.2. Clinical Virology Resistance Analyses for Trial MK-1654-004

Trial MK-1654-004 was an evaluation of clesrovimab treatment in healthy preterm (gestational age ≥29 weeks to <35 weeks) and full-term infants (gestational age ≥35 weeks) and was conducted across 192 study sites in 22 countries. A summary of the study protocol and efficacy results are provided in Section 6.2. The primary endpoint was the number of participants with RSV-associated MALRI from Days 1 through 150 postdose.

Initially, a total of 633 NP samples were collected from 575 participants in Trial MK-1654-004. Of these, 35 were removed: 33 were collected prior to dosing, one sample had an incorrect collection date, and one other did not have RSV RT-PCR results but had sequence data. The resulting 598 samples were from 544 participants. A further 30 samples were excluded because they failed RT-PCR amplification or sequencing, leaving a total of 568 samples collected from 523 participants, of whom 303 were in the clesrovimab arm, and 220 were in the placebo arm.

For the sequence analysis, unlike the efficacy endpoints, data from multiple RSV infections in the same participant were considered if they met certain criteria. Sequences that were collected within 30 days from the same participant and had the same consensus sequence were excluded from analysis (n=29 sequences from 27 participants). If the sequences were from the same participant and collected >30 days apart, they were not excluded, even if they were of the same subtype. Hence, the dataset that was analyzed included 539 sequences from 523 participants.

Table 116 shows the number of participants with RSV infection cases meeting protocol-defined endpoints, subdivided by RSV subtype, and the number of cases for which F protein sequence data were available. Included are the number of participants with RSV infection which met the primary endpoint, and the number which met secondary endpoints of RSV-associated MALRI from Days 1 through 180 postdose, and RSV-associated hospitalization from Days 1 through 150 postdose. Also shown are the number of participants with RSV infection which met exploratory endpoints of RSV-associated MALRI from Days 364 through 515 postdose, RSV-associated hospitalization from Days 1 through 180 and Days 364 through 515 postdose, RSV-associated acute respiratory infection (ARI) from Days 1 through 150 postdose and Days 1 through 180 postdose, and the number of participants with RSV infection which did not meet the definition for any endpoint.

For the primary endpoint, sequence data were available for 58/62 (94%) of qualifying infections in the clesrovimab arm, which included one participant with a mixed (RSV A + RSV B) infection (# (b) (6)), and one participant with RSV B infection on Day 14 postdose, and RSV A

on Day 27 (# (b) (6)). For the placebo arm, sequence data were available for 67/74 (91%) of qualifying infections. For other secondary and exploratory endpoints, overall, there were few cases for which sequence data were not available.

Table 116. Number of RSV Infection Cases, by RSV Subtype[a], and by Efficacy Evaluation Period[b], Full Analysis Set, Trial MK-1654-004

	Day 1 to 150 Postdose		Day 1 to 180 Postdose		Day 365 to 515 Postdose	
Case Definition RSV Subtype	Clesrovimab (N=2398)	Placebo (N=1201)	Clesrovimab (N=2398)	Placebo (N=1201)	Clesrovimab (N=1008)	Placebo (N=501)
RSV-associated MALRI	60	74	64	77	53	26
RSV A[c]	29 (28)	26 (23)	32 (30)	29 (26)	25 (24)	14 (13)
RSV B[c]	33 (30)	48 (44)	34 (31)	48 (44)	29 (29)	13 (12)
RSV hospitalization	9	28	11	29	3	2
RSV A[c]	4 (4)	12 (11)	5 (4)	13 (12)	1 (1)	1 (1)
RSV B[c]	5 (5)	16 (14)	6 (6)	16 (14)	2 (2)	1 (1)
RSV ARI[d]	148	148	161	154	N/A	N/A
RSV A[c]	74 (69)	58 (53)	82 (74)	63 (58)	N/A	N/A
RSV B[c]	78 (72)	91 (87)	83 (77)	92 (88)	N/A	N/A
RSV infection not meeting any endpoint	27	8	28	8	69	36
RSV A[c]	12 (12)	5 (5)	13 (12)	5 (5)	37 (36)	22 (21)
RSV B[c]	15 (13)	3 (3)	15 (13)	3 (3)	32 (31)	16 (16)

Sources: Clinical study report P004V01MK1654: Table 11-1 (page 62), 11-2 (page 65), Table 14.2-7 (page 389), Table 14.2-9 (page 392), Table 14.2-14 (page 398), Table 14.2-15 (page 399), 14.2-23 (page 407), 14.2-24 (page 408); Response to FDA IR; FDA analysis (Merck 2024j; Merck 2024b)

[a] There were several cases with mixed RSV A and RSV B infections, hence the combined RSV A + RSV B cases may exceed the total number of cases.

[b] Efficacy was not evaluated from Days 181 to 364 postdose in Trial MK-1654-004.

[c] Number of cases with sequencing data available for each subtype shown in parentheses.

[d] RSV ARI not evaluated for Day 365 to 515 postdose.

Abbreviations: ARI, acute respiratory infection; IR, Information Request; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; N/A, not applicable; RSV, respiratory syncytial virus

There were generally more cases of RSV B compared with RSV A infections within each trial arm, particularly in the placebo arm: for RSV-associated MALRI Day 1 through 180 postdose, in the clesrovimab arm there were 32/66 (48%) with RSV A and 34/66 (52%) with RSV B, and in the placebo arm there were 29/77 (38%) with RSV A and 48/77 (62%) with RSV B. Clesrovimab has similar activity in cell culture against RSV A and RSV B clinical isolates (see Section 20.4), so differential activity is unlikely to account for the lower number of RSV B infections in the clesrovimab arm compared with the placebo arm.

Overall, there were few cases of mixed (RSV A + RSV B) infection. By endpoint and study arm, these included:

- RSV-associated MALRI Days 1 to 150/1 to 180 in clesrovimab arm: Participants (b) (6) (infections on Days 14 and 27) and (b) (6). Sequence data were available for both RSV A and RSV B for both participants.
- RSV-associated MALRI Days 365 to 515 in clesrovimab arm: Participant (b) (6) Sequence data were available for RSV B only.

- RSV-associated MALRI Days 365 to 515 in placebo arm: Participant (b) (6). Sequence data were available for RSV A only.
- RSV ARI Days 1 to 150/Days 1 to 180 in clesrovimab arm: Participants (b) (6) (no sequence data), (b) (6) (sequence data for both RSV A and RSV B), (b) (6) (sequence data for RSV B only), (b) (6) (sequence data for both RSV A and B).
- RSV ARI Days 1 to 150/Days 1 to 180 in placebo arm: Participant (b) (6) (infections on Days 41 and 67; first infection also MALRI). Sequence data were available for both RSV A and RSV B.
- RSV infection not meeting any endpoint in placebo arm: Participants (b) (6) (sequence data for both RSV A and RSV B), (b) (6) (sequence data for RSV B only).

For the analysis of sequence data from Trial MK-1654-004 discussed in the following sections, the main focus was to identify amino acid substitutions which occurred in or near the clesrovimab binding site and determine whether there was an increased prevalence of these substitutions in clesrovimab-treated participants with RSV-associated MALRI or RSV-associated hospitalization. Sequence data from different evaluation periods, Days 1 through 180, Days 181 through 364, and Days 365 through 515 postdose, were considered separately. Because the data from Days 1 through 150 are encompassed within the Days 1 through 180 evaluation period, they were not considered separately.

18.4.2.1. Analysis of RSV F Protein Substitutions Within or Near the Clesrovimab Binding Site From Days 1 Through 180 Postdose

The FDA conducted an analysis of individual amino acid substitutions which occurred in or near the clesrovimab binding site, based on the crystal structure of the clesrovimab parent RB-1 Fab and RSV prefusion F complex (see Section 20.2.1). These included Site IV amino acid substitutions at positions 426 to 447 and/or within 5Å of clesrovimab binding site (161, 182 to 184, 430, 431, 442, 464, 465, 468, 470), and residues directly adjacent to these positions.

Table 117 lists the substitutions within or near the clesrovimab binding seen in RSV infection cases from Days 1 through 180 postdose, regardless of whether they met any endpoint definition. A cutoff VAF of 3% was used, and substitutions were included if they were identified in at least one participant in either study arm.

For RSV A cases, a total of 10/76 (13%) RSV infections in clesrovimab-treated participants had substitutions in or near the clesrovimab epitope, compared with 2/59 (3%) placebo participants. These include 7/76 (9%) RSV infections in clesrovimab-treated participants with a substitution in the clesrovimab binding Site IV (positions 426-447), compared with 1/59 (2%) placebo participants. A total of 6/10 substitutions in the clesrovimab arm were seen at a VAF of >50%; the two substitutions in the placebo arm were seen at VAFs of 21.5% and 4%, respectively.

For RSV B cases, a total of 11/80 (14%) RSV infections in clesrovimab-treated participants had substitutions in or near the clesrovimab binding site, compared with 3/91 (3%) placebo participants. These included 8/80 (10%) RSV infections in clesrovimab-treated participants with a substitution in the clesrovimab binding Site IV (positions 426 to 447), compared with 1/91

(1%) placebo participants. A total of 3/10 substitutions in the clesrovimab arm were seen at a VAF of >50%, and the three substitutions in the placebo arm were seen at a VAF of <10%.

The increased frequency of substitutions in the clesrovimab arm compared with placebo arm indicates that they may be treatment-emergent, particularly considering that all of the substitutions identified were seen rarely (<1%) in surveillance studies (see Section 18.1). Of the substitutions identified, phenotypic data were available for RSV A G446E and G446W, both of which caused a >2,941-fold loss of susceptibility to clesrovimab, and for RSV A G446R, which caused a >1,563-fold loss of susceptibility to clesrovimab (see Section 20.6.3). Against RSV B, G446E and G446W both reduced susceptibility to clesrovimab by 1,299-fold (see Section 20.6.3; G446R was not assessed). G446E was also selected in cell culture passage of RSV in the presence of clesrovimab (see Section 20.6.1). There were six cases (three of each RSV subtype) in clesrovimab-treated participants where G446E substitution was detected, four instances of G446R (three in RSV A, one in RSV B), and one instance of G446W, with none in the placebo arm, indicating that these substitutions were treatment-emergent.

In studies of nirsevimab, another F protein targeting monoclonal antibody, treatment-emergent resistance-associated substitutions were not seen in pivotal trials. However, it is possible that the difference is related to sampling procedures rather than the antibodies: for clesrovimab, nasopharyngeal samples were collected within 12 days of symptom onset per protocol, whereas for nirsevimab they were collected from participants with medically attended lower respiratory tract infection or hospitalization due to RSV illness within approximately 2 days after the initial healthcare provider assessment and diagnosis (Griffin et al. 2020; Hammitt et al. 2022).

For both RSV A and RSV B cases, the day of swabbing and day of sample collection relative to the onset of symptoms differed across instances of substitutions. There was also no clear association of substitutions with clinical events of RSV-associated MALRI or hospitalization, although one participant (# (b) (6)) with RSV A G446W substitution at 97% VAF had RSV-associated hospitalization, and for other participants with RSV-associated MALRI the substitutions were seen at <5% VAF.

Table 117. Substitutions in or Near Clesrovimab Binding Site[a], Seen at ≥3% VAF in ≥1 Participant, Days 1 to 180 Postdose

Position	Substitution	Clesrovimab	Placebo	Participant ID[b]	VAF (%)	Day of Swabbing[c]	Day of Sample[d]	Clinical Endpoint
RSV A		*n=76*	*n=59*					
426	N426H	1	0	(b) (6)	3.8	22	6	MALRI
433	K433T	0	1		21.5	21	4	-
446	G446E	3	0		93.4	16	8	-
					6.3	8	6	-
					4.3	29	3	MALRI
	G446R	3	0		3.3	9	2	MALRI
					22.7	8	6	-
					51.4	42	8	
	G446W	1	0		96.9	70	16	HOSP
457	Y457H	0	1		4.0	146	4	-
466	S466N	2	0		99.9	79	3	-
					99.8	79	3	-
470	K470R	1	0		99.7	28	10	-

Position	Substitution	Clesrovimab	Placebo	Participant ID[b]	VAF (%)	Day of Swabbing[c]	Day of Sample[d]	Clinical Endpoint
RSV B		*n=80[e]*	*n=91[e]*					
435	F435S	1	0	(b) (6)	7.1	28	1	HOSP
443	S443L	1	0		3.5	6	3	-
		0	1		3.2	6	4	MALRI HOSP
446	G446E	3	0		99.8	42	2	-
					5.1	36	8	-
					99.8	23	8	-
	G446R	1	0		63.9	43	1	-
	G446V	2	0		4.1	51	3	MALRI
					5.8	7	5	-
447	V447I	1	0		3.9	22	6	MALRI
452	V452E	0	1		3.5	28	4	-
		2	0		3.4	43	5	-
					3.3	39	6	-
454	N454T	1	0		3.7	118	9	MALRI
470	K470E	0	1		8.7	43	8	-
Total RSV A[f]		*10 (13%)*	*2 (3%)*					
Total RSV B[f]		*11 (14%)*	*3 (3%)*					

Source: FDA analysis
[a] Includes amino acids within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
[b] Two participants had RSV with two binding-site substitutions each.
[c] Relative to dosing day, for each instance.
[d] Day of swabbing relative to symptom onset, for each instance.
[e] For RSV B, there were 80 and 91 qualifying infections in 79 and 89 clesrovimab and placebo participants, respectively.
[f] Sequences with more than one binding-site substitution were counted once.
Abbreviations: F, fusion protein; HOS, RSV hospitalization; ID, identifier; n, number of participants in treatment group; MALRI, medically attended lower respiratory infection; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.2.2. Analysis of RSV F Protein Substitutions in Participants With RSV-Associated MALRI

Individual substitutions in RSV F were evaluated in samples from participants who met the definition of RSV-associated MALRI, from Days 1 to 180 postdose, and Days 365 to 515 postdose). Efficacy was not evaluated for Days 181 to 364. For this analysis, two VAF% cutoffs were used, 3% and 30%. Overall, there were 6 additional participants with RSV-associated MALRI, and sequence data for Days 1 to 180 compared with Days 1 to 150 (Table 116), which didn't impact the conclusions with respect to the sequence analysis.

For RSV A, three clesrovimab-treated participants had RSV with substitutions in or near the clesrovimab binding site (N426H, G446E and G446R, respectively, all at low VAF%) from Days 1 to 180, which were not seen in participants in the placebo group (Table 118**)**. For Days 365 to 515, substitutions S436F and D440G+L467I were seen in two clesrovimab-treated participants, but not in the placebo arm. RSV A D440G substitution does not confer reduced susceptibility to clesrovimab (see Section 20.6.3). For other substitutions outside the clesrovimab binding site, there were none which were clearly increased in clesrovimab-treated participants compared with placebo, using either a 3% or a 30% VAF cutoff.

For RSV B, there were three clesrovimab-treated participants in the Days 1 to 180 time-period with RSV harboring substitutions in or near the clesrovimab binding site at low VAF%, which were not seen in participants in the placebo group: G446V, V447I, and N454T group (Table 119). In the Days 365 to 515 time-period, one clesrovimab-treated participant had RSV with V185I substitution at >99% VAF, and one other had an F435S substitution at low VAF%. Other RSV B F protein substitutions outside the clesrovimab binding site were not clearly increased in clesrovimab-treated participants compared with placebo, using either a 3% or a 30% VAF cutoff.

It is likely that for participants with RSV-associated MALRI, the more important RSV population is in the lung, and may differ from the population sampled in the nasopharyngeal compartment. Hence, it is possible that the lack of clesrovimab binding-site substitutions in clesrovimab-treated participants is because they were not selected in the upper respiratory tract.

Table 118. Number of RSV A F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF Seen in ≥2[a] Clesrovimab-Treated Participants With RSV-Associated MALRI

			MALRI Days 1 to 180		MALRI Days 365 to 515	
Position	Substitution[b]	GenBank® Prevalence (%)[c]	Clesrovimab (N=30[d])	Placebo (N=26[d])	Clesrovimab (N=24[d])	Placebo (N=13[d])
7	K7E	0.0	6 (6)	2 (2)	1 (1)	0 (0)
8	A8T	98.6	30 (30)	26 (26)	24 (24)	13 (13)
12	T12I	11.4	15 (15)	12 (12)	6 (6)	5 (5)
20	F20L	98.6	30 (30)	25 (26)	22 (22)	12 (12)
23	A23S	0.1	0 (0)	1 (1)	2 (2)	0
80	N80K	99.9	29 (29)	26 (26)	24 (24)	13 (13)
101	T101P	99.9	30 (30)	26 (26)	24 (24)	13 (13)
103	A103T	5.6	2 (2)	4 (3)	3 (3)	3 (3)
105	N105S	93.8	30 (30)	26 (26)	24 (24)	13 (13)
122	T122A	18.2	7 (7)	10 (9)	10 (10)	4 (4)
124	K124N	0.7	29 (29)	26 (26)	24 (24)	13 (13)
127	V127I	0.6	4 (4)	4 (4)	3 (3)	2 (2)
130	S130R	0.0	2 (2)	1 (1)	-	-
213	R213S	99.6	30 (30)	26 (26)	24 (24)	13 (13)
276	N276S	91.4	22 (21)	17 (17)	22 (22)	11 (11)
384	V384I	96.8	29 (29)	25 (25)	24 (24)	13 (13)
426[e]	N426H[e]	0.0	1 (0)	0 (0)	-	-
436[e]	S436F[e]	0.1	-	-	1 (1)	0 (0)
440[e]	D440G[e]	0.0	-	-	1 (1)	0 (0)
446[e]	G446E[e]	0.0	1 (0)	0 (0)	-	-
446[e]	G446R[e]	0.0	1 (0)	0 (0)	-	-

Position	Substitution[b]	GenBank® Prevalence (%)[c]	MALRI Days 1 to 180 Clesrovimab (N=30[d])	MALRI Days 1 to 180 Placebo (N=26[d])	MALRI Days 365 to 515 Clesrovimab (N=24[d])	MALRI Days 365 to 515 Placebo (N=13[d])
457[e]	Y457H[e]	0.0	-	-	0 (0)	1 (0)
467[e]	L467I[e]	0.0	-	-	1 (0)	0 (0)
515	H515N	99.9	30 (30)	26 (26)	24 (24)	13 (13)
518	A518V	4.6	2 (2)	0 (0)	1 (1)	0 (0)
540	S540A	93.7	30 (30)	26 (26)	24 (24)	13 (13)
563	Q563H	0.0	0 (0)	1 (0)	3 (0)	0 (0)

Source: FDA analysis
"-": Substitution not observed.
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants in either time-period, or in ≥1 participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV A Long (NCBI 2005).
[c] Estimated from 6,964 RSV A sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

Table 119. Number of RSV B F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF Seen in ≥2[a] Clesrovimab-Treated Participants With RSV-Associated MALRI

Position	Substitution[b]	GenBank® Prevalence (%)[c]	MALRI Days 1 to 180 Clesrovimab (N=31[d])	MALRI Days 1 to 180 Placebo (N=44[d])	MALRI Days 365 to 515 Clesrovimab (N=29[d])	MALRI Days 365 to 515 Placebo (N=12[d])
12	F12I	0.8	1 (1)	2 (2)	3 (3)	0 (0)
18	N18D	0.0	7 (0)	6 (0)	2 (0)	2 (0)
19	A19T	1.8	5 (0)	5 (1)	2 (0)	2 (0)
21	Y21H	0.3	1 (1)	1 (1)	2 (2)	0 (0)
42	R42K	3.4	12 (12)	4 (4)	2 (2)	2 (2)
45	F45L	96.3	31 (31)	44 (44)	29 (29)	12 (12)
73	D73E	0.2	0 (0)	1 (1)	2 (2)	2 (2)
97	T97M	99.9	31 (31)	44 (44)	29 (29)	12 (12)
103	A103V	91.5	31 (31)	43 (43)	29 (29)	12 (12)
111	A111P	0.0	2 (0)	0 (0)	1 (0)	0 (0)
120	N120S	0.1	2 (2)	1 (1)	-	-
172	L172Q	90.7	31 (31)	44 (44)	29 (29)	12 (12)
173	S173L	88.0	31 (31)	44 (44)	29 (29)	12 (12)
185[e]	V185I[e]	0.0	-	-	1 (1)	0 (0)
189	S190N	10.3	18 (18)	28 (28)	24 (24)	8 (8)
191	K191R	66.9	31 (31)	44 (44)	29 (29)	12 (12)
197	S197N	99.5	31 (31)	44 (44)	29 (29)	12 (12)
198	Y198S	0.0	6 (0)	1 (0)	3 (0)	1 (0)
206	I206M	67.3	31 (31)	44 (44)	29 (29)	12 (12)
209	Q209R	66.4	29 (29)	40 (40)	28 (28)	10 (10)
211	S211N	9.3	18 (18)	28 (28)	24 (24)	8 (8)
294	E294K	-	-	-	2 (2)	1 (1)
368	D368Y	0.0	3 (0)	3 (0)	-	-
389	S389P	8.6	20 (20)	29 (29)	23 (23)	8 (8)
389	S389Y	0.0	4 (0)	3 (0)	2 (0)	0 (0)

Position	Substitution[b]	GenBank® Prevalence (%)[c]	MALRI Days 1 to 180 Clesrovimab (N=31[d])	MALRI Days 1 to 180 Placebo (N=44[d])	MALRI Days 365 to 515 Clesrovimab (N=29[d])	MALRI Days 365 to 515 Placebo (N=12[d])
425[e]	S425T[e]	0.0	-	-	0 (0)	1 (0)
435[e]	F435S[e]	0.0	-	-	1 (0)	0 (0)
441[e]	Y441H[e]	0.0	-	-	0 (0)	1 (0)
443[e]	S443L[e]	0.0	0 (0)	1 (0)	-	-
446[e]	G446V[e]	0.0	1 (0)	0 (0)	-	-
447[e]	V447I[e]	0.0	1 (0)	0 (0)	-	-
454[e]	N454T[e]	0.0	1 (0)	0 (0)	-	-
458[e]	V458H[e]	0.0	-	-	0 (0)	1 (0)
529	T529A	97.3	31 (31)	43 (43)	29 (29)	12 (12)
561	K561N	0.0	-	-	2 (0)	0 (0)

Source: FDA analysis
"-": Substitution not observed.
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants in either time-period, or in ≥1 participant for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV B 9320 (NCBI 2004).
[c] Estimated from 5,799 RSV B sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.2.3. Analysis of RSV F Protein Substitutions in Participants With RSV-Associated Hospitalization

Individual substitutions in RSV F were evaluated in samples from participants who met the definition of RSV-associated hospitalization, from Days 1 to 180 postdose, and Days 365 to 515 postdose. Efficacy was not evaluated for Days 181 to 364. For this analysis, two VAF% cutoffs were used, 3% and 30%. Overall, there were two additional participants with RSV hospitalization and sequence data for Days 1 to 180 compared with Days 1 to 150 (Table 116), which did not impact the conclusions with respect to the sequence analysis.

For RSV A, one clesrovimab-treated participant had RSV with a substitution in the clesrovimab binding site (G446W, 97% VAF), which was not seen in the placebo group (Table 120). There was no clear difference between study arms with respect to RSV F substitutions seen at ≥3% or ≥30% VAF outside the clesrovimab binding site, although for Days 365 to 515, only one participant was hospitalized from each arm.

For RSV B, one clesrovimab-treated participant had RSV with a substitution near the clesrovimab binding site (F435S), which was not seen in the placebo group (Table 121). There was no clear difference between study arms with respect to RSV F substitutions seen at ≥3% or ≥30% VAF outside the clesrovimab binding site.

Table 120. Number of RSV A F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF Seen in ≥1 Clesrovimab-Treated Participant[a] With RSV-Associated Hospitalization

			Days 1 to 180		Days 365 to 515	
Position	Substitution[b]	GenBank® Prevalence (%)[c]	Clesrovimab (N=4[d])	Placebo (N=12[d])	Clesrovimab (N=1[d])	Placebo (N=1[d])
4	P4S	0.1	1 (1)	0 (0)	-	-
8	A8T	98.6	4 (4)	12 (12)	1 (1)	1 (1)
12	T12I	11.4	3 (3)	3 (3)	1 (1)	0 (0)
15	L15F	3.6	1 (1)	0 (0)	-	-
20	F20L	98.6	4 (4)	11 (11)	1 (1)	1 (1)
22	F22C	0.0	1 (1)	0 (0)	-	-
80	N80K	99.9	4 (4)	12 (12)	1 (1)	1 (1)
101	T101P	99.9	4 (4)	12 (12)	1 (1)	1 (1)
105	N105S	93.8	4 (4)	12 (12)	1 (1)	1 (1)
122	T122A	0.1	1 (1)	6 (5)	0 (0)	1 (1)
124	K124N	98.8	4 (4)	12 (12)	1 (1)	1 (1)
213	R213S	99.6	4 (4)	12 (12)	1 (1)	1 (1)
276	N276S	91.4	3 (3)	10 (10)	1 (1)	1 (1)
384	V384I	96.8	4 (4)	11 (11)	1 (1)	1 (1)
393	C393Y	0.0	1 (0)	0 (0)	-	-
446[e]	G446W[e]	0.0	1 (1)	0 (0)	-	-
515	H515N	99.9	4 (4)	12 (12)	1 (1)	1 (1)
540	S540A	93.7	4 (4)	12 (12)	1 (1)	1 (1)

Source: FDA analysis
"-": Substitution not observed.
[a] Substitutions are shown if they were seen in at least one clesrovimab-treated participant in either time-period, or at least one participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV A Long (NCBI 2005).
[c] Estimated from 6,964 RSV A sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

Table 121. Number of RSV B F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF Seen in ≥1 Clesrovimab-Treated Participant[a] With RSV-Associated Hospitalization

			Days 1 to 180		Days 365 to 515	
Position	Substitution[b]	GenBank® Prevalence (%)[c]	Clesrovimab (N=6[d])	Placebo (N=14[d])	Clesrovimab (N=2[d])	Placebo (N=1[d])
2	E2K	0.1	1 (1)	0 (0)	-	-
7	R7K	0.3	1 (1)	0 (0)	-	-
12	F12I	0.8	2 (2)	1 (1)	-	-
45	F45L	96.3	6 (6)	14 (14)	2 (2)	1 (1)
64	I64T	0.0	1 (0)	0 (0)	-	-
97	T97M	99.9	6 (6)	14 (14)	2 (2)	1 (1)
103	A103V	91.5	6 (6)	13 (13)	2 (2)	1 (1)
111	A111P	0.0	1 (0)	0 (0)	-	-
125	L125P	1.3	2 (2)	0 (0)	-	-
172	L172Q	90.7	6 (6)	14 (14)	2 (2)	1 (1)
173	S173L	88.0	6 (6)	14 (14)	2 (2)	1 (1)

Position	Substitution[b]	GenBank® Prevalence (%)[c]	Days 1 to 180 Clesrovimab (N=6[d])	Days 1 to 180 Placebo (N=14[d])	Days 365 to 515 Clesrovimab (N=2[d])	Days 365 to 515 Placebo (N=1[d])
190	S190N	10.3	2 (2)	10 (10)	2 (2)	1 (1)
191	K191R	66.9	6 (6)	14 (14)	2 (2)	1 (1)
197	S197N	99.5	6 (6)	14 (14)	2 (2)	1 (1)
206	I206M	67.3	6 (6)	14 (14)	2 (2)	1 (1)
209	Q209R	66.4	4 (4)	14 (14)	2 (2)	1 (1)
211	S211N	9.3	2 (2)	10 (10)	2 (2)	1 (1)
294	E294K	0.2	1 (1)	0 (0)	-	-
368	D368Y	0.0	1 (0)	2 (0)	-	-
373	L373F	0.0	1 (0)	0 (0)	-	-
389	S389P	8.6	2 (2)	10 (10)	2 (2)	1 (1)
	S389Y	0.0	2 (0)	1 (0)	-	-
435[e]	F435S[e]	0.0	1 (0)	0 (0)	-	-
443[e]	S443L[e]	0.0	0 (0)	1 (0)	-	-
482	V482M	0.0	1 (1)	0 (0)	-	
522	T522S	0.0	1 (0)	0 (0)	-	-
529	T529A	97.3	6 (6)	14 (14)	2 (2)	1 (1)
561	K561N	0.0	1 (0)	0 (0)		

Source: FDA analysis
"-": Substitution not observed.
[a] Substitutions are shown if they were seen in at least one clesrovimab-treated participant in either time-period, or at least one participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV B 9320 (NCBI 2004).
[c] Estimated from 5,799 RSV B sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.2.4. Analysis of RSV F Protein Substitutions in All RSV-Infected Participants

The FDA conducted an analysis of individual RSV F protein substitutions seen in any RSV infected participants with sequence data regardless of whether they met an efficacy endpoint, and according to time-period postdose (Days 1 to 180, Days 181 to 364, and Days 365 to 515), using a ≥3% or ≥30% VAF cutoff. All substitutions seen in or near the clesrovimab binding site were noted, regardless of whether they were seen in the clesrovimab or placebo arms.

For RSV A, in addition to the substitutions identified in or near the clesrovimab binding site from Days 1 to 180, which are detailed in Table 117, one substitution (Y457H) was seen in one participant in each study arm from Days 181 to 364, and substitutions were seen in three clesrovimab-treated participants and not in placebo participants from Days 365 to 515: S436F, D440G+L467I, and E463G (Table 122). Of these substitutions, only S436F and S440G were seen at ≥30% VAF (both >99%).

For RSV B, in addition to the substitutions identified in or near the clesrovimab binding site from Days 1 to 180, which are detailed in Table 117, one substitution (I432V) was seen at low

VAF% in one participant in each study arm from Days 181 to 364, and one other substitution (F435S), also at low VAF%, in the clesrovimab arm only from Days 365 to 511 (Table 123).

Overall, for RSV A and RSV B, there was no clear difference between study arms with respect to RSV F substitutions seen at ≥3% or ≥30% VAF outside the clesrovimab binding site in any time-period.

Table 122. Number of RSV A F Protein Sequences With Individual Substitutions ≥3% (or ≥30%) VAF Seen in ≥2 Clesrovimab-Treated Participants[a], for Each Postdose Period

Position	Substitution[b]	GenBank® Prevalence (%)[c]	Days 1 to 180		Days 181 to 364		Days 365 to 515	
			Clesrovimab (N=76[d])	Placebo (N=59[d])	Clesrovimab (N=18[d])	Placebo (N=9[d])	Clesrovimab (N=62[d])	Placebo (N=34[d])
7	K7E	0.0	6 (6)	4 (4)	-	-	2 (2)	1 (1)
8	A8T	98.6	75 (75)	59 (59)	18 (18)	9 (9)	62 (62)	34 (34)
12	T12I	11.4	31 (31)	21 (21)	7 (7)	3 (3)	20 (20)	10 (10)
13	T13A	4.5	3 (3)	3 (3)	2 (2)	1 (1)	2 (2)	2 (2)
15	L15F	3.6	5 (5)	1 (1)	1 (1)	0 (0)	5 (5)	0 (0)
20	F20L	98.6	74 (74)	57 (57)	18 (18)	8 (8)	57 (57)	33 (33)
23	A23S	0.1	0 (0)	3 (3)	2 (2)	2 (2)	3 (3)	1 (1)
	A23T	3.5	3 (3)	3 (3)	1 (1)	0 (0)	-	-
57	I57V	0.3	2 (2)	6 (6)	-	-	0 (0)	2 (2)
63	N63S	0.2	1 (1)	1 (1)	3 (3)	2 (2)	3 (3)	0 (0)
80	N80K	99.9	74 (74)	59 (59)	18 (18)	9 (9)	62 (62)	34 (34)
101	T101P	99.9	75 (75)	59 (59)	18 (18)	9 (9)	62 (62)	34 (34)
103	A103T	5.6	15 (15)	7 (6)	1 (1)	0 (0)	12 (12)	9 (9)
105	N105S	93.8	74 (74)	58 (58)	18 (18)	9 (9)	62 (62)	34 (34)
111	L111I	0.3	2 (2)	6 (6)	-	-	0 (0)	2 (2)
114	F114S	0.6	2 (2)	0 (0)	-	-	-	-
	F114Y	0.3	1 (1)	0 (0)	1 (1)	0 (0)	2 (2)	0 (0)
122	T122A	0.1	26 (26)	22 (21)	8 (8)	5 (5)	25 (25)	15 (15)
	T122I	0.1	2 (2)	0 (0)	-	-	-	-
	T122N	0.1	3 (3)	3 (3)	-	-	-	-
123	K123Q	2.4	3 (3)	3 (3)	1 (1)	0 (0)	-	-
124	K124N	98.8	74 (74)	58 (58)	17 (17)	9 (9)	62 (62)	34 (34)
127	V127I	0.6	6 (6)	4 (4)	1 (1)	0 (0)	6 (6)	5 (5)
130	S130R	0.0	3 (3)	2 (2)	-	-	-	-
160[e]	L160P[e]	0.0	-	-	-	-	0 (0)	1 (0)
181[e]	L181P[e]	0.0	-	-	-	-	0 (0)	1 (0)
185[e]	V185A[e]	0.0	-	-	-	-	0 (0)	1 (0)
213	R213S	99.6	75 (75)	59 (59)	18 (18)	9 (9)	62 (62)	34 (34)
276	N276S	91.4	61 (60)	46 (46)	16 (16)	8 (8)	56 (56)	31 (30)

Position	Substitution[b]	GenBank® Prevalence (%)[c]	Days 1 to 180		Days 181 to 364		Days 365 to 515	
			Clesrovimab (N=76[d])	Placebo (N=59[d])	Clesrovimab (N=18[d])	Placebo (N=9[d])	Clesrovimab (N=62[d])	Placebo (N=34[d])
384	V384I	96.8	72 (72)	56 (56)	18 (18)	9 (9)	62 (62)	33 (33)
	V384T	2.8	3 (3)	3 (3)	1 (1)	0 (0)	0 (0)	1 (1)
426[e]	N426H[e]	0.0	1 (0)	0 (0)	-	-	-	-
433[e]	K433T[e]	0.0	0 (0)	1 (0)	-	-	-	-
436[e]	S436F[e]	0.1	-	-	-	-	1 (1)	0 (0)
440[e]	D440G[e]	0.0	-	-	-	-	1 (1)	0 (0)
446[e]	G446E[e]	0.0	3 (1)	0 (0)	-	-	-	-
	G446R[e]	0.0	3 (1)	0 (0)	-	-	-	-
	G446W[e]	0.0	1 (1)	0 (0)	-	-	-	-
457[e]	Y457H[e]	0.0	0 (0)	1 (0)	1 (0)	1 (0)	0 (0)	1 (0)
463[e]	E463G[e]	0.0	-	-			1 (0)	0 (0)
466[e]	S466N[e]	1.0	2 (2)	0 (0)	-	-	-	-
467[e]	L467I[e]	0.2	-	-	-	-	1 (0)	0 (0)
470[e]	K470R[e]	0.0	1 (1)	0 (0)	-	-	-	-
515	H515N	99.9	75 (75)	59 (59)	18 (18)	9 (9)	62 (62)	34 (34)
518	A518V	4.6	2 (2)	0 (0)	-	-	1 (1)	1 (1)
534	I534T	0.0	0 (0)	1 (0)	-	-	2 (0)	0 (0)
540	S540A	93.7	75 (75)	59 (59)	18 (18)	9 (9)	62 (62)	34 (34)
563	Q563H	0.0	1 (0)	4 (0)	-	-	4 (0)	0 (0)

Source: FDA analysis
"-": Substitution not observed.
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants in any time-period, or in ≥1 participant in either study arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV A Long (NCBI 2005).
[c] Estimated from 6,964 RSV A sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

Table 123. Number of RSV B F Protein Sequences With Individual Substitutions ≥3% (or ≥30%) VAF Seen in ≥2 Clesrovimab-Treated Participants[a], for Each Postdose Period

Position	Substitution[b]	GenBank® Prevalence (%)[c]	Days 1 to 180		Days 181 to 364		Days 365 to 515	
			Clesrovimab (N=80[d])	Placebo (N=91[d])	Clesrovimab (N=13[d])	Placebo (N=7[d])	Clesrovimab (N=63[d])	Placebo (N=28[d])
12	F12I	0.8	6 (6)	4 (4)	2 (2)	0 (0)	5 (5)	1 (1)
18	N18D	0.0	14 (0)	15 (0)	0 (0)	1 (0)	7 (0)	3 (0)
19	A19T	1.8	12 (0)	15 (3)	0 (0)	1 (0)	9 (2)	2 (0)
21	Y21H	0.3	1 (1)	1 (1)	-	-	4 (4)	1 (1)
42	R42K	3.4	18 (18)	18 (18)	3 (3)	3 (3)	3 (3)	4 (4)
45	F45L	96.3	80 (80)	91 (91)	13 (13)	7 (7)	63 (63)	28 (28)
73	D73E	0.2	0 (0)	1 (1)	1 (1)	0 (0)	2 (2)	2 (2)
88	N88S	0.1	1 (1)	0 (0)	-	-	2 (2)	1 (1)
97	T97M	99.9	80 (80)	91 (91)	13 (13)	7 (7)	63 (63)	28 (28)
103	A103I	0.2	3 (3)	3 (3)	-	-	1 (1)	0 (0)
	A103V	91.5	77 (77)	88 (88)	13 (13)	7 (7)	63 (62)	27 (27)
111	A111E	0.0	-	-	-		2 (2)	0 (0)
	A111P	0.0	5 (0)	1 (0)	-	-	3 (0)	2 (0)
116	N116S	0.2	3 (3)	4 (4)	1 (1)	0 (0)	1 (1)	0 (0)
118	T118I	0.2	-	-	-	-	2 (2)	0 (0)
120	N120S	0.1	2 (2)	1 (1)	-	-	1 (1)	0 (0)
123	K123E	0.0	2 (1)	0 (0)	-	-	-	-
125	L125P	1.3	7 (7)	3 (3)	0 (0)	1 (1)	0 (0)	1 (1)
172	L172Q	90.7	80 (80)	91 (91)	13 (13)	7 (7)	63 (63)	28 (28)
173	S173L	88.0	80 (80)	91 (91)	12 (12)	7 (7)	63 (63)	28 (28)
185[e]	V185I[e]	0.0	-	-	-	-	1 (1)	0 (0)
190	S190N	10.3	49 (49)	65 (65)	9 (9)	5 (5)	48 (48)	22 (22)
191	K191R	66.9	80 (80)	91 (91)	13 (13)	7 (7)	63 (63)	28 (28)
197	S197N	99.5	80 (80)	91 (91)	13 (13)	7 (7)	63 (63)	28 (28)
198	Y198S	0.0	9 (0)	9 (0)	-	-	4 (0)	2 (2)
206	I206M	67.3	80 (80)	91 (91)	13 (13)	7 (7)	63 (63)	28 (28)
209	Q209R	66.4	71 (71)	86 (86)	13 (13)	6 (6)	60 (60)	26 (26)
211	S211N	9.3	50 (50)	65 (65)	9 (9)	5 (5)	48 (48)	22 (22)
273	L273I	0.1	-	-	-	-	2 (1)	0 (0)
368	D368Y	0.0	6 (0)	4 (0)	2 (0)	0 (0)	-	-

Position	Substitution[b]	GenBank® Prevalence (%)[c]	Days 1 to 180		Days 181 to 364		Days 365 to 515	
			Clesrovimab (N=80[d])	Placebo (N=91[d])	Clesrovimab (N=13[d])	Placebo (N=7[d])	Clesrovimab (N=63[d])	Placebo (N=28[d])
389	S389P	8.6	49 (49)	66 (66)	10 (10)	5 (5)	51 (51)	20 (20)
	S389Y	0.0	9 (0)	4 (0)	1 (0)	0 (0)	3 (0)	2 (0)
425[e]	S425T[e]	0.0	-	-	-	-	0 (0)	1 (1)
432[e]	I432V[e]	0.0	-	-	1 (0)	1 (0)	-	-
435[e]	F435S[e]	0.0	1 (0)	0 (0)	-	-	1 (0)	0 (0)
441[e]	Y441H[e]	0.0	-	-	-	-	0 (0)	1 (1)
443[e]	S443L[e]	0.0	1 (0)	1 (0)	-	-	-	-
446[e]	G446E[e]	0.0	3 (2)	0 (0)	-	-	-	-
	G446R[e]	0.0	1 (1)	0 (0)	-	-	-	-
	G446V[e]	0.0	2 (0)	0 (0)	-	-	-	-
447[e]	V447I[e]	0.0	1 (0)	0 (0)	-	-	-	-
452[e]	V452E[e]	0.0	2 (0)	1 (0)	-	-	-	-
454[e]	N454S[e]	0.0	-	-	-	-	0 (0)	1 (1)
	N454T[e]	0.0	1 (0)	0 (0)	-	-	-	-
458[e]	Y458H[e]	0.0	-	-	-	-	0 (0)	1 (1)
470[e]	K470E[e]	0.0	0 (0)	1 (0)	-	-	-	-
514	H514R	0.1	2 (1)	0 (0)	-	-	-	-
529	T529A	97.3	78 (78)	87 (87)	13 (13)	7 (7)	62 (62)	28 (28)
545	G545D	0.0	2 (0)	1 (0)	-	-	1 (0)	0 (0)
561	K561N	0.0	2 (0)	1 (0)	1 (0)	0 (0)	2 (0)	1 (0)

Source: FDA analysis
"-": Substitution not observed
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants in any time-period, or in ≥1 participant in either study arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV B 9320 (NCBI 2004).
[c] Estimated from 5,799 RSV B sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.2.5. Analysis of RSV F Protein Concurrent Substitutions in Clesrovimab-Treated Participants

The FDA conducted an analysis of RSV variants with concurrent F protein substitutions in clesrovimab-treated participants compared with placebo participants (Table 124). The most frequently occurring concurrent substitutions (consensus sequence) were assessed, along with the consensus sequence plus other frequently occurring substitutions seen at ≥3% VAF in RSV from at least five clesrovimab-treated participants regardless of meeting an endpoint from Days 1 to 180 postdose. Analyses were also conducted for these concurrent substitutions in participants with RSV infection which met the endpoints of RSV-associated MALRI or RSV-associated hospitalization.

For RSV A, overall, and for participants with RSV-associated MALRI or RSV-associated hospitalization, there was no clear association of any variant with clesrovimab treatment. For some variants (e.g., consensus + L15F substitution) there were too few participants with RSV-associated MALRI or RSV-associated hospitalization to be able to draw firm conclusions. Similarly, for RSV B, there was no clear association of any variant with clesrovimab treatment. The RSV B analysis included variants harboring the consensus sequence and three concurrent substitutions seen in contemporary isolates, S190N+S211N+S389P.

There was no clear association of variants with RSV-associated MALRI or RSV-associated hospitalization, although for many variants there were too few cases to draw firm conclusions.

Table 124. RSV F Protein Concurrent Substitutions Seen at ≥3% VAF in ≥5 Clesrovimab-Treated Participants With Breakthrough RSV Infections From Days 1 to 180 Postdose

	All Cases		MALRI		Hospitalization	
Variant[a]	Clesrovimab	Placebo	Clesrovimab	Placebo	Clesrovimab	Placebo
RSV A	n=75 (%)	n=59 (%)	n=30 (%)	n=26 (%)	n=4 (%)	n=12 (%)
Consensus[b]	57 (76)	39 (66)	20 (67)	15 (58)	3 (75)	8 (67)
Consensus + T12 + T122	13 (17)	15 (25)	7 (23)	5 (19)	0 (0)	4 (33)
Consensus + T12I	17 (23)	6 (10)	7 (23)	2 (8)	2 (50)	0 (0)
Consensus + L15F	5 (7)	1 (2)	1 (3)	0 (0)	1 (25)	0 (0)
Consensus + A103T	15 (20)	6 (10)	2 (7)	3 (12)	0 (0)	0 (0)
Consensus + T122A	22 (29)	17 (29)	5 (17)	8 (31)	1 (25)	4 (33)
Consensus + V127I	6 (8)	4 (7)	4 (13)	4 (15)	0 (0)	2 (17)

	All Cases		MALRI		Hospitalization	
Variant[a]	**Clesrovimab**	**Placebo**	**Clesrovimab**	**Placebo**	**Clesrovimab**	**Placebo**
RSV B	n=80 (%)	n=91 (%)	n=31 (%)	n=44 (%)	n=6 (%)	n=14 (%)
Consensus[c]	67 (84)	77 (85)	29 (94)	38 (86)	4 (67)	13 (93)
Consensus +S190N+S211N+S389P	43 (54)	56 (62)	18 (58)	26 (59)	2 (33)	9 (64)
Consensus + S190+S211+S389	20 (25)	18 (20)	9 (29)	11 (25)	2 (33)	4 (29)
Consensus + F12I	6 (8)	4 (4)	1 (3)	2 (5)	2 (33)	1 (7)
Consensus + N18D	14 (18)	14 (15)	7 (23)	5 (11)	0 (0)	2 (14)
Consensus + A19T	12 (15)	15 (16)	5 (16)	5 (11)	0 (0)	2 (14)
Consensus + R42K	18 (23)	17 (19)	12 (39)	3 (7)	0 (0)	1 (7)
Consensus + A111P	5 (6)	1 (1)	2 (6)	0 (0)	1 (17)	0 (0)
Consensus + Y198S	9 (11)	8 (9)	6 (19)	1 (2)	0 (0)	1 (7)
Consensus + D368Y	5 (6)	3 (3)	3 (10)	3 (7)	0 (0)	2 (14)

Source: FDA analysis
[a] May include F protein substitution(s) in addition to the ones listed.
[b] RSV A consensus substitutions (concurrent in 57/75 [76%] variants from clesrovimab-treated participants): A8T+F20L+N80K+T101P+N105S+K124N+R213S+N276S+V384I+H515N+S540A.
[c] RSV B consensus substitutions (seen together in 67/80 [84%] variants from clesrovimab-treated participants): F45L+T97M+A103V+L172Q+S173L+K191R+S197N+I206M+Q209R+T529A.
Abbreviations: F, fusion protein; MALRI, medically attended lower respiratory infection; n, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.3. Clinical Virology Resistance Analyses for Trial MK-1654-007

Ongoing Trial MK-1654-007 is an evaluation of clesrovimab compared with palivizumab treatment in infants at increased risk for severe RSV disease due to risk factors of CHD, CLD, or prematurity (born at ≤35 weeks gestational age) and entering their first RSV season at the time of informed consent. Participants were eligible for RSV Season 2 if they had CHD, CLD, or other eligible condition resulting in increased risk of severe RSV disease in the second season. The trial was conducted across 109 study sites in 27 countries. A summary of the study protocol and efficacy results are provided in Section 6.2. The primary endpoints were related to safety in Season 1; RSV-associated MALRI and RSV-associated hospitalization from Days 1 through 150 were evaluated as secondary endpoints. RSV-associated ARI was not assessed in MK-1654-007.

A total of 66 NP samples from 57 participants in trial MK-1654-007 were analyzed as of the cutoff date of February 5, 2024. Of these, one sample was collected prior to dosing and five samples were removed because they were collected within 30 days from the same participant and had the same consensus amino acid sequence. Like the analysis for Trial MK-1654-004, sequences from the same participant and collected >30 days apart, were not excluded, even if they were of the same subtype. Hence, a total of 60 samples from 56 participants (29 in the clesrovimab arm and 27 in the palivizumab arm) were in the dataset that was analyzed.

Table 125 shows the number of participants with RSV infection cases meeting protocol-defined endpoints, subdivided by RSV subtype, and the number of cases for which F protein sequence data were available.

For the secondary endpoint of RSV-associated MALRI in Season 1 from Day 1 through 150, sequence data were available for 12/14 (86%) of qualifying infections in the clesrovimab arm,

and 11/12 (92%) in the palivizumab arm. For RSV-associated hospitalization, RSV-associated MALRI from Days 1 through 180, and RSV-associated MALRI in Season 2 Days 1 through 180, overall, there were few cases for which sequence data were not available.

Table 125. Number of RSV Infection Cases, by RSV Subtype[a], and by Efficacy Evaluation Period, Full Analysis Set, Trial MK-1654-007

	Season 1 Day 1 to 150 Postdose		Season 1 Day 1 to 180 Postdose		Season 2 Day 1 to 180
Case Definition RSV Subtype	Clesrovimab (N=446)	Palivizumab (N=450)	Clesrovimab (N=446)	Palivizumab (N=450)	Clesrovimab (N=117)
RSV-associated MALRI	14	12	15	12	6
RSV A[b]	6 (6)	10 (9)	6 (6)	10 (9)	1 (1) [c]
RSV B[b]	8 (6)	2 (2)	9 (7)	3 (3)	5 (4)
RSV hospitalization	5	6	6	6	3
RSV A[b]	2 (2)	5 (4)	2 (2)	5 (4)	1 (1)
RSV B[b]	3 (3)	1 (1)	4 (4)	2 (2)	2 (1)
RSV infection not meeting any endpoint	7	13	8	13	5
RSV A[b]	5 (5)	8 (6)	6 (5)	8 (6)	3 (3)
RSV B[b]	2 (2)	5 (5)	2 (2)	5 (5)	2 (1)

Sources: Clinical study report P007V01MK1654: Table 11-1, page 77; 11-2, page 80; Table 14.2-17, page 345; Table 14.2-18, page 346; Response to FDA IR; FDA analysis (Merck 2024j; Merck 2024b)
[a] One palivizumab-treated participant ((b) (6)) had RSV A infection on Day 42 and RSV B infection on Day 167, with both infections meeting MALRI and hospitalization endpoints, and both with sequence data available.
[b] Number of cases with sequencing data available for each subtype shown in parentheses.
[c] One additional sample (Participant (b) (6) was reported as RSV A in the sequencing dataset, but RSV B in the GenMark eSensor RP1 assay dataset and was excluded from analysis.
Abbreviations: IR, Information Request; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; RP1, respiratory panel 1; RSV, respiratory syncytial virus

18.4.3.1. Analysis of RSV F Protein Substitutions Within or Near Clesrovimab Binding Site From Days 1 Through 180 Postdose

The FDA conducted an analysis of amino acid substitutions which occurred in or near the clesrovimab binding site, based on the crystal structure of the clesrovimab parent RB-1 Fab and RSV prefusion F complex (see Section 20.2.1). These included Site IV amino acid substitutions at positions 426 to 447 and/or within 5Å of clesrovimab binding site (161, 182 to 184, 430, 431, 442, 464, 465, 468, 470), and residues directly adjacent to these positions. For comparison, substitutions which occurred in the palivizumab binding site (F protein amino acids 262 to 275) were also noted.

Table 126 lists the substitutions within or near the clesrovimab binding site or in the palivizumab binding site in RSV infection cases from Days 1 through 180 postdose, regardless of whether they met any endpoint definition. A cutoff VAF of 3% was used, and substitutions are included if they were identified in at least one participant.

For RSV A cases, a total of 1/12 (8%) substitutions were seen in or near the clesrovimab binding site in samples from clesrovimab-treated participants, compared with 2/17 (12%) in the palivizumab binding site in samples from palivizumab-treated participants. For RSV B cases, a

total of 3/9 (33%) clesrovimab binding-site substitutions were seen in samples from clesrovimab-treated participants, compared with 1/17 (11%) palivizumab binding-site substitutions in the palivizumab arm. For RSV A and RSV B combined, most (3/4) sequences in the clesrovimab arm and all (3/3) sequences in the palivizumab arm had substitutions at a VAF of >50%.

While the numbers of sequences with substitutions are small for each study arm, they are consistent with the data from Trial MK-1654-004, indicating that the substitutions are likely treatment-emergent. Given that palivizumab resistant-associated substitutions were seen only in the palivizumab arm, it seems likely that this treatment emergence is not specific to clesrovimab.

For both RSV A and RSV B cases, the day of swabbing and day of sample collection relative to the onset of symptoms differed across instances of substitutions. There was also no clear association of substitutions with clinical events of RSV-associated MALRI or RSV-associated hospitalization, although there were proportionately more clinical events compared with Trial MK-1654-004, but overall, too few instances to draw firm conclusions.

Table 126. Substitutions in Clesrovimab Binding Site IV and/or Positions Within Five Angstroms of Clesrovimab Binding Site[a], or Palivizumab Binding Site[b], Seen at ≥3% VAF in ≥1 Participant, Days 1 to 180 Postdose

Position	Substitution	Clesrovimab	Palivizumab	Participant ID[c]	VAF (%)	Day of Swabbing[d]	Day of Sample[e]	Clinical Endpoint
RSV A		*n=12*	*n=17*					
185	V185A	0	1	(b) (6)	5.4	85	13	MALRI
275	S275F[f]	0	2		99.3	102	2	-[g]
					78.1	102	1	-
	S275Y	0	1		16.3	102	1	-
435	F435L	1	0		6.14	44	3	-
446	G446R				13.3			
	G446W				54.5			
470	K470R	0	1		3.2	85	13	MALRI
RSV B		*n=9*	*n=9*					
275	S275L[f]	0	1		86.0	124	3	-
446	G446E	2	0		3.4	9	2	MALRI HOSP
					99.9	28	9	-
446	G446R	1	0		99.7	13	5	MALRI HOSP
455	T455A	1	0		10.9	13	5	
Total RSV A[h]		*1 (8%)*	*2 (12%)*					
Total RSV B[h]		*3 (33%)*	*1 (11%)*					

Source: FDA analysis
[a] Includes amino acid substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
[b] Palivizumab binding site: amino acids 262 to 275.
[c] Four participants had RSV with ≥2 binding-site substitutions each.
[d] Relative to dosing day, for each instance.
[e] Day of swabbing relative to symptom onset, for each instance.
[f] Substitutions S275F and S275L confer >25,000-fold reduced susceptibility to palivizumab (MedImmune 1998).
[g] Participant (b) (6) had two cases of RSV infection within 30 days, with different consensus sequences. The first case met the endpoint of RSV-associated MALRI, and the second case where S275F substitution was seen did not meet any endpoint.
[h] Sequences with more than one binding-site substitution were counted once, and totals are for substitutions in the binding site of the respective antibody.
Abbreviations: HOSP, RSV hospitalization; ID, identifier; MALRI, medically attended lower respiratory infection; n, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.3.2. Analysis of RSV F Protein Substitutions in Participants With RSV-Associated MALRI

Individual substitutions in RSV F were evaluated in samples from participants who met the definition of RSV-associated MALRI, from Days 1 through 180 postdose, and Season 2 Days 1 through 180 postdose). For this analysis, two VAF% cutoffs were used, 3% and 30%. Overall, there were 2 additional participants with RSV-associated MALRI, and sequence data for Days 1 to 180 compared with Days 1 to 150 (Table 125), which didn't impact the conclusions with respect to the sequence analysis.

For RSV A (Table 127), no clesrovimab-treated participants had RSV with substitutions in or near the clesrovimab binding site from Days 1 to 180, and one had RSV with a G446R substitution at 53% VAF in Season 2. In the palivizumab arm, there was one participant with RSV harboring substitutions in or near the clesrovimab binding site, V185A+K470R, seen at low VAF% from Days 1 to 180, and there were no substitutions in the palivizumab binding site in either time-period. For other substitutions outside the clesrovimab binding site, there were none which were clearly increased in clesrovimab-treated participants compared with palivizumab-treated participants.

For RSV B (Table 128), there were two clesrovimab-treated participants in the Days 1 to 180 time-period with RSV harboring substitutions in or near the clesrovimab binding site which were not seen in participants in the palivizumab group: G446E and V446R+T455A, of which V446R was seen at >99% VAF, the others at low VAF % (see Table 126). In Season 2, one clesrovimab-treated participant had RSV with a V446R substitution at low VAF%. There were no substitutions in the palivizumab binding site in either time-period for either study group. Other RSV B F protein substitutions outside the clesrovimab binding site were not clearly increased in clesrovimab-treated participants compared with palivizumab-treated participants.

Table 127. Number of RSV A F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF in ≥2 Clesrovimab-Treated Participants[a] With RSV-Associated MALRI

			MALRI Days 1 to 180		Season 2 Days 1 to 180
Position	Substitution[b]	GenBank® Prevalence (%)[c]	Clesrovimab (N=6[d])	Palivizumab (N=9[d])	Clesrovimab (N=1[d])
8	A8T	98.6	6 (6)	9 (9)	1 (1)
12	T12I	11.4	2 (2)	4 (4)	-
20	F20L	98.6	5 (5)	6 (6)	1 (1)
80	N80K	99.9	6 (6)	9 (9)	1 (1)
101	T101P	99.9	6 (6)	9 (9)	1 (1)
103	A103T	5.6	2 (2)	0 (0)	-
105	N105S	93.8	6 (6)	8 (8)	1 (1)
122	T122A	18.2	2 (2)	2 (2)	-
124	K124N	98.8	6 (6)	9 (9)	1 (1)
185[f]	V185A[f]	0.0	0 (0)	1 (0)	-
213	R213S	99.6	6 (6)	9 (9)	1 (1)

Position	Substitution[b]	GenBank® Prevalence (%)[c]	MALRI Days 1 to 180 Clesrovimab (N=6[d])	MALRI Days 1 to 180 Palivizumab (N=9[d])	Season 2 Days 1 to 180 Clesrovimab (N=1[d])
276	N276S[e]	91.4	5 (5)	6 (6)	1 (1)
384	V384I	96.8	6 (6)	9 (9)	1 (1)
446[f]	G446R[f]	0.0	-	-	1 (1)
470[f]	K470R[f]	0.0	0 (0)	1 (0)	-
515	H515N	99.9	6 (6)	9 (9)	1 (1)
540	S540A	93.7	6 (6)	9 (9)	1 (1)

Source: FDA analysis
"-": Substitution not observed in ≥2 participants (or ≥1 participant if within binding site).
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants, or at least one participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV A Long (NCBI 2005).
[c] Estimated from 6,964 RSV A sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] N276S substitution, directly adjacent to the palivizumab binding site, does not confer reduced susceptibility to palivizumab (MedImmune 1998).
[f] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

Table 128. Number of RSV B F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF in ≥2 Clesrovimab-Treated Participants[a] With RSV-Associated MALRI

Position	Substitution[b]	GenBank® Prevalence (%)[c]	MALRI Days 1 to 180 Clesrovimab (N=7[d])	MALRI Days 1 to 180 Palivizumab (N=3[d])	Season 2 Days 1 to 180 Clesrovimab (N=4[d])
45	F45L	96.3	7 (7)	3 (3)	4 (4)
97	T97M	99.9	7 (7)	3 (3)	4 (4)
103	A103V	91.5	7 (7)	3 (3)	4 (4)
172	L172Q	90.7	7 (7)	3 (3)	4 (4)
173	S173L	88.0	7 (7)	3 (3)	4 (4)
190	S190N	10.3	7 (7)	2 (2)	2 (2)
191	K191R	66.9	7 (7)	3 (3)	4 (4)
197	S197N	99.5	7 (7)	3 (3)	4 (4)
206	I206M	67.3	7 (7)	3 (3)	4 (4)
209	Q209R	66.4	7 (7)	3 (3)	4 (4)
211	S211N	9.3	7 (7)	3 (3)	3 (3)

Position	Substitution[b]	GenBank® Prevalence (%)[c]	MALRI Days 1 to 180 Clesrovimab (N=7[d])	MALRI Days 1 to 180 Palivizumab (N=3[d])	Season 2 Days 1 to 180 Clesrovimab (N=4[d])
389	S389P	8.6	6 (6)	1 (1)	2 (2)
446[e]	G446E[e]	0.0	1 (0)	0	-
	G446R[e]	0.0	1 (1)	0	1 (0)
455[e]	T455A[e]	0.0	1 (0)	0	-
529	T529A	97.3	7 (7)	2 (2)	3 (3)

Source: FDA analysis
"-": Substitution not observed in ≥2 participants (or ≥1 participant if within binding site).
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants, or at least one participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV B 9320 (NCBI 2004).
[c] Estimated from 5,799 RSV B sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; MALRI, medically attended lower respiratory infection; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.3.3. Analysis of RSV F Protein Substitutions in Participants With RSV-Associated Hospitalization

Individual substitutions in RSV F were evaluated in samples from participants who met the definition of RSV-associated hospitalization, from Days 1 through 180 postdose, and Season 2, Days 1 through 180 postdose. For this analysis, two VAF% cutoffs were used, 3% and 30%. Overall, there were 2 additional participants with RSV hospitalization and sequence data for Days 1 to 180 compared with Days 1 to 150 (Table 125), which did not impact the conclusions with respect to the sequence analysis.

For RSV A (Table 129), no clesrovimab- or palivizumab-treated participants with RSV-associated hospitalization had RSV with a substitution in or near the clesrovimab binding site or in the palivizumab binding site.

For RSV B (Table 130), two clesrovimab-treated participants in the Days 1 to 180 time-period had RSV with substitutions in or near the clesrovimab binding site which were not seen in participants in the palivizumab group: G446E and G446R+T455A, of which G446R substitution was seen at >99% VAF, the others at low VAF % (see Table 126). In Season 2, one clesrovimab-treated participant had RSV with a G446R substitution at low VAF%. There were no substitutions in the palivizumab binding site in either time-period for either study group.

With respect to F protein substitutions seen at ≥3% or ≥30% VAF outside the clesrovimab binding site, there was no clear difference for either RSV A or RSV B infections between study arms.

Table 129. Number of RSV A F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF in ≥1 Clesrovimab-Treated Participant[a] With RSV-Associated Hospitalization

			Days 1 to 180		Season 2 Days 1 to 180
Position	Substitution[b]	GenBank® Prevalence (%)[c]	Clesrovimab (N=2[d])	Palivizumab (N=4[d])	Clesrovimab (N=2[d])
8	A8T	98.6	2 (2)	4 (4)	2 (2)
12	T12I	11.4	0 (0)	3 (3)	1 (1)
15	L15F	3.6	-	-	1 (1)
20	F20L	98.6	2 (2)	2 (2)	2 (2)
80	N80K	99.9	2 (2)	4 (4)	2 (2)
101	T101P	99.9	2 (2)	4 (4)	2 (2)
102	A102V	0.3	-	-	1 (1)
103	A103T	5.6	1 (1)	0 (0)	-
105	N105S	93.8	2 (2)	3 (3)	1 (1)
108	R108K	0.1	-	-	1 (0)
122	T122A	18.2	1 (1)	0 (0)	-
124	K124N	98.8	2 (2)	4 (4)	2 (2)
213	R213S	99.6	2 (2)	4 (4)	2 (2)
276	N276S [e]	91.4	2 (2)	1 (1)	2 (2)
377	S377N	1.0	1 (1)	0 (0)	-
384	V384I	96.8	2 (2)	4 (4)	2 (2)
418	G418S	0.0	1 (0)	0 (0)	-
515	H515N	99.9	2 (2)	4 (4)	2 (2)
540	S540A	93.7	2 (2)	4 (4)	2 (2)
574	N574S	1.1	1 (0)	0 (0)	-

Source: FDA analysis
"-": Substitution not observed in ≥2 participants (or ≥1 participant if within binding site).
[a] Substitutions are shown if they were seen in at least 1 clesrovimab-treated participant in either time-period, or at least one participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV A Long (NCBI 2005).
[c] Estimated from 6,964 RSV A sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] N276S substitution, directly adjacent to the palivizumab binding site, does not confer reduced susceptibility to palivizumab (MedImmune 1998).
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

Table 130. Number of RSV B F Protein Sequences With Individual Substitutions at ≥3% (or ≥30%) VAF in ≥1 Clesrovimab-Treated Participant[a] With RSV-Associated Hospitalization

			Season 1 Days 1 to 180		Season 2 Days 1 to 180
Position	Substitution[b]	GenBank® Prevalence (%)[c]	Clesrovimab (N=4[d])	Palivizumab (N=2[d])	Clesrovimab (N=1[d])
18	N18D	0.0	1 (0)	1 (0)	-
19	A19T	1.8	1 (0)	1 (0)	-
45	F45L	96.3	4 (4)	2 (2)	1 (1)
97	T97M	99.9	4 (4)	2 (2)	1 (1)
103	A103V	91.5	4 (4)	2 (2)	1 (1)
172	L172Q	90.7	4 (4)	2 (2)	1 (1)
173	S173L	88.0	4 (4)	2 (2)	1 (1)
190	S190N	10.3	4 (4)	1 (1)	1 (1)

Position	Substitution[b]	GenBank® Prevalence (%)[c]	Season 1 Days 1 to 180 Clesrovimab (N=4[d])	Season 1 Days 1 to 180 Palivizumab (N=2[d])	Season 2 Days 1 to 180 Clesrovimab (N=1[d])
191	K191R	66.9	4 (4)	2 (2)	1 (1)
197	S197N	99.5	4 (4)	2 (2)	1 (1)
206	I206M	67.3	4 (4)	2 (2)	1 (1)
209	Q209R	66.4	4 (4)	2 (2)	1 (1)
211	S211N	9.3	4 (4)	2 (2)	1 (1)
389	S389P	8.6	3 (3)	0 (0)	1 (1)
446[e]	G446E[e]	0.0	1 (0)	0 (0)	-
	G446R[e]	0.0	1 (1)	0 (0)	1 (0)
455[e]	T455A[e]	0.0	1 (0)	0 (0)	-
529	T529A	97.3	4 (4)	1 (1)	1 (1)

Source: FDA analysis.
"-": Substitution not observed in ≥2 participants (or ≥1 participant if within binding site)
[a] Substitutions are shown if they were seen in at least one clesrovimab-treated participant in either time-period, or at least one participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV B 9320 (NCBI 2004).
[c] Estimated from 5,799 RSV B sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[d] Number seen at ≥30% shown in parentheses.
[e] Amino acid positions/substitutions within the linear region of Site IV positions 426-470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.3.4. Analysis of RSV F Protein Substitutions in All RSV-Infected Participants

Individual RSV F protein substitutions seen in any RSV-infected participants with sequence data, regardless of whether they met an efficacy endpoint, were analyzed according to time-period postdose (Days 1 to 180, and Season 2 Days 1 through 180), using a ≥3% or ≥30% VAF cutoff. All substitutions seen in or near the clesrovimab binding site were noted, regardless of whether they were seen in the clesrovimab or palivizumab arms.

For RSV A (Table 131), in addition to the substitutions identified in or near the clesrovimab binding site from Days 1 to 180, which are detailed in Table 126, one substitution (G446R) was seen 53% VAF in one clesrovimab-treated participant in Season 2, and not in the palivizumab arm.

For RSV B (Table 132), in addition to the substitutions identified in or near the clesrovimab binding site from Days 1 to 180, which are detailed in Table 126, one substitution (G446R) was seen at low VAF% in one clesrovimab-treated participant in Season 2, and not in the palivizumab arm.

Overall, for RSV A and RSV B, there was no clear difference between study arms with respect to RSV F substitutions seen at ≥3% or ≥30% VAF outside the clesrovimab binding site.

Table 131. Number of RSV A F Protein Sequences With Individual Substitutions ≥3% (or ≥30%) VAF Seen in ≥2 Clesrovimab-Treated Participants[a], for Each Postdose Period[b]

			Season 1 Days 1 to 180		Season 2 Days 1 to 180
Position	Substitution[c]	GenBank® Prevalence (%)[d]	Clesrovimab (N=12[e])	Palivizumab (N=17[e])	Clesrovimab (N=4[e])
8	A8T	98.6	12 (12)	17 (17)	4 (4)
12	T12I	11.4	2 (2)	5 (5)	2
15	L15F	3.6	-	-	2
20	F20L	98.6	10 (10)	14 (14)	4 (4)
23	A23S	0.1	2 (2)	2 (2)	-
65	K65R	0.1	2 (2)	1 (1)	-
80	N80K	99.9	12 (12)	17 (17)	4 (4)
101	T101P	99.9	12 (12)	17 (17)	4 (4)
103	A103T	5.6	2 (2)	1 (1)	1 (1)
105	N105S	93.8	12 (12)	16 (16)	2 (2)
122	T122A	18.2	4 (4)	6 (6)	1 (1)
124	K124N	98.8	12 (12)	16 (16)	4 (4)
185[g]	V185A[g]	0.0	0 (0)	1 (0)	-
213	R213S	99.6	12 (12)	17 (17)	4 (4)
276	N276S [f]	91.4	10 (10)	14 (14)	4 (4)
384	V384I	96.8	12 (12)	17 (17)	4 (4)
435[g]	F435L[g]	0.0	1 (0)	0 (0)	-
446[g]	G446R[g]	0.0	1 (0)	0 (0)	1 (1)
	G446W[g]	0.0	1 (1)	0 (0)	-
470[g]	K470R[g]	0.0	0 (0)	1 (0)	-
515	H515N	99.9	12 (12)	17 (17)	4 (4)
540	S540A	93.7	12 (12)	17 (17)	4 (4)

Source: FDA analysis
"-": Substitution not observed in ≥2 participants (or ≥1 participant if within binding site).
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants, or at least one participant in either arm for substitutions at bolded positions.
[b] There was only one participant with RSV infection in the period between Season 1 Day 180 and Season 2 Day 1, and there were no binding-site substitutions in the RSV F protein from this participant.
[c] RSV F amino acid substitutions compared with reference sequence RSV A Long (NCBI 2005).
[d] Estimated from 6,964 RSV A sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[e] Number seen at ≥30% shown in parentheses.
[f] N276S substitution, directly adjacent to the palivizumab binding site, does not confer reduced susceptibility to palivizumab (MedImmune 1998).
[g] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

Table 132. Number of RSV B F Protein Sequences With Individual Substitutions ≥3% (or ≥30%) VAF Seen in ≥2 Clesrovimab-Treated Participants[a], for Each Postdose Period[b]

			Season 1 Days 1 to 180		Season 2 Days 1 to 180
Position	Substitution[c]	GenBank® Prevalence (%)[d]	Clesrovimab (N=9[e])	Palivizumab (N=9[e])	Clesrovimab (N=5[e])
45	F45L	96.3	9 (9)	9 (9)	5 (5)
97	T97M	99.9	9 (9)	9 (9)	5 (5)
103	A103V	91.5	9 (9)	8 (8)	5 (5)
172	L172Q	90.7	9 (9)	9 (9)	5 (5)
173	S173L	88.0	9 (9)	9 (9)	5 (5)
190	S190N	10.3	8 (8)	8 (8)	3 (3)
191	K191R	66.9	9 (9)	9 (9)	5 (5)
197	S197N	99.5	9 (9)	9 (9)	5 (5)
206	I206M	67.3	9 (9)	9 (9)	5 (5)
209	Q209R	66.4	9 (9)	9 (9)	5 (5)
211	S211N	9.3	8 (8)	9 (9)	4 (4)
389	S389P	8.6	7 (7)	7 (7)	3 (3)
446[f]	G446E[f]	0.0	2 (1)	0 (0)	-
	G446R[f]	0.0	1 (1)	0 (0)	1 (0)
455[f]	T455A[f]	0.0	1 (0)	0 (0)	-
529	T529A	97.3	9 (9)	8 (8)	4 (4)

Source: FDA analysis
"-": Substitution not observed in ≥2 participants (or ≥1 participant if within binding site).
[a] Substitutions are shown if they were seen in at least two clesrovimab-treated participants, or at least one participant in either arm for substitutions at bolded positions.
[b] RSV F amino acid substitutions compared with reference sequence RSV B 9320 (NCBI 2004).
[c] There were no clesrovimab-treated participants who had an RSV infection between Season 1 Day 180 and Season 2 Day 1.
[d] Estimated from 5,799 RSV B sequences in GenBank®, annotated with subtype and collection date as of April 15, 2024.
[e] Number seen at ≥30% shown in parentheses.
[f] Amino acid positions/substitutions within the linear region of Site IV positions 426 to 470 (encompasses the nonlinear clesrovimab contact residues within 426 to 447) and other residues within 5Å of the clesrovimab binding site (161, 182 to 184), and adjacent residues.
Abbreviations: F, fusion protein; N, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.3.5. Analysis of RSV F Protein Concurrent Substitutions in Clesrovimab-Treated Participants

RSV variants with concurrent F protein substitutions in clesrovimab-treated participants were compared with palivizumab-treated participants (Table 133). The most frequently occurring concurrent substitutions (consensus sequence) were assessed, along with the consensus sequence plus other frequently occurring substitutions seen at ≥3% VAF in RSV from at least three clesrovimab-treated participants regardless of meeting an endpoint from Days 1 to 180 postdose. Analyses were also conducted for these concurrent substitutions in participants with RSV infection which met the endpoints of RSV-associated MALRI or RSV-associated hospitalization.

For RSV A, there was only one variant with ≥3 instances (consensus + T122A substitution), which was not clearly associated with clesrovimab treatment. For RSV B, there was also only one variant with ≥3 instances (consensus + S190R+S211N+S389P substitutions, seen in contemporary isolates), which was also not clearly associated with clesrovimab treatment.

There was no clear association of variants with RSV-associated MALRI or RSV-associated hospitalization, although there were too few cases to draw firm conclusions.

Table 133. RSV F Protein Concurrent Substitutions Seen at ≥3% VAF in ≥3 Clesrovimab-Treated Participants With Breakthrough RSV Infections From Days 1 to 180 Postdose

	All Cases		MALRI		Hospitalization	
Variant[a]	Clesrovimab	Palivizumab	Clesrovimab	Palivizumab	Clesrovimab	Palivizumab
RSV A	n=12 (%)	n=17 (%)	n=6 (%)	n=9 (%)	n=2 (%)	n=4 (%)
Consensus[b]	10 (83)	12 (71)	5 (83)	5 (56)	2 (100)	1 (25)
Consensus + T12 + T122	5 (42)	7 (41)	2 (33)	3 (33)	1 (50)	1 (25)
Consensus + T122A	4 (33)	5 (29)	2 (33)	2 (22)	1 (50)	0 (0)
RSV B	n=9 (%)	n=9 (%)	n=7 (%)	n=3 (%)	n=4 (%)	n=2 (%)
Consensus[c]	9 (100)	7 (78)	7 (100)	2 (67)	4 (100)	1 (50)
Consensus +S190R+S211N+S389P	7 (78)	6 (86)	6 (86)	1 (33)	3 (75)	0 (0)

Source: FDA analysis
[a] May include F protein substitution(s) in addition to the ones listed.
[b] RSV A consensus substitutions: A8T+F20L+N80K+T101P+N105S+K124N+R213S+N276S+V384I+H515N+S540A.
[c] RSV B consensus substitutions: F45L+T97M+A103V+L172Q+S173L+K191R+S197N+I206M+Q209R+T529A.
Abbreviations: F, fusion protein; MALRI, medically attended lower respiratory infection; n, number of participants in treatment arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

18.4.4. Independent Assessment of Next Generation Sequencing Data

NGS analysis was performed for 587 participants from two clinical trials, including 530 participants from Trial MK-1654-004 (CLEVER; NCT04767373) and 57 participants from Trial MK-1654-007 (SMART; NCT04938830) using the Illumina MiSeq platform. An independent assessment of the NGS data was performed by the Division of Antivirals. The NGS sequencing results and resistance analyses generated by the Division of Antivirals from NP samples collected in the two trials (MK-1654-004 and MK-1654-007) were largely in agreement with the results reported by the Applicant. The most common epitope substitution associated with clesrovimab administration was at position G446 in both RSV A (five participants with G446R, three participants with G446E, and two participants with G446W) and RSV B (five participants with G446E, three participants with G446R, and one participant with G446V).

Additional epitope substitutions were detected for RSV A at D440 (n=1; D440G) and K470 (n=1; K470R) and RSV B at I432 (n=1; I432V) and V447 (n=1; V447I). Clesrovimab substitutions at positions within 4Å of an epitope amino acid were detected at F435 (n=1; F435L) and S466 (n=3; S466N) in RSV A participants and substitution N466S was detected in one RSV B participant who received clesrovimab. Of note, substitutions at position 466 were reciprocal in that they each exhibited an emergent amino acid that was the baseline amino acid for the other RSV subtype. Reciprocal substitutions are not expected to impact clesrovimab activity given that the mAb has activity against both RSV A and RSV B.

Two substitutions occurring at position 462 of the F protein (RSV A, n=1, Q462L and RSV B, n=1, L462Q) were within 8Å of an epitope amino acid but were also reciprocal substitutions not expected to impact clesrovimab activity. Clesrovimab substitutions E356D and N380S/D within

20Å of an epitope amino acid were detected in two and three RSV A participants, respectively, who received clesrovimab and substitution I402V within 20Å of an epitope amino acid was detected in two RSV B participants who received clesrovimab. Phenotypic information was not provided for the majority of these substitutions and phenotypic assessments for most of these substitutions will be requested as a PMR in concordance with the primary Clinical Virology review. The NGS data submitted, and the independent analyses of these data, are supportive of approval.

18.5. Compilation of F Protein Substitutions Seen Within or Near Clesrovimab Binding Site

Table 134 summarizes the F protein amino acid substitutions and polymorphisms occurring within or near the clesrovimab binding site, which were identified in GenBank®, surveillance studies, and/or clinical trials of clesrovimab at any time point. There are only a few for which phenotypic data are available, so it will be important to conduct additional assessments for other substitutions which were seen, particularly those occurring at contact residues, and identified in clinical trials, which are potentially treatment-emergent. Table 135 lists substitutions which are recommended for phenotyping. In general, the following criteria were used:

- Substitution occurs within clesrovimab epitope, with ≥1 instance seen in clesrovimab-treated participants in clinical trials, and/or ≥2 instances at same position in GenBank®/surveillance studies.
- Substitution occurs at position ≤5Å of clesrovimab epitope, or >5Å of clesrovimab epitope but within the linear region 426 to 470, with ≥2 instances at same position seen in clesrovimab-treated participants in clinical trials and/or GenBank®.

Table 134. Summary of RSV F Protein Substitutions Occurring in or Near the Clesrovimab Epitope, Observed in GenBank®, Published Literature, Surveillance Activities, and/or Clinical Trials of Clesrovimab

					Instances (Subtype)[c]		
Position	Proximity[a]	Substitution	Subtype	Source[b]	GenBank®	Study or Trial	Fold Change[d] (Subtype)
160	>5Å	L160P	RSV A	Trial MK-1654-004 (P)	0	1 (A)	
161	≤5Å	E161Q	RSV A	GenBank®	1 (A)	-	
181	>5Å	L181P	RSV A	Trial MK-1654-004 (P)	0	1 (A)	
182	≤5Å	S182A	RSV B	GenBank®	2 (B)	-	
		S182I+N183D	NR	GenBank®	1 (A or B)	-	
183	≤5Å	S182I+N183D	NR	GenBank®	1 (A or B)	-	
		N183T	RSV A	GenBank®	1 (A)	-	
		N183Y	RSV B	GenBank®	1 (B)	-	
184	≤5Å	None	-	-	0	-	
185	>5Å	V185A	RSV A	GenBank® Trial MK-1654-004 (P) Trial MK-1654-007 (P)	1 (A)	2 (A)	
		V185I	RSV B	Trial MK-1654-004 (C)	0	1 (B)	
425	>5Å	S425T	RSV B	Trial MK-1654-004 (P)	0	1 (B)	
426	Epitope	N426H	RSV A	Trial MK-1654-004 (C)	0	1 (A)	
		N426T	RSV A, B	GenBank®	1 (A), 1 (B)	-	
427	Epitope	None	-	-	-	-	
428	Epitope	N428D	RSV A	GenBank®	1 (A)	-	
429	Epitope	K429C	RSV B	Surveillance	1 (B)	1 (B)	
		R429H	RSV A	Surveillance	1 (A)	1 (A)	
430	>5Å	None	-	-	0	-	
431	≤5Å	L131T	RSV B	GenBank®	1 (B)	-	
432	Epitope	I432T	RSV A, B	GenBank®	5 (A), 1 (B)	-	4 (A) 1.6 (B)
		I432V	RSV A RSV B	GenBank® Trial MK-1654-004 (C, P)	1 (A)	2 (B)	3 (B)
433	Epitope	K433Q	RSV B	GenBank®	1 (B)	-	
		K433R	RSV B	GenBank®	4 (B)	-	
		K433T	RSV A	Trial MK-1654-004 (P)	0 (A)	1 (A)	

Position	Proximity[a]	Substitution	Subtype	Source[b]	Instances (Subtype)[c] GenBank®	Instances (Subtype)[c] Study or Trial	Fold Change[d] (Subtype)
435	>5Å	F435L	RSV A	Trial MK-1654-007 (C)	0	1 (A)	
		F435S	RSV B	Trial MK-1654-004 (C)	0	2 (B)	
436	>5Å	S436F	RSV A	GenBank® Trial MK-1654-004 (C)	5 (A)	1 (A)	
440	Epitope	D440G	RSV A	Trial MK-1654-004 (C)	0 (A)	1 (A)	1.1 (A)
		D440N	RSV B	GenBank®	2 (B)	-	
441	Epitope	Y441H	RSV B	Trial MK-1654-004 (P)	0	1 (B)	
442	≤5Å	V442A	NR	GenBank®	1 (A or B)	-	
		V442M	RSV B	GenBank®	2 (B)	-	
443	Epitope	S443L	RSV B	Trial MK-1654-004 (C, P)	0	2 (B)	
		S443P	RSV A, B	Cell culture	0 (A), 0 (B)	-	>3,800 (A) >360 (B)
		S443T	RSV A, B	GenBank®	2 (A), 1 (B)	-	
445	Epitope	K445N	RSV A	GenBank® cell culture	3 (A)	-	
		K445R	RSV A, B	GenBank® Surveillance	3 (A), 1 (B)	1 (B)	0.6 (B)
446	Epitope	G446E	RSV A, B	GenBank® Cell culture Trial MK-1654-004 (C) Trial MK-1654-007 (C)	3 (A), 0 (B)	3 (A), 5 (B)	>3,800 (A) >1,299 (B)
		G446R	RSV A, B	Trial MK-1654-004 (C) Trial MK-1654-007 (C)	0 (A), 0 (B)	5 (A), 2 (B)	>1,563 (A)
		G446V	RSV B	GenBank® Trial MK-1654-004 (C)	0 (A), 1 (B)	2 (B)	
		G446W	RSV A	Trial MK-1654-004 (C) Trial MK-1654-007 (C)	0 (A), 0 (B)	2 (A)	>2,941 (A) >1,299 (B)
447	Epitope	V447I	RSV B	Trial MK-1654-004 (C)	NR	1 (B)	
		V447L	RSV B	GenBank®	1 (B)	-	
		V447M	RSV A	GenBank®	3 (A)	-	
452	>5Å	V452E	RSV B	Surveillance Trial MK-1654-004 (C)	0 (B)	3 (B)	
454	>5Å	N454S	RSV B	Trial MK-1654-004 (P)	0	1 (B)	
		N454T	RSV B	Trial MK-1654-004 (C)	0	1 (B)	

Position	Proximity[a]	Substitution	Subtype	Source[b]	Instances (Subtype)[c] GenBank®	Instances (Subtype)[c] Study or Trial	Fold Change[d] (Subtype)
457	>5Å	Y457H	RSV A	Surveillance Trial MK-1654-004 (C, P)	0 (A)	4 (A)	
458	>5Å	Y458H	RSV B	Trial MK-1654-004 (P)	0	1 (B)	
463	>5Å	E463D	RSV B	Tabor et al.	262 (B)		
		E463G	RSV A	Trial MK-1654-004 (C)	0	1 (A)	
464	≤5Å	None	-		0	-	
465	≤5Å	K465E	RSV A	GenBank®	1 (A or B)	-	
		K465R	RSV A	GenBank®	5 (A or B)	-	
466	≤5Å	S466N	RSV A	GenBank® Trial MK-1654-004 (C) Tabor et al.	70 (A)	2 (A)	
467	>5Å	L467I	RSV A	Trial MK-1654-004 (C)	13	1 (A)	
468	≤5Å	Y468C	NR	GenBank®	1 (A or B)	-	
		Y468F	RSV B	GenBank®	1 (B)	-	
470	≤5Å	K470E	RSV A, B	GenBank® Trial MK-1654-004 (P)	1 (A or B)	1 (B)	
		K470N	RSV B	GenBank®	1 (B)	-	
		K470R	RSV A	GenBank® Trial MK-1654-004 (C) Trial MK-1654-007 (P)	4 (A or B)	2 (A)	
		K470T	RSV B	GenBank®	1 (B)	-	

Source: FDA analysis (see Sections 18.1, 18.4, 20.2, 20.6)
[a] Proximity to epitope, based on crystallography studies of parental antibody RB-1 (Section 20.2). Positions are shown which interact with RB-1 (epitope) or occur ≤5Å of the epitope or >5Å but within linear region 426 to 470 if substitutions were identified at these positions.
[b] Source column indicates whether substitution was observed in GenBank®, published literature (Tabor et al. 2020), surveillance studies, and/or clinical trials of clesrovimab.
[c] Instances columns show the number of sequences harboring substitution as seen in GenBank® (n=15,527), or in studies of surveillance (at ≥5% VAF in 555 clinical isolates) or clinical trials of clesrovimab (at ≥3% VAF in Trials MK-1654-004 and MK-1654-007 combined).
[d] Fold change of cell culture EC_{50} value for variant with substitution, compared with wild-type.
Abbreviations: C, clesrovimab arm; EC_{50}, half-maximal effective concentration; n, number of participants in treatment arm; NR, subtype not specified; P, placebo or palivizumab arm; RSV, respiratory syncytial virus; VAF, variant allele frequency

Table 135. Substitutions Recommended for Phenotyping

Position	RSV A	RSV B	Reason
High priority			
426	N426H	N426T	Within epitope, two instances in GenBank®, seen in Trial MK-1654-004
429	R429H	K429C	Within epitope, each seen in surveillance; loss of binding to R429A in alanine scanning experiment
432	I432V	I432V	Within epitope, seen in Trial MK-1654-004
433	K433R	K433R	Within epitope, seen in GenBank® and Trial MK-1654-004
435	F435L	F435S	Seen in Trials MK-1654-004 and MK-1654-007
436	S436F	S436F	Seen in GenBank® and Trial MK-1654-004
440	Data	D440N	Seen in GenBank® and Trial MK-1654-004
442	V442M	V442M	Adjacent to epitope residues, seen in GenBank®
443	S443L	S443L	Within epitope, seen in Trial MK-1654-004
	S443T	S443T	Within epitope, seen in GenBank®
445	Data	K445N	Within epitope, seen in GenBank® and cell culture selection
	K445R	Data	Within epitope, seen in GenBank® and surveillance
446	Data	Data	Within epitope, seen in GenBank®, cell culture selection, Trials MK-1654-004 and MK-1654-007
	G446R	G446R	Within epitope, seen in Trials MK-1654-004 and MK-1654-007
	G446V	G446V	Within epitope, seen in GenBank® and Trial MK-1654-004
	Data	Data	Within epitope, seen in Trials MK-1654-004 and MK-1654-007
447	V447M	V447I	Within epitope, seen in GenBank® and Trial MK-1654-004
452	V452E	V452E	Seen in Trial MK-1654-004
457	Y457H	Y457H	Seen in Trial MK-1654-004
463	E463G	E463D	Seen in GenBank®, reported by (Tabor et al. 2020)
465	K465R	K465R	Seen in GenBank®
466	S466N	N466S	Seen in GenBank®, Trial MK-1654-004, reported by (Tabor et al. 2020)
470	K470R	K470R	Seen in GenBank®, Trials MK-1654-004 and MK-1654-007
Medium priority			
182		S182A	Seen in GenBank®
183	N183T	N183Y	Seen in GenBank®
185	V185A	V185I	Seen in GenBank®, Trial MK-1654-004
356	E356D		Seen in Trial MK-1654-004
380	N380S		Seen in Trial MK-1654-004
402		I402V	Seen in Trial MK-1654-004
428	N428D		Seen in GenBank®

Source: Table 18.3.1
Data = phenotypic data available
Abbreviation: RSV, respiratory syncytial virus

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

20.1. Mechanism of Action

Clesrovimab is a recombinant human IgG1κ mAb that targets antigenic Site IV of the RSV fusion (F) protein. Clesrovimab binds with high affinity to the prefusion conformation of F protein (see Section 20.3) and neutralizes RSV in cell culture assays with activity (EC_{50} values) in the picomolar range (see Section 20.4). The precursor to clesrovimab, RB-1, is a human anti-RSV IgG1κ mAb which was produced by isolating an RSV fusion protein-specific B lymphocyte from primary human memory cells (Tang et al. 2019). Clesrovimab was generated from the RB-1 mAb by introducing three amino acid substitutions (YTE), into the heavy chain. The YTE substitutions increase the binding between the Fc region of IgG and neonatal Fc receptor extending the serum half-life in humans (Robbie et al. 2013; Griffin et al. 2017). The YTE modification also reduces IgG binding to FcγRIIIA, which mediates antibody-dependent cellular cytotoxicity, and therefore substantially reduces this effector function (Dall'Acqua et al. 2006).

Co-crystallography studies of RB-1 Fab with prefusion F protein showed that RB-1 binds to antigenic Site IV, which likely locks the protein in its prefusion state and prevents the irreversible conformational change to the more stable postfusion conformation, similar to the action of the Site Ø targeting antibody nirsevimab (McLellan et al. 2013). The postfusion F protein brings viral and host membranes together prior to viral entry and is an essential process in the viral replication cycle.

The Applicant conducted crystallography and binding studies to identify the epitope to which clesrovimab binds, and assessed the neutralization activity of clesrovimab in cell culture against diverse isolates of RSV A and RSV B. The effector function of clesrovimab was evaluated using a cotton rat model of RSV infection.

20.2. Characterization of the Clesrovimab Binding Site

The following was derived from study reports submitted by the Applicant (Merck 2024e; Merck 2024g). The clesrovimab binding epitope was determined through crystallography of the parental mAb RB-1 Fab region bound to the RSV F protein. In addition, a shotgun mutagenesis study was conducted using alanine scanning to identify amino acid residues involved in binding to RB-1.

20.2.1. Co-Crystallization of RSV Prefusion F Protein and Clesrovimab Parental Antibody RB-1

Methodology

The RSV prefusion F protein was modified to include a C-terminal T4 fibritin trimerization motif, thrombin cleavage site, 6x Histag, and StreptagII tag (prefusion F protein [DS-Cav1]; (McLellan et al. 2013). The DS-Cav1 protein was expressed in Expi 293F cells (InVitrogen) from plasmids containing a mammalian codon-optimized version of the construct, then purified from cell culture supernatants using nickel Sepharose affinity chromatography, based on a

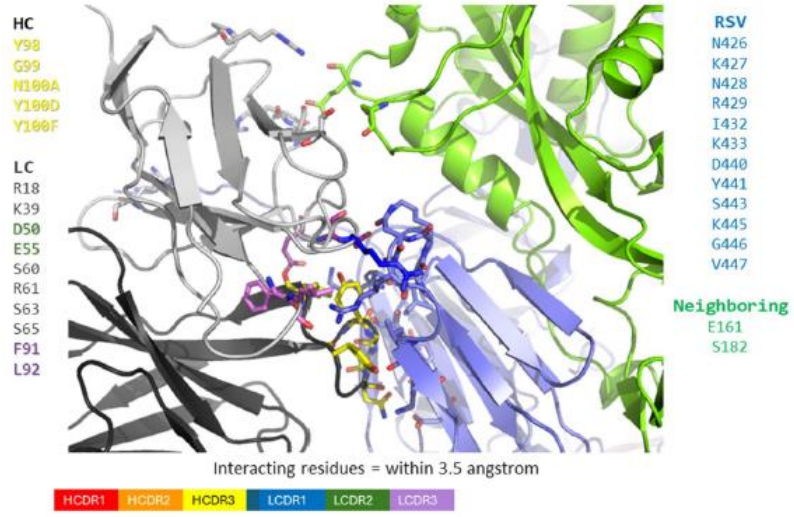
published method (McLellan et al. 2013). Affinity tags were removed by thrombin cleavage, and the protein further purified by Sepharose chromatography.

The RB-1 antibody was cleaved into Fab fragments using the Pierce™ Fab Preparation Kit, following the manufacturer's instructions. The Fab fragments were mixed 1.3:1 (w/w) with DS-Cav1 and incubated overnight at 4°C. The bound complex was purified on a Superdex 200 column (GE Healthcare) in a solution of 50mM HEPES, pH. 7.5, 300mM sodium chloride, and concentrated to 10 mg/mL in 20 mN HEPES, pH 7.5, 100mM sodium chloride. Crystals were generated in a solution of 100mM Tris, pH 8.5, 12% polyethylene 8000, and 200mM ammonium sulfate, and through experimenting with conditions a crystal was obtained which diffracted beyond 3.5 angstroms. The crystal was dehydrated in 100mM Tris pH 8.5 and 35% polyethylene 1500 for 4 days and vitrified for data collection by rapid submersion into liquid nitrogen. Crystal structure analysis was conducted with the collected data.

Results

Crystallography of RB-1 Fab complexed with DS-Cav1 revealed that three copies of RB-1 were bound to the F prefusion protein trimer, and that both heavy and light chains of RB-1 interact with the F protein via the complementarity determining region. The interaction occurs with the F1 subunit of F protein at a location which overlaps antigenic Site IV. The interaction points of RB-1 were used to define the clesrovimab binding epitope and identify residues within 5Å of the epitope (Figure 28), contact residues shown in blue font). In addition to the F1 residues, E161 and S182 in the F2 subunit were shown to reside near RB-1 using a 3.5Å cutoff. The E161 residue is located closest to S60 and S63 residues on the RB-1 light chain which are not optimally located to form H-bond contacts with E161. Also, S182 (and N183) interact with S52 and S65 on the RB-1 light chain, and RB-1 retained binding affinity and neutralization activity when S52 and/or S65 were changed to alanine (data not shown).

Figure 28. Crystal Structure of the Clesrovimab Parent RB-1 Fab and RSV Prefusion F Complex Showing the Interaction Points Between RB-1 and F Protein



Source: Figure 11, page 48, RSV Surveillance and Clinical Virology report (Merck 2024e); (Tang et al. 2019)
Contact residues of F protein with RB-1 Fab are shown in blue font.
Abbreviation: F, fusion protein; Fab, fragment antigen-binding; HC, heavy chain; LC, light chain; RSV, respiratory syncytial virus

Because RB-1 was not modified at any of the amino acids found to be involved in binding to the F protein epitope, the crystal structure also defines the binding of clesrovimab. The diversity of the 12 amino acids in the clesrovimab epitope (contact residues shown in Figure 26) is discussed in Section 18.1. The F protein amino acid residues located ≤5Å of the clesrovimab epitope are listed in Table 136, along with the number of polymorphisms at these positions seen in GenBank® (accessed April 15, 2024; total of 15,527 sequences, of which 6,964 RSV A and 5,799 RSV B sequences were annotated with subtype and collection date). Only RSV A K470R and RSV B K470E polymorphisms were observed in an analysis of breakthrough infections in clinical studies (see Section 18.4).

Table 136. Polymorphisms at F Protein Amino Acid Positions Located ≤5Å of the Clesrovimab Binding Epitope

AA Position #	Distance (Å)	AA Substitution	GenBank® Entries[b] RSV A	RSV B	Total
E161	3.8	E161Q	1	0	1
S182	3.8	S182A	0	2	2
	3.8	S182I+N183D[a]	RSV subtype unspecified		1
	3.8	S182T	0	1	1
N183	3.8	N183D+S182I[a]	RSV subtype unspecified		1
	3.8	N183T	1	0	1
	3.8	N183Y	0	1	1
G184	5	None	0	0	0
G430	3.8	None	0	0	0
I431	5	I431T	0	1	1
V442	5	V442A	RSV subtype unspecified		1
	5	V442M	0	2	2
G464	5	None	0	0	0
K465	3.8	K465E	1	0	1
	3.8	K465R	4	2	6
Y468	4	Y468C	RSV subtype unspecified		1
	4	Y468F	0	1	1
K470	3.8	K470E	1	0	1
	3.8	K470N	0	1	1
	3.8	K470R	3	1	4
	3.8	K470T	0	1	1

Source: Table 21, page 49, RSV Surveillance and Clinical Virology report; Response to FDA IR (Merck 2024e; Merck 2025c)
[a] Same entry in GenBank®
[b] Total GenBank® sequences analyzed =15,527 (accessed April 15, 2024; 6,964 RSV A and 5,799 RSV B sequences annotated with subtype and collection date)
Abbreviations: Å, angstroms; AA, amino acid; F, fusion protein; IR, Information Request; RSV, respiratory syncytial virus

20.2.2. Epitope Mapping Using Alanine Scanning Mutagenesis

Methodology

Epitope mapping of the RSV F protein clesrovimab binding site was conducted by (b) (4) using RSV F from the laboratory strain RSV A2 (NCBI 2009). A comprehensive alanine scanning mutagenesis library was created and expressed in eukaryotic cells using a high-throughput cellular expression technology (Davidson and Doranz 2014). The alanine scanning mutagenesis targeted 368 surface-exposed residues which had been

identified from crystal structures of RSV F protein in prefusion and postfusion conformations (McLellan et al. 2011; McLellan et al. 2013). Residues were substituted to alanine individually, and native alanine residues to serine, through mutation of the expression construct. Screening of constructs was conducted following published methodology (Fong et al. 2014).

The library of 368 mutated constructs was transfected as individual clones into human 293T cells in a 384-well plate. Proteins were expressed for 16 hours and cells fixed with 4% paraformaldehyde. Test antibodies in 10% goat serum were added to the fixed cells for 1 hour at room temperature. As positive controls, RSV mAbs D25 (precursor to nirsevimab; (McLellan et al. 2013) and palivizumab were used. Fab fragments of RB-1 and D25 were also generated through papain digestion of the parental antibody and tested in parallel. A secondary antibody, Alexa Fluor 488-conjugated antihuman IgG heavy and light chains, was added to the cells for 30 minutes, then cells were washed, and cellular fluorescence measured using the Intellicyt high throughput flow cytometer.

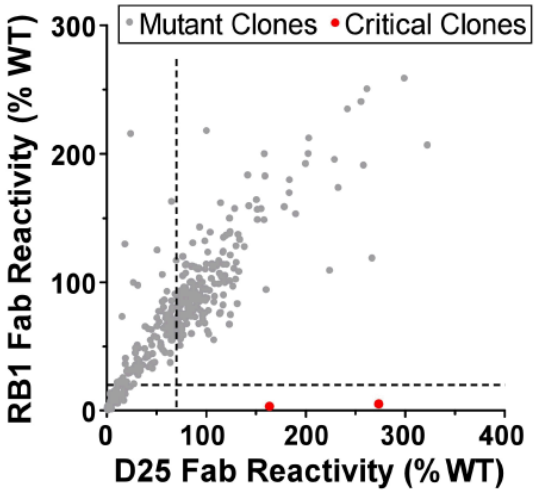
The degree of antibody binding compared with wild-type protein was determined for each expressed clone. Amino acid residues were deemed critical to binding of RB-1 if binding was reduced for the substituted residue but for not the D25 or palivizumab control antibodies.

Results

Figure 29 shows the overall antibody binding results with the alanine scanning library of 368 F protein expression constructs and identifies the expression clones that had reduced binding activity to RB-1 or the control D25 antibody. In agreement with published studies (Beeler and van Wyke Coelingh 1989; McLellan et al. 2010; Zhu et al. 2011; McLellan et al. 2013), loss of binding activity was observed for D25 against five clones; the substituted residues with reduced binding, and the two identified for palivizumab, are shown in Table 137. The data for D25 and palivizumab provided validation for the alanine scanning approach for identifying F protein residues critical to antibody binding.

For RB-1, two residues of the RSV F protein, arginine 429 and isoleucine 432, were identified as critical for binding; both these positions, when substituted to alanine residues, did not reduce binding of D25 or palivizumab antibodies (Table 137). Both of these residue positions were also identified as interacting with RB-1 in crystallography studies (Figure 29).

Figure 29. Epitope Mapping of RB-1 Using a Panel of 368 Variant F Protein Clones



Source: Figure 1, page 15, PD003-MK-1654 (Merck 2024g)
Abbreviations: F, fusion protein; Fab, fragment antigen-binding; WT, wild-type

To map the binding of mAb RB-1 to an epitope on the RSV F protein, an analysis of contact residues was performed using a shotgun mutagenesis methodology (Davidson and Doranz 2014). Expression constructs were generated for each of 368 surface exposed residues, where every residue of interest was individually substituted to an alanine, or in the case of a native alanine, changed to serine. Library screening was performed with RB-1 (shown on the y-axis) and D25 as a validation control (x-axis). Each dot on the graph represents an RSV F protein clone. Variants with RB-1 binding of <20% relative to that of wild-type RSV F protein (horizontal line) and >70% binding for control antibody D25 (vertical line) were identified as critical for RB-1 binding (red dots), specifically, arginine 429 and isoleucine 432.

Table 137. Epitope Mapping of Clesrovimab Binding to RSV F Protein Variants Using Parental Antibody RB-1 Fab

	Percent Relative Binding		
RSV Fusion Glycoprotein Substitution	D25 Antibody (Nirsevimab Precursor)	Palivizumab	RB-1 Fab (Clesrovimab Parental Antibody)
I64A	18.3[a]	126.1	129.9
Y198A	24.0[a]	405.7	215.8
L204A	26.5[a]	83.4	99.9
V207A	31.2[a]	134.8	97.7
N208A	15.3[a]	75.1	73.3
D269A	155.1	4.4[a]	157.4
K272A	79.3	10.7[a]	84.0
R429A	273.4	311.1	5.1[a]
I432A	163.4	261.7	3.6[a]

Source: Table 5, page 14, PD003-MK-1654 (Merck 2024g)
[a] Critical residues identified for binding of each antibody. Clesrovimab parental antibody RB-1 was used in this study.
D25/nirsevimab epitope: antigenic Site Ø, amino acid residues 62 to 69 and 196 to 212
Palivizumab epitope: antigenic Site II, amino acid residues 262 to 275
Abbreviations: F, fusion protein; Fab, fragment antigen-binding; RSV, respiratory syncytial virus

It should be noted that binding data for residues associated with resistance to clesrovimab, including S443P and G446E (see Section 20.6) showed minor or no reduction in binding activity of RB-1 or RB-1 Fab compared with palivizumab or D25 (Table 138). For S443A and G446A, RB-1 Fab had 37.4% and 87.3% relative binding, respectively, and D25 had 63.7% and 90.8% relative binding, respectively). Hence, there are instances of poor correlation between binding data from this experiment and cell culture neutralization activity.

Table 138. Binding of Clesrovimab Parental Antibody RB-1 to RSV F Protein Variants of the Linear Region Encompassing the Epitope, Residues Within 5Å of Epitope, and Adjacent Residues

F Protein AA Position[a]	F Protein AA Substitution	Percent Relative Binding[b]			
		D25 Fab	Palivizumab	RB-1	RB-1 Fab
160	L160A	80.6	119.1	101.8	67.7
161	E161A	87.4	112.0	94.7	78.3
162	G162A	30.6	114.4	76.0	51.0
182	S182A	98.6	181.2	89.5	68.2
183	N183A	32.3	93.8	36.5	37.7
184	G184A	2.2	16.7	1.5	3.8
185	V185A	113.2	151.3	108.8	107.2
425	S425A	133.5	168.7	143.7	133.4
426[c]	N426A[c]	223.9[c]	291.4[c]	98.4[c]	109.4[c]
427[c]	K427A[c]	130.1[c]	191.4[c]	135.0[c]	115.6[c]
428[c]	N428A[c]	322.2[c]	345.6[c]	207.1[c]	206.9[c]
429[c]	R429A[c]	273.4[c]	311.1[c]	33.1[c]	5.1[c]
430	G430A[c]	266.6[c]	397.4[c]	120.9[c]	118.9[c]
431	I431A[c]	199.8[c]	265.1[c]	115.1[c]	192.4[c]
432[c]	I432A[c]	163.5[c]	261.7[c]	36.7[c]	3.6[c]
433[c]	K433A[c]	123.2[c]	148.2[c]	71.6[c]	67.3[c]
434	T434A	72.1	80.5	69.7	60.6
435	F435A	2.6	9.6	-1.3	4.1
436	S436A	92.1	79.1	93.4	110.3
437	N437A	118.7	123.2	96.3	105.3
438	G438A	45.3	69.1	68.2	51.1
439	C439A	1.3	15.1	-0.7	0.6
440[c]	D440A[c]	45.8[c]	74.4[c]	53.1[c]	32.9[c]
441[c]	Y441A[c]	2.5[c]	5.0[c]	-1.7[c]	1.8[c]
442	V442A	33.7	34.8	63.6	31.0
443	S443A	63.7	76.7	56.2	37.4
444	N444A	64.0	67.7	54.7	44.7
445[c]	K445A[c]	129.8[c]	160.1[c]	133.1[c]	128.5[c]
446[c]	G446A[c]	90.8[c]	70.1[c]	68.9[c]	87.3[c]
448	D448A	124.3	124.2	112.5	74.9
449	T449A	123.8	140.1	130.9	139.5
451	S451A	64.6	87.4	49.2	77.4
453	G453A	47.8	153.2	92.5	57.9
454	N454A	128.5	192.5	167.1	157.5
456	L456A	93.7	112.5	107.8	88.1
457	Y457A	112.4	185.0	103.4	116.9
458	Y458A	31.9	172.0	58.9	48.7
460	N460A	12.1	105.4	39.0	19.2

F Protein AA Position[a]	F Protein AA Substitution	Percent Relative Binding[b]			
		D25 Fab	Palivizumab	RB-1	RB-1 Fab
461	K461A	29.6	71.5	42.4	29.8
462	Q462A	86.8	94.2	74.2	80.6
463	E463A	66.4	79.4	71.9	80.6
464	G464A	3.7	7.3	12.4	4.1
465	K465A	98.5	143.2	125.5	132.3
466	S466A	77.2	98.1	63.1	75.3
467	L467A	92.7	149.4	82.9	111.2
468	Y468A	17.0	45.1	80.3	14.3
469	V469A	50.5	94.7	83.8	56.9
470	K470A	78.5	103.5	104.8	95.6

Source: (Merck 2025a)
[a] The alanine scanning mutagenesis assessed surface exposed residues, hence not all positions were evaluated.
[b] Antibody reactivity against each variant clone was calculated as percentile relative to WT protein reactivity and normalized to the signal from WT controls (WT protein is normalized to 100). Low or negative percentile values across all three antibodies indicate disruption of the F protein folding and/or expression as a result of the alanine substitution at this particular position.
[c] Epitope contact residues based on crystal structure (Figure 28).
Abbreviations: Å, angstroms; AA, amino acid; F, fusion protein; Fab, fragment antigen-binding; WT, wild-type

Additional details of the alanine scanning experiment were provided for the nirsevimab binding site, based on data using the D25 Fab fragment. Table 139 shows the relative binding of alanine substitutions in the nirsevimab epitope, showing that clesrovimab parental antibody RB-1, RB-1 Fab, and palivizumab, did not lose binding activity to any of the substitutions tested. However, while validation with the D25 Fab showed a reduction in binding to alanine substitutions at some positions, as expected based on published neutralization data (ASTRAZENECA°AB 2023), the K68A substitution did not result in a loss of binding, whereas a reduction in susceptibility for RSV A K68E has been reported (13-fold change). Substitutions I64T and N208S cause loss of susceptibility to nirsevimab (>496- and >387-fold, respectively).

Table 139. Relative Binding of F-Targeting Antibodies to Alanine-Substituted Amino Acids in the Nirsevimab Epitope

RSV Fusion Glycoprotein Substitution	Percent Relative Binding			
	Palivizumab	D25 Fab	RB-1 mAb	RB-1 Fab
I64A	126.1	18.3[a]	110.8	129.9
K68A	280.4	228.9[a]	161.6	195.7
K201A	152.68	65.0[a]	173.1	163.0
L204A	83.4	26.5	99.2	100.0
I206A	130.6	80.0	137.4	114.4
N208A	75.1	15.3[a]	110.9	73.3
K209A	325.5	114.3	142.4	162.0
S211A	93.6	70.0	117.7	89.6

Source: Table 9, page 29, RSV Surveillance and Clinical Virology report (Merck 2024e)
[a] Cells indicate amino acid positions associated with reduced susceptibility to nirsevimab neutralization (RSV A or RSV B; (ASTRAZENECA°AB 2023)).
Abbreviation: F, fusion protein; Fab, fragment antigen-binding; mAb, monoclonal antibody; RSV, respiratory syncytial virus

Conclusion

The Applicant identified F protein amino acid residues which interact with clesrovimab parental antibody RB-1 using crystallography and confirmed by alanine scanning mutagenesis that substitution of amino acids within the presumed epitope impacted RB-1 binding to F protein. However, some contact residues did not lose binding activity in the alanine scanning mutagenesis, including resistance-associated residues S443 and G446, did not show clear loss of RB-1 binding activity when changed to alanine. The RSV A F-protein residues identified in crystallography as interacting with RB-1 included those at positions 426 to 429, 432, 433, 440, 441, 443, 445 to 447. Two positions outside this region with close contact to RB-1 were 161 and 182, but these were not considered as important for binding because E161 is not likely to form H-bond contacts based on the location of the interacting light chain residues, and E161A and S182A both retained binding activity in the alanine scanning assessment.

While the alanine scanning experiment did not identify residues outside of the clesrovimab binding site as being critical to RB-1 binding to F protein, given that substitutions of some contact residues did not confer reduced binding, the significance of these findings is not clear.

20.3. Binding Activity of Clesrovimab to RSV F Protein

The following was derived from study reports submitted by the Applicant (Merck 2024d). The binding activity of clesrovimab and its parental antibody RB-1 were evaluated against prefusion and postfusion conformations of RSV F protein using surface plasmon resonance. These studies were also conducted in the presence of palivizumab to assess for competition with this Site II targeting antibody. The Applicant also determined the binding of clesrovimab to prefusion F protein harboring antigenic Site II substitutions, and to a Site Ø (target of nirsevimab) knockout prefusion F protein (Ngwuta et al. 2015) using immunoassay.

Methodology

Surface plasmon resonance using a Biacore™ T200 (GE Healthcare) was used to determine the binding affinity of clesrovimab and RB-1 to prefusion and postfusion trimeric conformations of RSV F protein. Following capture of the mAbs on a Protein A Sensor Chip, prefusion and postfusion F proteins were injected at concentrations of 0.1 to 100nM. Data were processed using Biacore™ T200 Evaluation software, with rate constants calculated by fitting binding curves to a 1:1 model.

For competition experiments, a Biacore™ 2000 (GE Healthcare) instrument was used. Palivizumab was amine-coupled to a CM5 sensor chip, and prefusion or postfusion F protein injected at a concentration of 40 µg/mL. The RB-1 antibody was then injected at 100 µg/mL over the captured protein. Data were processed using BIAevaluation Software v4.1.

For immunoassay of F protein harboring Site II substitutions, the RSV prefusion F protein was modified with N268R and K272E substitutions, which prevent binding by palivizumab (Ngwuta et al. 2015). The modified F protein was his-tagged and expressed by transient transfection. DS-Cav1, (see Section 20.2.1), or DS-Cav1 with N268R and K272E substitutions, were applied to nickel-coated assay plates and incubated for 1.5 hours. Plates were washed and blocked with 2%

bovine serum albumin for 1 hour. Test antibody dilution series were added to the plates for 1 hour at room temperature, then secondary horseradish peroxidase-conjugated IgG added for 1 hour. Super AquaBlue substrate was added, and the optical density read at 405nM.

The immunoassay was also conducted in a modified format, including using clesrovimab instead of RB-1, blocking with 3% bovine serum albumin, and using 3,3',5,5'-tetramethylbenzidine as the substrate. Optical density was read at 450nM.

Results

From the surface plasmon resonance study, clesrovimab bound to RSV prefusion and postfusion F proteins with affinities (K_D values) of 71pM and 480pM, respectively (Table 140; note that from the K_{on} and K_{off} values presented in the study report, the K_D values would be 72 and 500pM, respectively). The clesrovimab parental antibody RB-1 bound with similar affinities, of 31pM and 410pM, respectively. Binding to the postfusion conformation of F protein had a slower off-rate compared with binding to the prefusion version.

Table 140. Clesrovimab Binding Affinity to RSV Pre- and Postfusion F Proteins Using Surface Plasmon Resonance

	Prefusion F Protein			Postfusion F Protein		
Antibody	**k_{on} ($M^{-1}S^{-1}$)**	**k_{off} (S^{-1})**	**K_D (pM)**	**k_{on} ($M^{-1}S^{-1}$)**	**k_{off} (S^{-1})**	**K_D (pM)**
Parental RB-1	4.4×10^{6}	1.4×10^{-4}	31	2.2×10^{6}	9.0×10^{-4}	410
Clesrovimab	3.2×10^{6}	2.3×10^{-4}	71	1.4×10^{6}	7.0×10^{-4}	480

Source: Table 7, page 21, (Merck 2024d)
Abbreviations: F, fusion protein; K_D, affinity or equilibrium dissociation constant; k_{on}, association rate; k_{off}, dissociation rate; RSV, respiratory syncytial virus

In the binding competition experiment with palivizumab, under the conditions used, clesrovimab parental mAb RB-1 was able to bind both prefusion and postfusion conformations of F protein in the presence of chip-coupled palivizumab at 40 µg/mL (data not shown). These observations were based on sensorgrams demonstrating binding, and affinity values were not determined.

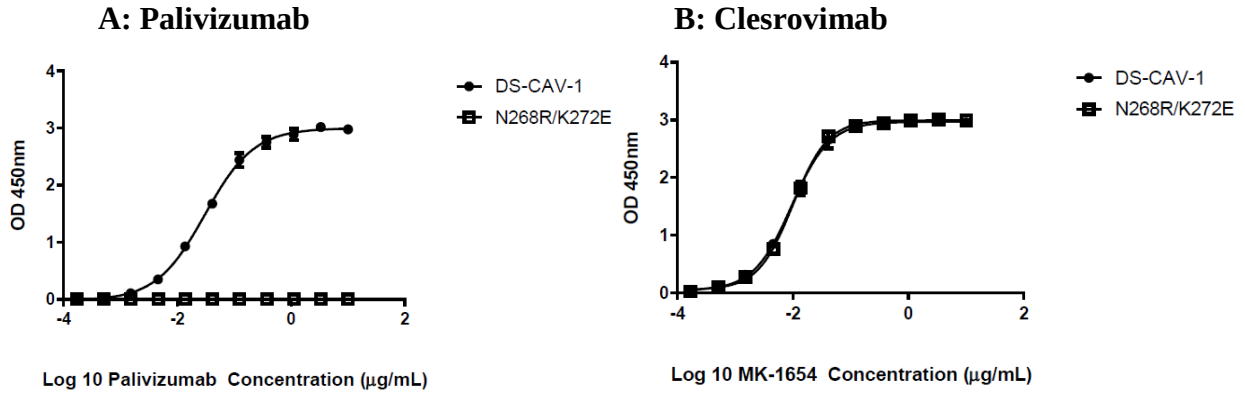
Immunoassay of clesrovimab binding to prefusion F protein harboring Site II substitutions N268R and K272E showed that binding activities (IC_{50} values) were similar for wild-type and variant proteins, of 64pM (9.5 ng/mL) and 67pM (10 ng/mL), respectively (Table 141). Palivizumab bound the prefusion F protein with an IC_{50} value of 207pM (30.7 ng/mL), but did not bind the Site II modified F protein, as expected. Figure 30 shows the binding curves for the experiment using clesrovimab. Similar results were seen with clesrovimab parental antibody RB-1, although IC_{50} values were not reported.

Table 141. Immunoassay of Clesrovimab and Palivizumab Binding to RSV Prefusion F Protein and Prefusion F Protein Harboring N268R + K272E Substitutions

	Prefusion F Protein DS-Cav1		Prefusion F Protein With N268R + K272E Substitutions	
Anti-RSV Antibody	**IC_{50} (ng/mL)**	**95% CI (ng/mL)**	**IC_{50} (ng/mL)**	**95% CI (ng/mL)**
Clesrovimab	9.5	8.62 to 10.46	10.0	9.39 to 10.71
Palivizumab	30.7	27.98 to 33.88	No binding	N/A

Source: Table 10, page 22, (Merck 2024d)
Abbreviations: CI, confidence interval; DS-Cav1, prefusion F protein; F, fusion protein; IC_{50}, half-maximal inhibitory concentration; N/A, not applicable; RSV, respiratory syncytial virus

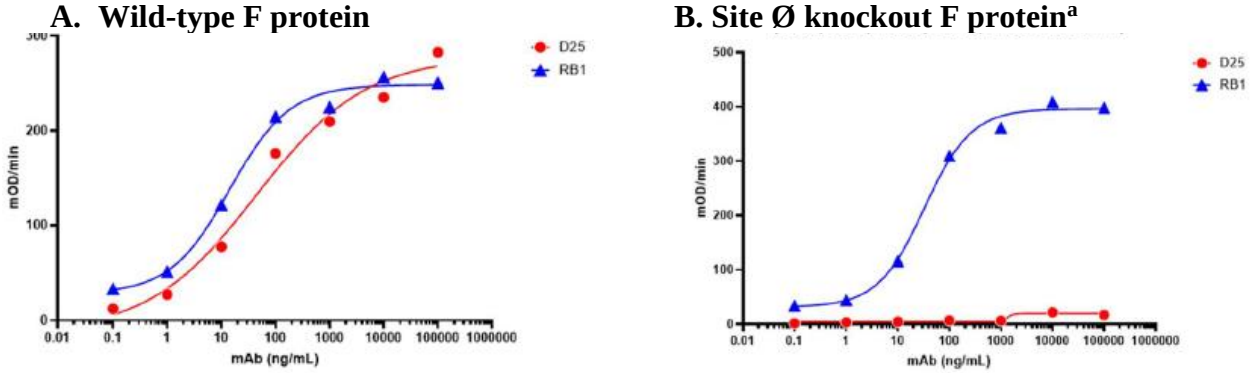
Figure 30. Binding Curves of Clesrovimab and Palivizumab With Prefusion F Protein and Prefusion F Protein Harboring N268R + K272E Substitutions



Source: Figure 4, page 26, (Merck 2024d)
Clesrovimab and palivizumab were assessed for binding to the purified RSV prefusion F protein (DS-Cav1) and prefusion F protein with a modified Site II (labeled as N268R/K272E), using an immunoassay format. Optical density at 450nM is shown versus log_{10} of the antibody concentration (ng/mL). Panel A depicts palivizumab binding. Panel B shows the binding of clesrovimab.
Abbreviation: F, fusion protein; MK-1654, clesrovimab; RSV, respiratory syncytial virus

In addition, clesrovimab was able to bind to the F protein Site Ø knockout, as determined using immunoassay (Figure 31). The D25 antibody (precursor to nirsevimab) did not bind the knockout protein as expected, although it was able to bind to the wild-type protein. No IC_{50} value data were reported for this experiment, although based on the graphs RB-1 bound to wild-type and Site Ø knockout proteins with IC_{50} values of approximately 10 and 30 ng/mL, respectively, and D25 bound wild-type protein with an IC_{50} value of approximately 50 ng/mL.

Figure 31. Binding Curves of RB-1 and Nirsevimab Precursor D25 With Prefusion F Protein and Prefusion F Protein Site Ø Knockout



Source: Figure 7, page 30, RSV Surveillance and Clinical Virology report (Merck 2024e)
[a] Includes RSV A F protein substitutions: K65N, N67T, P205N, V207T, K209N, and S211T (Ngwuta et al. 2015)
Abbreviations: F, fusion protein; mAb, monoclonal antibody; RSV, respiratory syncytial virus

Conclusion

The assessment of clesrovimab and parental antibody RB-1 binding to prefusion and postfusion F proteins showed that they were able to bind both conformations, and with approximately 7-fold higher affinity to the prefusion conformation. Clesrovimab was also able to bind prefusion and postfusion F proteins in the presence of palivizumab and had similar binding activity to prefusion F protein and prefusion F protein harboring Site II substitutions. Clesrovimab parental antibody

RB-1 was able to bind to a Site Ø knockout F protein. Binding to RSV B F protein, and binding competition experiments with nirsevimab were not conducted.

20.4. Antiviral Activity of Clesrovimab in Cell Culture

The following was derived from study reports submitted by the Applicant (Merck 2024d; Merck 2024h). The neutralization activity of clesrovimab and parental antibody RB-1 against laboratory strains of RSV A and RSV B was evaluated in cell culture and compared to the activity of palivizumab. A separate experiment was conducted to determine whether RB-1 interfered with the assay readout, which used immunostaining that employed murine anti-RSV mAbs. To determine the breadth of neutralization activity across RSV strains, panels of 47 historical clinical isolates and 12 contemporary isolates were assessed for susceptibility to neutralization by clesrovimab.

Methodology

Neutralization of RSV Laboratory Isolates

A cell-based neutralization assay was used to determine the activity of clesrovimab and clesrovimab parental antibody RB-1 against laboratory strains of RSV A and RSV B, with an immunostaining readout. Test and control antibody palivizumab were serially diluted on microtiter assay plates and mixed with 100 PFU RSV A Long (ATCC number VR-26™) or RSV B Washington 18573 (ATCC number VR-1580™) in cell culture medium. After 1 hour at 37°C, 100 µL of 1.5×10^5 cells/mL HEp-2 cells were added to the microtiter wells, and plates incubated for 3 days.

Cells were fixed with 80% acetone, and a mixture of anti-RSV F (Merck clone 143-F3-1B8) and anti-RSV N (Merck clone 34C9) murine mAb added to each well for 1 hour at room temperature. Secondary antibody, a biotinylated horse antimouse IgG, was added to each well for 1 hour at room temperature, followed by streptavidin-IRDye 800 to detect RSV-specific signal. Cell stains DRAQ5™ and Sapphire 700™ were added to the plates for 1 hour in the dark for assay normalization. Plates were analyzed using a Li-cor Aerius® Automated Imaging System with a 700-channel laser for cell normalization and an 800-channel laser for detection of RSV-specific signal. The 800/700 ratio was used to calculate the percent neutralization, and the EC_{50} values determined by four parameter curve fitting using GraphPad Prism version 6.

Neutralization of Clinical Isolates

The breadth of activity of clesrovimab in cell culture against clinical isolates was assessed using a panel of 47 historical clinical isolates and a more contemporary panel of 12 isolates from different geographical locations and collection years. Most assessments were conducted by the Applicant, but for the clinical isolates collected in Canada, a modified assay was performed by (b) (4)

Clinical RSV isolates were expanded in HEp-2 cells, and neutralization assays conducted using low-passage viral stocks, with viral titers being determined by plaque immunostaining assay. Of

the 47 historical isolates, 46 were sequenced to determine F protein changes. The F protein sequences for the 12 contemporary isolates were also determined.

Cell Culture Neutralization Assay

Clesrovimab was evaluated for activity against clinical RSV isolates following the same method as described for laboratory isolates, also using HEp-2 cells and 100 PFU per well of each isolate for testing. The assay was read using immunostaining at 3 days postinfection using a mixture of anti-RSV F and anti-RSV N antibodies. EC_{50} and EC_{90} values and fold difference of the EC_{50} values compared with those of the reference strains were determined.

(b) (4) Cell Culture Neutralization Assay

For the assessment of clinical isolates collected in Canada, a modified version of the neutralization assay was conducted. Following serial dilution of clesrovimab onto assay plates, 50 to 100 PFU RSV isolate, or control RSV A or RSV B was added to the microplate wells. After incubation at 37°C for 1 hour, the mixture was transferred to HEp-2 cells on 24 well plates for 90 minutes. Medium was removed and cells overlaid with culture medium containing 2× 4% fetal bovine serum (FBS) and 1.6% methylcellulose (1 to 1 mixture), then plates incubated at 37°C for 3 days. Following incubation, cells were fixed with 4% formalin for 1 hour at room temperature.

A goat anti-RSV (all antigens) antibody was used to detect RSV on the plates, with a horseradish peroxidase-labeled donkey antigoat-IgG antibody as secondary antibody. TrueBlue® peroxidase substrate was added to each well to detect RSV-specific signal. The percent neutralization was determined by counting the stained foci in each test and control well and dividing the number in each test well by the average of the count in the two control wells. The EC_{50} values and the EC_{90} values were determined by four parameter curve fitting using GraphPad Prism 7.

Results

Assessment of Assay Interference by RB-1 With Anti-RSV Antibodies Used for Readout

For the cell culture neutralization assay, a mixture of anti-RSV F and anti-RSV N antibodies was used. To determine whether the test antibody RB-1 might interfere with the anti-RSV F antibody and affect the readout, an experiment was conducted comparing the mixture of detection antibodies with only the anti-RSV N antibody in a neutralization assay using RSV A Long. The EC_{50} values determined in this experiment using two lots of RSV A Long were similar for the antibody mixture compared with the anti-RSV N antibody alone (Table 142), indicating that the RB-1 antibody does not interfere significantly with the anti-RSV F antibody used for detection.

Table 142. Assessment of Cell Culture Neutralization of RSV A by RB-1 Using Different Detection Antibodies

	Clesrovimab Parental RB-1 Antibody Neutralization Assays			
	Detection Using Anti-F and Anti-N Antibodies		Detection Using Only Anti-N Antibody	
RSV A Long Strain Lot Number	EC_{50} (ng/mL)	95% CI (ng/mL)	EC_{50} (ng/mL)	95% CI (ng/mL)
Lot 25 Jan 2016	0.51	0.32 to 0.78	2.66	1.42 to 5.05
Lot 02 Dec 2016	3.02	2.43 to 4.14	1.39	0.66 to 2.67

Source: Table 9, page 22, (Merck 2024d)
Abbreviations: CI, confidence interval; EC_{50}, half-maximal effective concentration; RSV, respiratory syncytial virus

Neutralization of Laboratory Isolates

Table 143 summarizes the neutralization activity (EC_{50} values) determined for the laboratory strains of RSV A and RSV B. For clesrovimab, the mean EC_{50} values against RSV A Long and RSV B 18537 were 40pM (6.0 ng/mL) and 20pM (3.0 ng/mL), respectively. The difference between the EC_{50} values for the RSV A and RSV B strains is within the margin of error of the experiment. Similar EC_{50} values were reported for the parental antibody RB-1.

For the control antibody palivizumab, the EC_{50} values against RSV A Long and RSV B 18537 were 1.4nM (211.5 ng/mL) and 1.1nM (165.9 ng/mL), respectively. These values are within the range of EC_{50} values reported for palivizumab against RSV A and RSV B clinical isolates (MedImmune 1998).

Table 143. Assessment of Cell Culture Neutralization Activity of Clesrovimab Against RSV A and RSV B

		EC_{50} Value (ng/mL) (Range)[a]		
		RSV A Long		RSV B Washington
Experiment	Antibody	Replicate 1	Replicate 2	18537
1	Parental RB-1	2.9 (2.4-3.7)	ND	1.7 (1.4-2.6)
	Palivizumab	211.5 (158.9-281.4)	ND	165.9 (107.2-256.6)
2	Parental RB-1	6.2 (4.4 - 8.6)	3.5 (3.1-4.0)	0.8 (0.4-1.4)
	Clesrovimab Lot 10AJF	11.6 (9.7-13.7)	6.1 (5.4-6.8)	2.6 (1.4-5.1)
	Clesrovimab Lot 46AJG	1.3 (1.1-1.7)	0.8 (0.7-9.4)	0.5 (0.3-0.6)
3	Parental RB-1	7.2 (5.5-9.5)	ND	9.0 (7.6-10.6)
	Clesrovimab lot 10AJF	9.6 (6.6-14.2)	ND	5.2 (3.5-7.7)
	Clesrovimab lot 25AJT	6.4 (5.0-8.3)	ND	3.6 (2.9-4.5)
Summary of Experiments[b]		RSV A EC_{50} ± SD (ng/mL) (N)		RSV B EC_{50} ± SD (ng/mL) (N)
Clesrovimab		6.0±4.3 (6)		3.0±2.0 (4)

Source: Table 8, page 21 (Merck 2024d)
[a] Each antibody was assayed in triplicate for each "replicate." The calculated value is reported along with the range.
[b] Clesrovimab mean EC_{50} values from Experiments 2 and 3 are shown for each RSV strain
Abbreviations: EC_{50}, half-maximal effective concentration; N, number; ND, not determined; RSV, respiratory syncytial virus; SD, standard deviation

Neutralization of Clinical Isolates

Table 144 shows the EC_{50} values for the 47 clinical isolates, which were collected from 1987 to 2016. Representative dose-response curves for this panel of isolates are shown in Figure 32. Most isolates (35/47) were collected in Texas, United States, the others were from Pennsylvania, United States (4/47), Quebec, Canada (6/47), or not reported (2/47). Hence, the panel was not geographically diverse; however, the Applicant determined the F protein sequence for 46 of these isolates and determined that they were broadly representative of a panel of 3,058 F protein sequences downloaded from GenBank® in 2020 (see Section 18.1).

Excluding laboratory isolates, clesrovimab neutralized the RSV A isolates with a median EC_{50} value of 25pM (3.71 ng/mL) (n=24; range of 1.2 to 74pM [0.18 to 11.11 ng/mL]). Clesrovimab neutralized each of the RSV B isolates with a comparable median EC_{50} value of 30pM (4.48 ng/mL) (n=23; range of 4 to 198pM [0.59 to 29.65 ng/mL]).

Table 144. Clesrovimab Cell Culture Neutralization of Clinical RSV Isolates Collected From 1961 to 2016

RSV Isolate or Laboratory Strain	Year Isolated	Isolate Origin	EC_{50}[a] (ng/mL)	Fold Change in EC_{50}	EC_{50} 95% CI (ng/mL)	EC_{90}[a] (ng/mL)	EC_{90} 95% CI (ng/mL)
RSV A isolates							
Long[b] (MSD)	N/A	N/A	4.588	1	4.019 to 5.239	24.06	18.26 to 32.39
Long[c] (Boivin laboratory)	N/A	N/A	1.547 [c]	1	1.25 to 1.908[c]	15.75[c]	9.801 to 26.35 [c]
RSV A2 Australia (A-BCM-1)	1961	N/A	39.61	8.63[f]	34.64 to 45.28	229	168.5 to 317.8
A-HMC-6	N/A	N/A	3.016	0.65	1.703 to 5.342	92.29	25.46 to 334.6
A-HMC-12	N/A	N/A	9.416	2.05	8.02 to 11.05	28	20.21 to 38.79
A-BCM-2	Jan 2005	Texas, United States	8.126	1.77	6.234 to 10.55	53.3	30.2 to 101.9
A-BCM-3	Jan 1991	Texas, United States	4.672	1.01	3.623 to 6.001	46.79	27.94 to 82.96
A-BCM-4	Dec 1987	Texas, United States	11.11	2.42	8.457 to 14.7	76.54	42.21 to 148.9
A-BCM-5	Dec 2004	Texas, United States	4.613	1	3.975 to 5.349	29.51	21.87 to 40.81
A-BCM-6	Dec 1994	Texas, United States	8.695	1.89	7.152 to 10.59	76.09	50.74 to 117.9
A-BCM-7	Jan 2005	Texas, United States	3.789	0.82	2.796 to 5.129	55.73	30.16 to 111
A-BCM-8	Feb 2005	Texas, United States	5.32	1.16	4.26 to 6.65	35.61	22.8 to 58.11
A-BCM-9	Nov 2004	Texas, United States	3.631	0.79	2.368 to 5.416	57.69	26.5 to 148.1
A-BCM-10	Feb 2012	Texas, United States	2.108	0.46	1.424 to 3.078	33.04	15.01 to 83.41
A-BCM-12	Jan 1991	Texas, United States	0.5667	0.12	0.3821 to 0.8028	11.49	5.3 to 28.86
A-BCM-13	Feb 1993	Texas, United States	1.025	0.22	0.6002 to 1.65	42.02	13.73 to 168.7
A-BCM-14	Nov 2004	Texas, United States	0.1769	0.04	0.02409 to 0.479	77.69	11.71 to 1050
A-BCM-15	Jan 2005	Texas, United States	3.189	0.69	1.998 to 5.111	18.47	6.567 to 98.25
A-BCM-16	Nov 2010	Texas, United States	1.724	0.37	1.359 to 2.189	17.06	9.967 to 30.96
A-BCM-18	Nov 2004	Texas, United States	1.432	0.31	0.8276 to 2.546	21.63	5.855 to 147.1
A-BCM-19	Jan 2012	Texas, United States	0.4601	0.1	0.0481 to 1.41	24.23	3.126 to 676.6
A-BCM-20	Dec 2004	Texas, United States	0.6899	0.15	0.02938 to 3.099	170.8	12.36 to 19462
RSV-44396[c]	Mar 2016	Quebec, Canada	2.365	1.5	1.81 to 3.062	28.93	16.95 to 51.91
RSV-16702[c]	Dec 2006	Quebec, Canada	6.215	4.02	4.79 to 8.067	59.48	35.26 to 106
RSV-23248[c]	Mar 2016	Quebec, Canada	6.152	3.97	4.079 to 9.244	183.5	82.51 to 451.8
RSV-23094[c]	Apr 2016	Quebec, Canada	4.105	2.6	3.276 to 5.152	46.68	29.05 to 77.92
RSV-46235[c]	Nov 2015	Quebec, Canada	10.76	6.95[f]	7.436 to 15.54	242.5	125.3 to 514.6

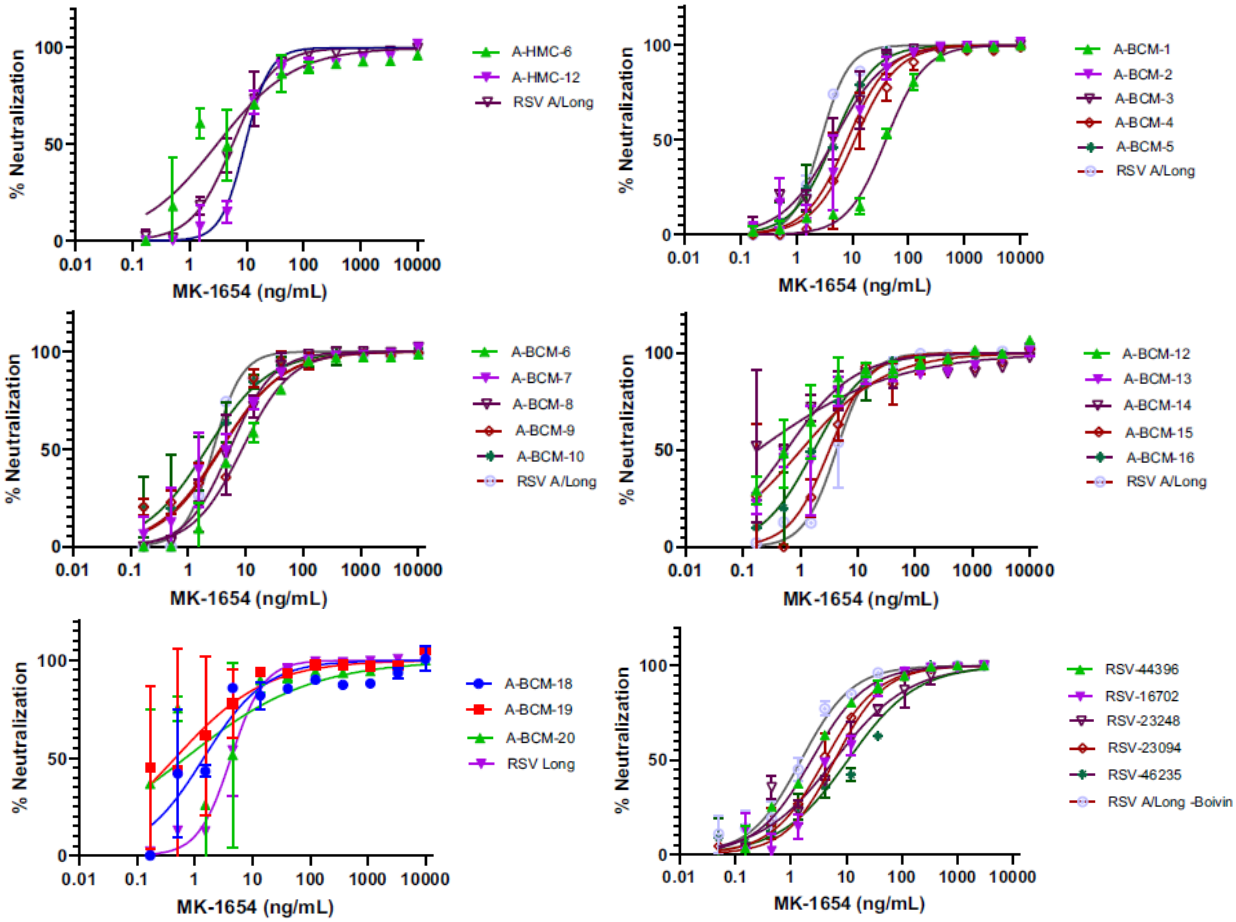
RSV Isolate or Laboratory Strain	Year Isolated	Isolate Origin	EC_{50}[a] (ng/mL)	Fold Change in EC_{50}	EC_{50} 95% CI (ng/mL)	EC_{90}[a] (ng/mL)	EC_{90} 95% CI (ng/mL)
RSV B isolates							
Washington[d] (MSD)	N/A	N/A	5.437	1	4.24 to 6.986	35.51	20.57 to 67.15
Washington[e] (Boivin laboratory)	N/A	N/A	4.153[e]	1	2.614 to 6.699	26.33	10.86 to 74.41
Washington (B-BCM-1)	1962	N/A	12.85	2.36	9.441 to 17.57	164.4	80.55 to 373.3
B-HMC-9	N/A	Pennsylvania, United States	5.595	1.02	3.436 to 9.111	182.5	61.38 to 542.8
B-HMC-11	N/A	Pennsylvania, United States	3.531	0.65	1.826 to 6.826	115.2	26.13 to 507.7
B-HMC-22	N/A	Pennsylvania, United States	29.65	5.45[f]	26.72 to 32.9	91.77	72.52 to 120.4
B-HMC-24	N/A	Pennsylvania, United States	2.898	0.53	1.457 to 5.763	85.43	18.15 to 402.2
B-BCM-2	Nov 2004	Texas, United States	7.042	1.3	2.966 to 16.95	1057	126.5 to 15509
B-BCM-3	Mar 1993	Texas, United States	7.028	1.3	3.247 to 15.91	822	84.75 to 12620
B-BCM-4	Jan 1993	Texas, United States	1.561	0.3	1.121 to 2.188	11.28	4.526 to 34.14
B-BCM-5	Feb 1994	Texas, United States	7.419	1.36	6.041 to 9.221	32.25	19.42 to 58.64
B-BCM-6	Dec 1993	Texas, United States	4.475	0.82	3.021 to 6.637	42.97	18.15 to 125.8
B-BCM-7	Dec 1991	Texas, United States	4.675	0.86	3.354 to 6.59	72.43	32.05 to 179.7
B-BCM-8	Dec 1992	Texas, United States	6.331	1.16	5.543 to 7.233	36.99	27.48 to 51.12
B-BCM-9	Feb 1993	Texas, United States	1.155	0.21	0.4352 to 2.488	87.81	19.76 to 652.6
B-BCM-10	Feb 1993	Texas, United States	1.371	0.25	1.059 to 1.761	30.17	17.86 to 53.77
B-BCM-11	Jan 2005	Texas, United States	2.956	0.54	1.883 to 4.296	10.68	4.603 to 46.11
B-BCM-12	Feb 2005	Texas, United States	4.827	0.88	3.484 to 6.647	24.32	12.28 to 56.6
B-BCM-13	Jan 1993	Texas, United States	3.213	0.6	2.059 to 4.887	23.88	9.212 to 72.71
B-BCM-14	Feb 1993	Texas, United States	4.795	0.88	3.597 to 6.455	24.83	13.16 -o 51.11

RSV Isolate or Laboratory Strain	Year Isolated	Isolate Origin	EC_{50}[a] (ng/mL)	Fold Change in EC_{50}	EC_{50} 95% CI (ng/mL)	EC_{90}[a] (ng/mL)	EC_{90} 95% CI (ng/mL)
B-BCM-15	1994	Texas, United States	5.726	1.05	4.241 to 8.024	28.08	12.63 to 80.81
B-BCM-17	1993	Texas, United States	2.045	0.37	1.387 to 2.985	15.28	6.649 to 43.55
B-BCM-18	1993	Texas, United States	5.03	0.92	2.723 to 11.86	31.9	NC
B-BCM-19	2005	Texas, United States	3.22	0.59	2.475 to 4.229	15.63	8.832 to 32.2
B-BCM-20	1993	Texas, United States	0.887	0.16	0.5514 to 1.359	8.445	3.596 to 24.44
RSV-22909[e]	2016	Quebec, Canada	0.585	0.14	0.3437 to 0.9496	41.3	16.31 to 122.7

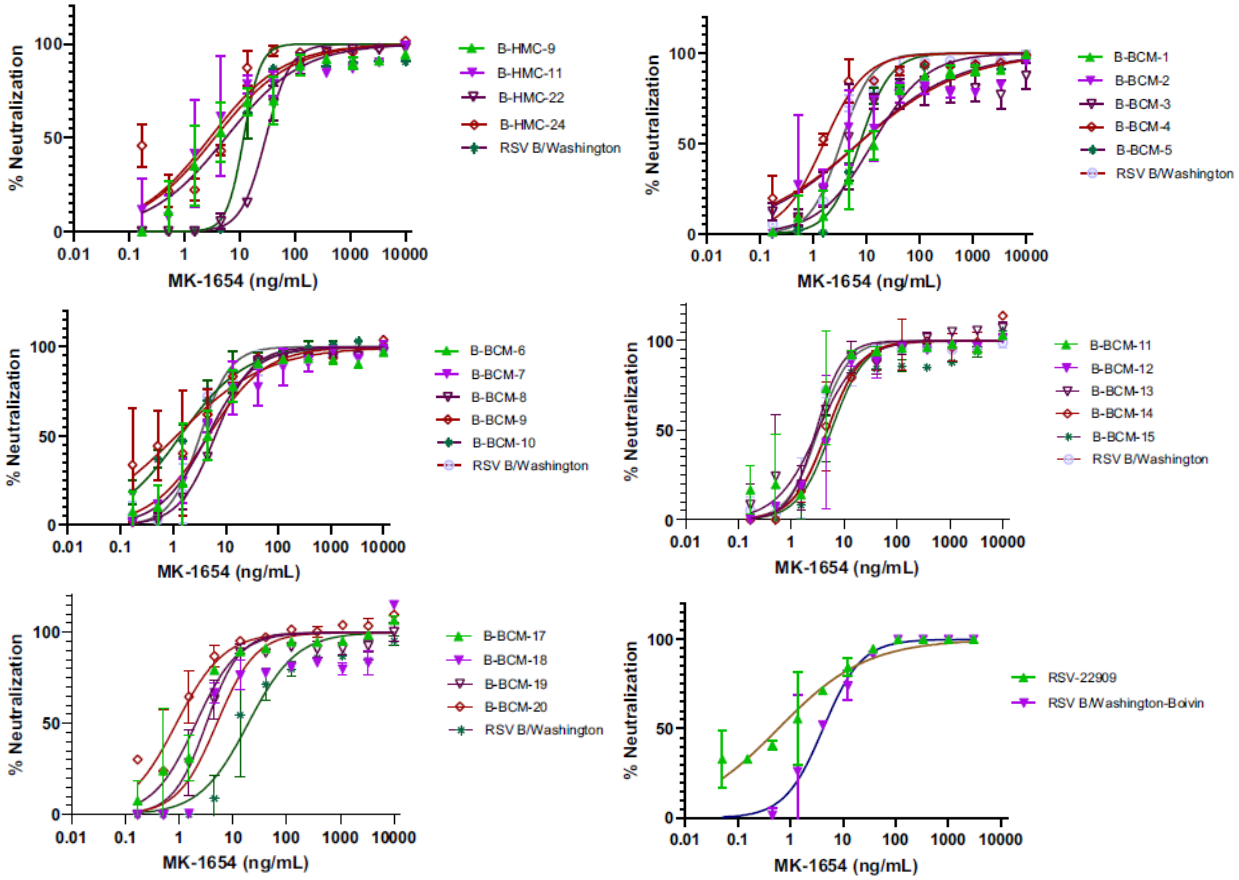
Source: Table 13, page 37, (Merck 2024h)
Clesrovimab lot number 25AJT was used in this study. RSV A2 Australia (A-BCM-1) and Washington (B-BCM-1) were provided by BCM. Strain RSV A2 Australia (A-BCM-1) is a standard laboratory strain isolated in Australia and adapted for laboratory use.
[a] Each RSV isolate was assayed in duplicate.
[b] RSV A Long strain (MSD) was obtained from ATCC, catalog number VR-26™ and cultured. Lot January 25, 2016, NB-furtek-0385734-0015 was used in this study.
[c] RSV A Long strain (Boivin laboratory) was used as the control for testing five RSV A isolates from Canada. The five clinical isolates tested in the Boivin laboratory are also identified by footnote "[c]." The RSV A Long strain was obtained by the Boivin laboratory from ATCC.
[d] RSV B Virus Washington strain (MSD) was obtained from ATCC, catalog number VR-1580™ and cultured. Lot January 25, 2016, NB-furtek-0385734-0015 was used in this study.
[e] RSV B virus Washington strain (Boivin laboratory) was used as the control for testing one RSV B isolate. The isolate tested in the Boivin laboratory is also identified by footnote "[e]." The RSV B Washington strain was obtained by the Boivin laboratory from ATCC.
[f] ≥5-fold change
Abbreviations: ATCC, American-type culture collection; BCM, Baylor College of Medicine, Houston, Texas, United States; CI, confidence interval; HMC, Hershey Medical Center, Hershey, Pennsylvania, United States; EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; MSD, Merck Sharp & Dohme, LLC; N/A, not applicable; NC, not calculated due to variability; RSV, respiratory syncytial virus

Figure 32. Representative Dose-Response Curves for Clesrovimab Neutralization of Historical RSV A and RSV B Clinical Isolates

A. RSV A isolates



B. RSV B isolates



Source: Figure 3, page 45, (Merck 2024h)
Representative clesrovimab neutralization assay curves are shown for the clinical isolates listed in Table 144. Panel A shows the dose-response curves for each of the 24 RSV A isolates, and Panel B shows the curves for each of the 23 RSV B isolates, with the curves for the reference strains used for determining fold-change values shown in each graph.
Abbreviations: MK-1654, clesrovimab; RSV, respiratory syncytial virus

Table 145 shows the EC_{50} values for the 12 contemporary clinical isolates collected from 2016 to 2021, all of which originated in Texas, United States. Representative dose-response curves for this panel of isolates are shown in Figure 33. The Applicant assessed the sequences of these isolates, showing that the F protein was identical for three of the 6 RSV A isolates (C02989, C03156, and R06687), and for four of the RSV B isolates (C03347, IP0187, R06526, and R06896).

Clesrovimab neutralized each of the 6 RSV A isolates with a median EC_{50} value of 121pM (18.02 ng/mL) (n=6; range of 59 to 186pM [8.79 to 27.74 ng/mL]), and each of the 6 RSV B isolates with a median EC_{50} value of 130pM (19.41 ng/mL) (n=6; range of 95 to 153pM [14.22 to 22.92 ng/mL]). Hence, the median EC_{50} values for RSV A and RSV B isolates are approximately 5-fold and 4-fold higher, respectively, than those for the larger panel of historical isolates. However, the EC_{50} values for the RSV A and RSV B reference strains were also 2- to 3-fold higher in the experiments with the contemporary isolates compared with those of the historical isolates, so the difference in median EC_{50} values between the two panels may be accounted for by assay variability, particularly considering the experiments were conducted several years apart.

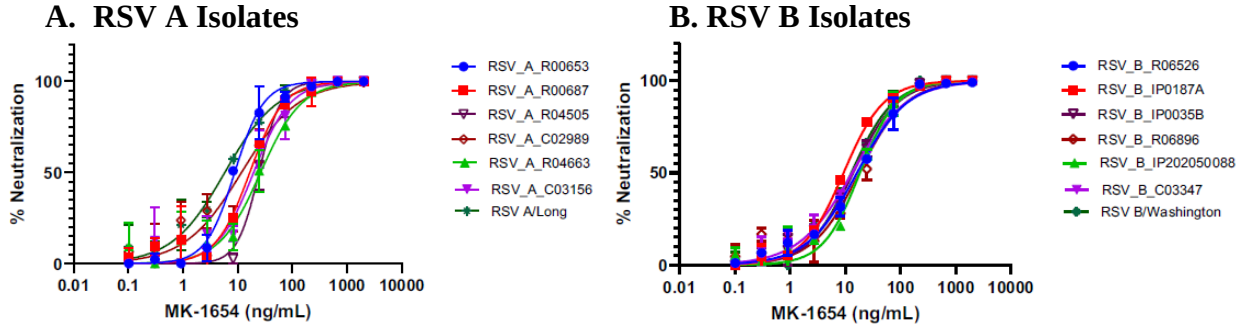
Table 145. Clesrovimab Cell Culture Neutralization of Clinical RSV Isolates Collected From 2016 to 2021

RSV Isolate or Laboratory Strain	Year Isolated	Isolate Origin	EC_{50} (ng/mL)[a]					EC_{50} Fold-Change[a]	EC_{90} (ng/mL)[a]				
			Expt 1		Expt 2				Expt 1		Expt 2		
			Value	95% CI	Value	95% CI	Average		Value	95% CI	Value	95% CI	Average
RSV A													
RSV A/Long (MSD)[b]	N/A	N/A	5.79	4.523 to 7.376	10.61	8.694 to 12.87	8.2	1.0	66.71	34.02 to 162.0	41.73	26.51 to 71.85	54.22
RSV_A_R00653	2017	Texas, USA	8.79	7.571 to 10.24	N/A	N/A	8.79	1.11	29.12	18.95 to 47.05	N/A	N/A	29.12
RSV_A_R06687	2021	Texas, USA	16.56	13.05 to 21.03	N/A	N/A	16.56	2.02	62	37.85 to 123.2	N/A	N/A	62
RSV_A_C03156	2018	Texas, USA	19.48	14.43 to 26.21	N/A	N/A	19.48	2.38	95.16	39.45 to 307.0	N/A	N/A	95.16
RSV_A_R04663	2019	Texas, USA	26.11	19.25 to 35.24	29.36	25.01 to 34.43	27.74	3.38	155.1	68.17 to 468.7	187	121.4 to 314.8	171.1
RSV_A_C02989	2018	Texas, USA	11.69	7.299 to 18.12	N/A	N/A	11.69	1.43	74.97	NC to 273.6	N/A	N/A	74.97
RSV_A_R04505	2019	Texas, USA	24.44	21.69 to 27.75	27.25	21.84 to 34.07	25.85	3.15	62.26	39.30 to 96.31	138.8	73.50 to 308.1	100.53

RSV Isolate or Laboratory Strain	Year Isolated	Isolate Origin	EC_{50} (ng/mL)[a]					EC_{50} Fold-Change[a]	EC_{90} (ng/mL)[a]				
			Expt 1		Expt 2				Expt 1		Expt 2		
			Value	95% CI	Value	95% CI	Average		Value	95% CI	Value	95% CI	Average
RSV B													
RSV B/Wash (MSD)[c]	N/A	N/A	12.91	10.86 to 15.33	15.93	12.65 to 20.04	14.42	1.0	96.39	61.92 to 164.5	116.3	60.82 to 274.8	106.35
RSV_B_C03347	2019	Texas, USA	13.4	10.75 to 16.62	19.17	15.38 to 23.80	16.29	1.13	172.1	96.75 to 370.9	184.9	99.40 to 436.1	178.5
RSV_B_R06526	2021	Texas, USA	16.3	13.65 to 19.42	26.12	19.53 to 34.48	21.21	1.47	164.4	102.8 to 294.7	222.2	119.5 to 532.4	193.3
RSV_B_IP0035B	2018	Texas, USA	13.9	11.87 to 16.24	29.05	23.83 to 35.09	21.48	1.49	115.2	75.69 to 191.4	105.7	65.74 to 183.6	110.45
RSV_B_R06896	2021	Texas, USA	17.85	12.67 to 24.58	27.99	22.35 to 34.72	22.92	1.59	113.4	68.85 to 213.2	167.1	92.97 to 362.4	140.25
RSV_B_IP0187A	2021	Texas, USA	9.34	8.654 to 10.08	19.1	15.85 to 22.96	14.22	0.99	56.62	44.84 to 73.02	239	138.4 to 489.8	147.81
RSV_B_IP202050088	2016	Texas, USA	18.43	15.49 to 21.86	16.88	14.78 to 19.27	17.61	1.22	87.32	59.21 to 138.2	126.1	86.62 to 195.1	106.71

Source: Table 14, page 40, (Merck 2024h)
Clesrovimab batch no. 6RSV 401 was used in this study.
[a] Each RSV isolate was assayed in duplicate in Experiment 1 and Experiment 2. All EC_{50}, EC_{90}, and 95% CI values were calculated with GraphPad Prism.
[b] RSV-A Virus Long strain (MSD) was obtained from ATCC, catalog number VR-26™ and cultured. Virus stock batch prepared in NB-touch-0375866-0074 was used in this study.
[c] RSV-B Virus Washington strain (MSD) was obtained from ATCC, catalog number VR-1580™ and cultured. Virus stock batch prepared in NB-touch-0375866-0074 was used in this study.
Abbreviations: ATCC, American-type culture collection; CI, confidence interval; EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; Expt, experiment; MSD, Merck Sharp & Dohme, LLC; N/A, not applicable; NC, not calculated; RSV, respiratory syncytial virus

Figure 33. Representative Dose-Response Curves for Clesrovimab Neutralization of Contemporary RSV-A and RSV-B Clinical Isolates



Source: Figure 5, page 50, (Merck 2024h)
Representative clesrovimab neutralization assay curves are shown for the clinical isolates listed in Table 144. Panel A shows the dose-response curves for each of the six RSV A isolates, and Panel B shows the curves for each of the six RSV B isolates, with the curves for the reference strains used for determining fold-change values shown in each graph.
Abbreviations: MK-1654, clesrovimab; RSV, respiratory syncytial virus

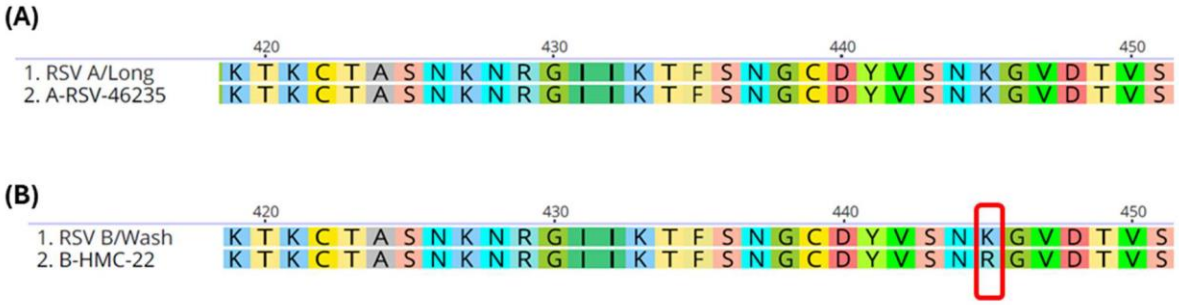
20.4.1. Sequence Analysis of Clinical Isolates Showing ≥5-Fold Change in Susceptibility to Clesrovimab

The following was derived from a study report submitted by the Applicant (Merck 2024h). An analysis of the sequence data from the clinical isolates with reduced susceptibility (≥5-fold; three isolates shown in Table 144) to clesrovimab was conducted to determine whether there were F protein amino acid differences compared with the reference strains which might be responsible for the reduced susceptibility. Because sequence data for the isolate RSV A2 Australia (A-BCM-1) were not available, only those for RSV A isolate RSV-46235 (7-fold change) and RSV B isolate B-HMC-22 (5.5-fold change) were analyzed.

For the RSV A isolate RSV-46235, no amino acid changes were identified in the clesrovimab binding site compared with the reference isolate RSV A Long (Figure 34). Outside the binding site, an N120S substitution was identified, which is at a predicted N-linked glycosylation site (Zimmer et al. 2001). However, this amino acid is not present in the mature F protein (comprising amino acids 26 to 109 [F2] and 137 to 574 [F1]), because it is removed by furin cleavage, and is therefore not likely responsible for the loss of susceptibility.

For the RSV B isolate B-HMC-22, a K445R substitution was seen in the clesrovimab binding site (Figure 34), which occurs at a position important for the selection of resistance in cell culture (see Section 20.6) and may therefore be responsible for the reduced susceptibility.

Figure 34. Alignment of the Clesrovimab Binding Site (F Protein Amino Acids 426 to 447) of RSV A and RSV B Isolates With Reduced Susceptibility to Clesrovimab



Source: Figure 9, page 62, (Merck 2024h)
Alignment of the clesrovimab binding site amino acid sequence with those of the RSV A isolate RSV-46235 (Panel A) and RSV B isolate B-HMC-22 (Panel B). The RSV A isolate was compared to the RSV A Long strain (Boivin laboratory) and the RSV B isolate was compared to the RSV B Washington strain. The red box indicates the K445R substitution seen for the RSV B isolate.
Abbreviation: F, fusion protein; RSV, respiratory syncytial virus

Conclusion

The Applicant assessed the neutralization activity of clesrovimab against a historical panel of 47 RSV clinical isolates, and a contemporary panel of 12 isolates. Compared with the respective reference strain, all but three historical clinical isolates and all contemporary isolates were susceptible (<5-fold difference in EC_{50} values). The three isolates with reduced susceptibility, two RSV A and one RSV B, all had <9-fold difference in EC_{50} values compared with the respective reference strain; it is not known what fold-change is clinically significant. The one RSV B isolate with reduced susceptibility had a K445R substitution within the clesrovimab binding site, which may have been responsible for the reduction in clesrovimab activity.

Based on the F protein sequence of 46 of the historical isolates, they appear to broadly represent F protein diversity seen in sequences downloaded from GenBank®, indicating that clesrovimab can neutralize a diverse range of RSV isolates. However, there was little F protein sequence diversity for the contemporary isolates, given that three of the six RSV isolates and four of the six RSV B isolates had identical F protein sequences.

The cell culture neutralization activity of clesrovimab in combination with palivizumab was determined. The Applicant did not conduct a similar experiment using nirsevimab.

20.5. Cell Culture Competition Studies With Clesrovimab and Palivizumab

The following was derived from a study report submitted by the Applicant (Merck 2024d). The cell culture neutralization activity of clesrovimab in combination with palivizumab was determined. The Applicant did not conduct a similar experiment using nirsevimab.

Methodology

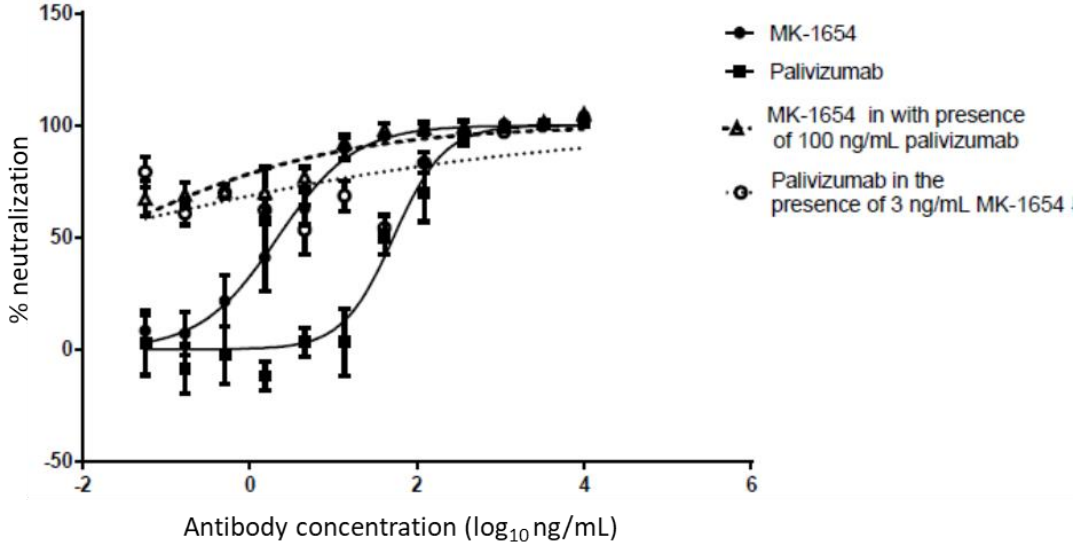
The methodology for determining cell culture neutralization activity is described in Section 20.4.1. The neutralization activity of clesrovimab against RSV A Long was determined at a range of concentrations spanning the EC_{50} value, from 0.3 to 67,000pM (0.05 to 10,000 ng/mL), in combination with palivizumab at the EC_{50} value of 676pM (100 ng/mL).

Similarly, palivizumab was assessed over the same range of concentrations, in combination with clesrovimab at the EC_{50} value of 20pM (3 ng/mL).

Results

Figure 35 shows the dose-response curves for the combinations of clesrovimab and palivizumab. In the presence of 100 ng/mL palivizumab, clesrovimab neutralized RSV A Long above 50% at all concentrations tested, and similarly for 3 ng/mL clesrovimab, palivizumab neutralized above 50% at all concentrations tested. While not all concentration combinations were tested in this experiment, the data indicate that there is no clear antagonism between clesrovimab and palivizumab.

Figure 35. Cell Culture Neutralization Activity of Clesrovimab and Palivizumab in Combination



Source: Figure 5, page 27, (Merck 2024d)
Abbreviations: MK-1654, clesrovimab

Clesrovimab and palivizumab were assessed in combination for cell culture neutralization activity. Clesrovimab was tested at concentrations ranging from 10,000 to 0.05 ng/mL in combination with a single concentration of palivizumab, at the palivizumab EC_{50} value of 100 ng/mL (depicted with the solid triangle and dashed line). Additionally, palivizumab was tested at concentrations ranging from 10,000 to 0.05 ng/mL in combination with a single concentration of clesrovimab, at the clesrovimab EC_{50} value of 3 ng/mL (depicted with the inverted triangle and dotted line). Shown is the percentage neutralization versus the log_{10} antibody concentration for each combination, and with clesrovimab alone (solid circle) and palivizumab alone (solid square).

Conclusion

An assessment of clesrovimab neutralization of RSV A in combination with palivizumab showed that there was no clear antagonism between the two antibodies, which might be expected given that they target different antigenic sites. These data concur with the binding experiment (see Section 20.3), in which clesrovimab parental mAb RB-1 was able to bind both prefusion and postfusion conformations of F protein in the presence of palivizumab at 40 µg/mL.

20.6. Clesrovimab Resistance and Cross-Resistance in Cell Culture

The ability of clesrovimab to select for resistance in cell culture was evaluated. The Applicant also determined the susceptibility to clesrovimab of RSV harboring F protein I432T substitution, which was the most frequently observed (0.04%) binding-site substitution seen in RSV sequences from GenBank® (see Section 18.1). To determine whether there may be cross-resistance with nirsevimab, the activity of clesrovimab against RSV harboring resistance-associated substitutions was assessed. In addition, the activity of nirsevimab and palivizumab was assessed against RSV harboring clesrovimab resistance-associated substitutions.

20.6.1. Cell Culture Selection of Resistance to Clesrovimab

The following was derived from a study report submitted by the Applicant (Merck 2024h). The selection of resistance in cell culture by clesrovimab was conducted by serial passage in the presence of RSV A or RSV B. Resistant virus was assessed for replication ability in HEp-2 cells.

Methodology

Cell Culture Selection of Resistance

Based on methodology described by (Zhu et al. 2011), RSV with reduced susceptibility to clesrovimab was selected in HEp-2 cells in the presence of increasing concentrations of clesrovimab parental antibody RB-1. For RSV A, HEp-2 cells were grown in six-well plates and infected with 7.5×10^6 PFU/well of RSV A2 (multiplicity of infection [MOI] approximately 10), in the presence of RB-1 at a starting concentration of 26 ng/mL (approximately 10× the EC_{50} value).

Cells were incubated at 37°C until visible cytopathic effect was observed, at which point the cells were harvested by scraping, along with the supernatant. Harvested cells were lysed to release virus by flash freezing, pelleted by centrifugation, and supernatant used to infect fresh monolayers of HEp-2 cells in the presence of 2- to 3-fold higher RB-1 concentrations. The passaging process was repeated to a maximum 10 µg/mL RB-1; resistant RSV A was successfully generated after six rounds of serial infection. Resistant virus was expanded in the presence of 10 µg/mL RB-1 before sequencing.

For serial passage of RSV B, HEp-2 cells were cultured in six-well plates and infected with 7.5×10^6 PFU/well of RSV B Washington (MOI =1), in the presence of 30 ng/mL RB-1 (approximately 10× the EC_{50} value). Virus was passaged as described for RSV A, with increasing concentrations of RB-1 antibody, up to a maximum concentration of 10 µg/mL. Resistant virus was generated following nine rounds of serial infection.

Evaluation of Resistant Virus Replication

Resistant viruses selected by cell culture passage were evaluated for their replication dynamics in HEp-2 cells using a plaque assay or microplaque assay.

Each resistant virus and the parental RSV A2 and RSV B Washington strains were used to infect HEp-2 cells at an MOI =0.01 in triplicate. Cell culture supernatants were harvested daily from 1 to 5 days postinfection (and Day 6 for RSV B), and immediately frozen. Plaque assays were conducted on each cell culture supernatant serially diluted 10-fold from neat to 1:10,000 added to HEp-2 cells in 24-well plates. After 1 hour adsorption, supernatants were removed, and cells overlaid with 0.75% methylcellulose in Williams E medium supplemented with 1.6% FBS. Cells were incubated at 37°C for 5 days, then fixed and stained with crystal violet solution containing 5% glutaraldehyde, and plaques counted.

For the microplaque assay, cell culture supernatants from the infection of HEp-2 cells with resistant and parental RSV strains were added in triplicate to poly-D-lysine coated 96-well plates, either diluted 1 to 10 for Day 1, 2, and 3 samples or 1 to 100 for Day 4, 5, and 6 samples. A 2-fold serial dilution of each sample was made across the plates, then HEp-2 cells added at 6×10^4 PFU/well. Plates were incubated at 37°C for 1 hour, then centrifuged, and overlaid with 1% methylcellulose in cell culture medium, 1.6% FBS. Plates were incubated at 37°C for 3 days, supernatants removed, and cells fixed with 80% acetone and stained with mAbs 143-F3-1B8 and 34C9 followed by antimouse IgG-Alexa 488 in Odyssey® Blocking Buffer. Plates were imaged using an EnSight™ multimode plate reader (Perkin Elmer) for plaque counting.

Results

Cell Culture Selection of Resistance

For RSV A, four viruses were selected after six rounds in HEp-2 cells which had reduced susceptibility to RB-1. The F gene for each virus was sequenced, and amino acid substitutions identified which resided in the clesrovimab binding site (Table 146). Neither clesrovimab nor RB-1 were able to neutralize the viruses in a cell culture assay up to the highest concentration tested of 6.7nM (1,000 ng/mL).

For RSV B, one variant virus was identified with reduced susceptibility to RB-1 after nine rounds in HEp-2 cells. This variant harbored an S443P substitution in the clesrovimab binding site and was not neutralized by clesrovimab up to the highest concentration tested of 67nM (10,000 ng/mL) (Table 146).

As noted in Section 20.2, in the alanine scanning mutagenesis experiment, S443A and G446A did not show clear loss of RB-1 binding activity compared with control antibodies palivizumab and D25. Also, the relative binding of RB-1 and RB-1 Fab to K445A was 133.1% and 128.5%, respectively.

Table 146. RSV A- and RSV B-Resistant Variants Identified in Cell Culture Passage Experiments

		EC_{50} Value (ng/mL)	
Virus Designation	**RSV F Protein Change**	**RB-1**	**Clesrovimab**
RSV A			
RSV A2 (wild-type)	-	0.478	0.263
RB-1-A1	G446E	>1,000	>1,000
RB-1-A2	S443P; K445N	>1,000	>1,000
RB-1-A5	S443P; G446E	>1,000	>1,000
RB-1-B6	S443P	>1,000	>1,000

Virus Designation	RSV F Protein Change	EC_{50} Value (ng/mL) RB-1 Clesrovimab	
RSV B			
RSV B Washington	-	NR	27.8
P1A1	S443P	NR	>10,000

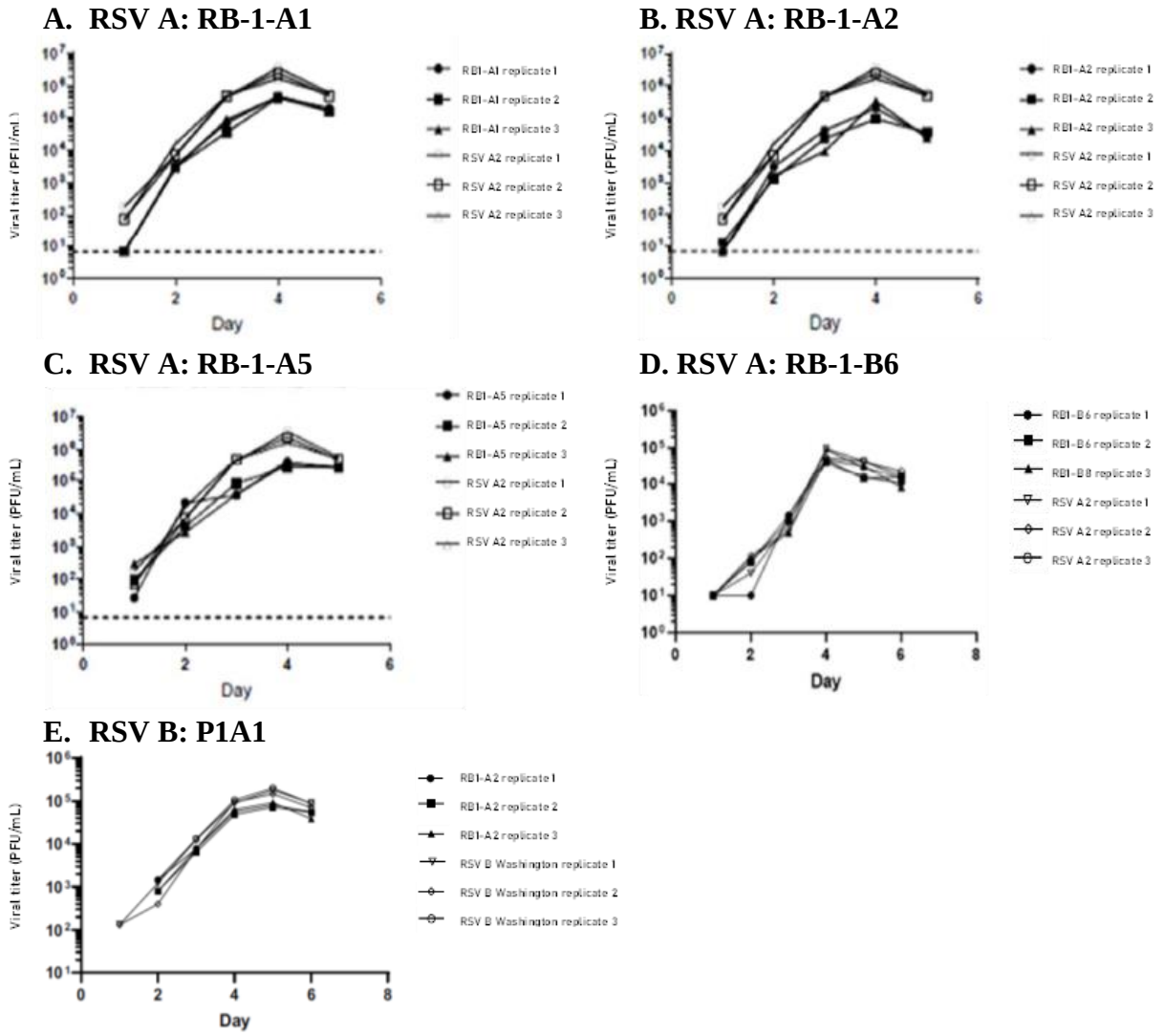
Source: Tables 15, 16, and 17, page 42, (Merck 2024h; Merck 2025c)
Abbreviations: EC_{50}, half-maximal effective concentration; F, fusion protein, NR, not reported; RSV, respiratory syncytial virus

Replication Dynamics of Clesrovimab-Resistant Viruses

Each variant virus was assessed for their replication ability in HEp-2 cells (Figure 36). RSV A variants RB-1-A1, RB-1-A2 and RB-1-A5, and RSV B variant P1A1, appeared to have reduced replication rates, with lower peak titers, compared to the parental RSV A2 or B Washington strains.

The RSV A RB-1-B6 variant had similar replication rates as the parental RSV A2 strain and harbors an S443P substitution. However, peak titers were approximately 1 $\log_{10}$ lower for this experiment, including for the parental strain, compared with the other RSV A assessments, indicating that cell culture conditions were not optimal for virus propagation. In addition, the RSV B variant P1A1, which showed lower peak titers, also harbors S443P substitution, indicating that the impact of this substitution on viral replication may be context dependent. For RSV B, the peak titers for the parental strain were approximately 1.5 $\log_{10}$ lower than those for RSV A.

Figure 36. Replication Dynamics of Cell Culture Selected RSV Variants With Reduced Susceptibility to Clesrovimab



Source: Figure 6, page 51 and Figure 7, page 52, (Merck 2024h)
Four RSV A and one RSV B variant harboring amino acid substitution(s) in the clesrovimab binding site were selected in cell culture. Each variant virus was assessed for replication characteristics in HEp-2 cells. Culture supernatants were harvested on Days 1, 2, 3, 4, and 5, after infection, and on Day 6 for panels D and E, and assessed for infectivity (PFU/mL) using a microplaque assay. Shown in each panel are the replication curves for each variant and the parental RSV A or RSV B strain, in triplicate.
Abbreviations: HEp-2, human epidermoid carcinoma #2; PFU, plaque-forming units; RSV, respiratory syncytial virus

Conclusion

Cell culture passage of RSV A or RSV B in the presence of the clesrovimab parental antibody, RB-1 selected for resistant variants harboring amino acid substitutions in the clesrovimab binding site. None of the four RSV A and 1 RSV B variants which were selected were susceptible to neutralization by clesrovimab up to the highest concentration tested. Based on the resistance-associated substitutions identified, these experiments validate the target of clesrovimab, and show that resistance may arise during viral infection in the presence of clesrovimab. While four of the five resistant variants appeared to have reduced replication ability in HEp-2 cells, it is not clear whether this is predictive of reduced fitness in humans. Even with

reduced replication, it is possible for such variants to pick up compensatory substitutions with continued drug exposure.

20.6.2. Evaluation of Clesrovimab Activity Against RSV F I432T Substitution Identified in GenBank®

The following was derived from a study report submitted by the Applicant (Merck 2024d). The F protein I432T substitution was the most frequently observed (0.04%) clesrovimab binding-site substitution seen in RSV sequences from GenBank® (see Section 18.1), and was seen in both RSV A (n=5) and RSV B (n=1) sequences. The Applicant assessed the potential impact on clesrovimab activity of this substitution in binding and neutralization assays, and determined whether it had a replication advantage compared with wild-type RSV in a competition assay.

Methodology

Binding Assessment by Immunoassay

The impact of I432T substitution on F protein binding by clesrovimab was assessed by enzyme-linked immunosorbent assay. Purified recombinant wild-type (WT) RSV A2 F protein or RSV A2 F protein with an I432T substitution were coated onto Nunc C96 Maxisorp Nunc-Immuno™ 96-well plates overnight at 4°C. Plates were blocked with 3% milk in PBS-Tween 20 for 1 hour at room temperature.

Following removal of blocking buffer, clesrovimab or control antibodies were added to the plates for 90 minutes at room temperature, and then horseradish peroxidase-conjugated goat antihuman IgG added for 1 hour at room temperature. For the substrate, SuperBlu (3,3',5,5'-tetramethylbenzidine) was added to each well, and optical density measured at 450nM on an EnSight™ multimode plate reader (PerkinElmer).

Neutralization Assay for RSV With an F Protein I432T Substitution

RSV A2 or RSV B Washington strains harboring I432T substitution and expressing green fluorescent protein (GFP) were assessed for susceptibility to clesrovimab.

Serial dilutions of clesrovimab, and control antibodies, were added to 96-well plates and mixed with 700 PFU/well of GFP-expressing RSV A or RSV B for 1 hour at 37°C. Antibody-virus mixtures were transferred to another 96-well plate seeded with 2×10^4 cells/well HEp-2 cells. Plates were incubated for 2 days, then GFP positive cells measured using an Acumen Cellista imager.

Competitive Replication of RSV With an F Protein I432T Substitution

RSV A2 or RSV B Washington with an I432T substitution was assessed for replication in a mixed culture with the respective WT virus.

For RSV A, a mixture of RSV A2 WT and RSV A2 with an I432T substitution were added to three wells of a 6-well plate seeded with 3×10^5 cells/well HEp-2 cells (MOI =0.1). Cells were incubated until cytopathic effect was evident, then virus harvested by scraping cells from the wells, snap freezing, and clarifying by centrifugation. A total of 0.3 mL of supernatant was used to infect new cells. Five successive rounds of infection were performed. After Rounds 0, 1, and

5, viral RNA was extracted from supernatants and RT-PCR conducted using the QIAGEN OneStep RT-PCR kit to amplify the RSV F gene spanning amino acids 379 to 558 with specific primers. PCR products were purified using QIAquick® PCR Purification Kit and sequenced using NGS and PAC Bio NGS (GENEWIZ) to determine the relative proportions of WT virus and virus harboring an I432T substitution.

For RSV B, successive rounds of replication were conducted in HEp-2 cells using an initial mixture of RSV B Washington and RSV B Washington with an I432T substitution (MOI =0.1). Virus was harvested as for RSV A, and five successive rounds performed. Unlike for RSV A, virus from the three replicate wells for each round of each infection was pooled prior to the subsequent round, and viral RNA from each of the five passages was sequenced. RNA extraction, RT-PCR amplification and NGS sequencing was conducted as described for RSV A, except the F gene region amplified encompassed amino acids 287 to 472.

Results

Binding of clesrovimab to RSV A2 harboring an F protein I432T substitution was slightly reduced compared with binding to WT RSV A2 protein (1.8-fold; Table 147). However, the control antibody D25 (nirsevimab precursor), which targets Site Ø, also a showed small reduction in neutralization activity of 1.3-fold. It is likely that these changes in binding activity are accounted for by assay variability.

There were also slight reductions in neutralization activity by clesrovimab against RSV A2 (4.0-fold) and RSV B Washington (1.6-fold) (Table 148). The control antibody RB11 (not described further), also showed small reductions in neutralization activity of 1.3- and 3.2-fold against RSV A and RSV B, respectively. The Applicant indicated with respect to the evaluation of clinical isolates that fold-change values of <5-fold in the cell-based neutralization assay are likely within the variability of the assay and not significant.

In the competition assay, for both RSV A and RSV B, the proportion of sequences harboring an I432T substitution declined over successive rounds of infection, indicating that the variants were outcompeted by WT virus (Table 149).

Table 147. Clesrovimab Binding to RSV A2 With an F Protein I432T Substitution by ELISA

	IC_{50} Value (ng/mL)			
Antibody	RSV F WT (His-Tagged)	RSV F I432T (His-Tagged)	RSV F WT	Fold-Change (His-Tagged F Protein)
Clesrovimab	28.4	50.2	25.2	1.8
D25 (positive control)	20.0	25.2	21.5	1.3
MSD RB11 anti-RSV antibody (positive control)	16.3	20.0	16.8	1.2
DD1L (negative control)	>10,000	>10,000	>10,000	1.0

Source: Table 9, page 34, (Merck 2024h)
DD1L is an antibody against dengue virus that was isolated from humans (Cox et al. 2015)
Abbreviations: F, fusion protein; IC_{50}, half-maximal inhibitory concentration; ELISA, enzyme-linked immunosorbent assay; F, fusion protein; His, histidine; MSD, Merck, Sharp & Dohme, LLC; RSV, respiratory syncytial virus; WT, wild-type

Table 148. Clesrovimab Neutralization of RSV I432T Variant

Antibody	EC_{50} Value (ng/mL)		Fold-Change
	GFP-RSV WT F	GFP-RSV F I432T	
RSV A2			
Clesrovimab	3.47	14.04	4.0
MSD RB11 anti-RSV antibody (positive control)	5.07	6.79	1.3
DD1L (negative control)	>1,000	>1,000	1.0
RSV B Washington			
Clesrovimab	3.1	5.1	1.6
MSD RB11 anti-RSV antibody (positive control)	3.4	10.8	3.2
DD1L (negative control)	>10,000	>10,000	1.0

Source: Table 10, page 35, (Merck 2024h)
DD1L is an antibody against dengue virus that was isolated from humans (Cox et al. 2015)
Abbreviations: F, fusion protein; GFP, green fluorescent protein; EC_{50}, half-maximal effective concentration; MSD, Merck, Sharp & Dohme, LLC; RSV, respiratory syncytial virus; WT, wild-type

Table 149. Competitive Fitness (% Sequences) of RSV Variants With an I432T Substitution

	RSV A2			RSV B Washington	
Infection Round[a]	RSV A2 I432T	RSV A2 WT	Passage[a]	RSV B I432T	RSV B WT
Round 0	66	34	Passage 0	94.4	5.5
Round 1, Well 1	54	46	Passage 1	22.3	77.6
Round 1, Well 2	55	45	Passage 2	4.7	95.3
Round 1, Well 3	55	45	Passage 3	1.6	98.4
Round 5, Well 1	38	62	Passage 4	0.8	99.2
Round 5, Well 2	38	62	Passage 5	0.4	99.6
Round 5, Well 3	39	61			

Source: Tables 11 and 12, page 36 (Merck 2024h)
[a] For RSV A2, virus from 3 replicate wells was sequenced from infection Rounds 0, 1, and 5; for RSV B, virus from each round of infection was pooled and sequenced (Passage 0 to Passage 5).
Abbreviations: RSV, respiratory syncytial virus; WT, wild-type

Conclusion

The binding activity of clesrovimab against RSV A harboring an F protein I432T substitution, and the neutralization activity of clesrovimab against RSV A or RSV B with this substitution were reduced slightly, likely within the variability of the respective assays. Hence, it is not clear that this substitution has a significant impact on virus susceptibility to clesrovimab, although it is not known whether small fold-changes might be important with respect to clinical efficacy.

While the viruses with an I432T substitution appeared to be outcompeted by wild-type viruses, the strains being used were not contemporary ones and were laboratory adapted, and it is not clear whether compensatory substitutions in the variants in which an I432T substitution was identified might correct for any replication deficiency in the clinic.

20.6.3. Cell Culture Evaluation of Clesrovimab Cross-Resistance With Nirsevimab and Palivizumab

The following was derived from study reports submitted by the Applicant (Merck 2024e; Merck 2025b). Palivizumab (MedImmune 1998) targets antigenic Site II on RSV F protein, and nirsevimab (ASTRAZENECA°AB 2023) targets Site Ø, and for both antibodies, resistance-associated substitutions have been identified in their respective binding sites, which cause

reduced susceptibility to neutralization. Should variants with reduced susceptibility to approved drugs become widely circulating, it will be important to know whether other approved prophylactic drugs may be effective. Hence, the Applicant assessed the neutralization activity of clesrovimab against RSV harboring palivizumab or nirsevimab resistance-associated substitutions. In response to FDA proposed Prescribing Information changes, the Applicant also provided data for the activity of nirsevimab and palivizumab against RSV harboring clesrovimab resistance-associated substitutions.

Binding activity data are described in Section 20.3 and showed that clesrovimab was able to bind to Site II or Site Ø knockout proteins, indicating that cross-resistance may be unlikely.

Methodology

The potential for clesrovimab cross resistance with other approved F protein targeting antibodies was evaluated in a cell culture neutralization assay using methodology described in Section 20.4. For determining the impact of susceptibility to clesrovimab by palivizumab resistance-associated substitutions, the cell culture neutralization activity of clesrovimab was determined against clinical isolates which were identified as harboring F protein palivizumab resistance-associated substitution N262Y.

For evaluating cross-resistance to nirsevimab, the activity of clesrovimab was determined against four RSV B variants harboring substitutions which reduced susceptibility to nirsevimab, including N208S (>24,000 fold-change), I64T+K68E (>280-fold), I64T+K68E+I206M+Q209R (not previously evaluated), and L204S+I206M+Q209R+S211N (not previously evaluated). It should be noted that I206M+Q209R, and I206M+Q209R+S211N concurrent substitutions do not confer reduced susceptibility to nirsevimab, and phenotypic data for L204S substitution were not previously reported (ASTRAZENECA°AB 2023).

GFP-expressing recombinant RSV B viruses harboring nirsevimab resistance-associated substitutions were constructed using a bacterial artificial chromosome reverse genetics system (Kleiner et al. 2023). Variant viruses were propagated in HEp-2 cells and assessed for susceptibility to each mAb using the method described for the I432T variant in Section 20.6.2.

Results

For the clinical isolates harboring palivizumab resistance-associated substitution N262Y, clesrovimab and clesrovimab parental antibody RB-1 had EC_{50} values similar to those determined for the wild-type RSV A or RSV B strains (Table 150). Palivizumab did not have activity against RSV A or RSV B harboring N262Y substitution up to the highest concentration tested (68nM [10 µg/mL]). Published data report the EC_{50} value for palivizumab against RSV A2 with N262Y substitution as 32nM (4.8 µg/mL) (8.4-fold change; (Bates et al. 2014)), but there may be differences depending on the sequence context and methodology used.

Table 150. Neutralization of Wild-Type and RSV Variants Harboring Palivizumab Resistance-Associated Substitutions by Clesrovimab, EC_{50} Values (ng/mL)

Antibody	A/Long (WT RSV A)	B/Washington (WT RSV B)	Palivizumab-Resistant Isolate RSV A (N262Y)	Palivizumab-Resistant Isolate RSV B (N262Y)	Fold Change (RSV A)	Fold Change (RSV B)
Clesrovimab	6.43	4.85	1.23	2.78	0.2	0.6
RB-1	3.98	4.18	2.46	1.49	0.6	0.4
Palivizumab	237.5	87.37	>10,000	>10,000	>42	>114

Source: Table 7, page 25, RSV Surveillance and Clinical Virology report (Merck 2024e)
Abbreviations: $EC_{50,}$ half-maximal effective concentration; RSV, respiratory syncytial virus; WT, wild type

For the evaluation of clesrovimab activity against nirsevimab resistance-associated substitutions, recombinant GFP-expressing RSV B variants were tested (Table 151 and Figure 37). No loss of activity was reported for clesrovimab against the recombinant RSV B variant viruses, other than for L204S+I206M+Q209R+S211N substitutions; however, this variant replicated poorly and the EC_{50} value was interpolated and not reliable based on the dose response curve (Figure 37 panel E). In addition, anti-RSV F Site II and Site III human mAbs also showed 50% inhibition of this variant at concentrations ≥3,000 ng/mL (data not provided).

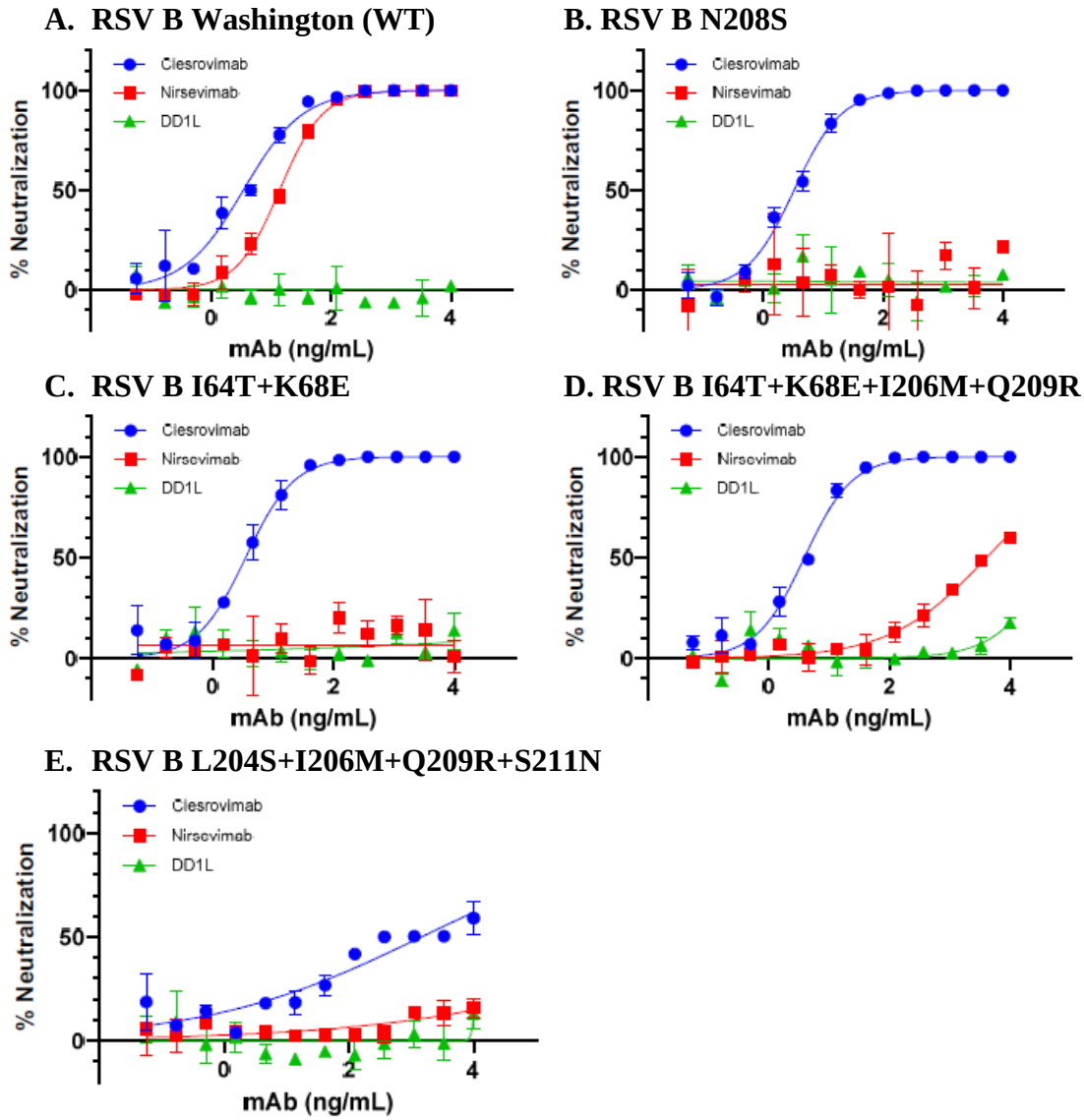
Nirsevimab lost activity against all the recombinant viruses; the EC_{50} value reported for RSV B Washington was relatively high, but within the expected range for RSV B [0.3 to 59.7 ng/mL; (ASTRAZENECA°AB 2023)].

Table 151. Neutralization of Wild-Type and RSV Variants Harboring Nirsevimab Resistance-Associated Substitutions by Clesrovimab[a]

		Clesrovimab		Nirsevimab	
RSV B F Protein Substitutions	Virus Titer (PFU/mL)	EC_{50} (ng/mL)	Fold Change	EC_{50} (ng/mL)	Fold Change
None (WT)	1.62×10^6	3.44	-	13.86	-
N208S	1.09×10^6	3.31	1.0	>10,000	>722
I64T+K68E	5.06×10^5	3.52	1.0	>10,000	>722
I64T+K68E+I206M+Q209R	6.01×10^5	3.95	1.1	3,615[b]	261
L204S+I206M+Q209R+S211N[c]	3.45×10^3	3,161[b]	919	>10,000	>722

Source: Table 8, page 27, RSV Surveillance and Clinical Virology report (Merck 2024e)
[a] DD1L antibody (antidengue virus, isolated from humans (Cox et al. 2015) was used as a negative control and had EC_{50} values >10,000 ng/mL against WT and all variants.
[b] The 50% inhibition value was interpolated because the dose response curve was not fully sigmoidal due to poor growth of the variant
[c] This variant did not grow to sufficiently high titers in HEp-2 cells, which could explain why it was not phenotypically characterized in a previous publication of the nirsevimab clinical trial (Ahani et al. 2023).
[d] ≥5-fold change
Abbreviations: EC_{50}, half-maximal effective concentration; HEp-2, human epidermoid carcinoma #2; PFU, plaque-forming units; RSV, respiratory syncytial virus; WT, wild-type

Figure 37. Dose-Response Curves for Cell Culture Neutralization of RSV B Variants by Clesrovimab



Source: Figure 6, page 28, RSV Surveillance and Clinical Virology report (Merck 2024e)
The ability of clesrovimab to neutralize WT RSV-B Washington (panel A) and the following nirsevimab resistant variants was evaluated: N208S (panel B), I64T+K68E (panel C), I64T+K68E+I206M+Q209R (panel D), and L204S+I206M+Q209R+S211N (panel E). DD1L is a negative control antibody.
Abbreviations: mAb, monoclonal antibody; RSV, respiratory syncytial virus; WT, wild-type

Additional data were provided late in the review cycle for the activity of clesrovimab, nirsevimab, and palivizumab against RSV harboring clesrovimab binding-site substitutions (Table 152; data provided from two separate experiments). Clesrovimab was not active against RSV A harboring G446E, G446R, or G446W substitutions, or RSV B with G446E or G446W substitutions, and was reduced (3-fold change) against RSV B with I432V substitution. Nirsevimab retained activity (<5-fold change) against all RSV A and RSV B variants tested in both experiments; palivizumab was only included in the first experiment and retained activity (<5-fold change) against all variants tested in this experiment. Resistance control viruses for nirsevimab or palivizumab were not included in these experiments.

Table 152. Neutralization of Wild-Type and RSV Variants Harboring Clesrovimab Binding-Site Substitutions by Nirsevimab and Palivizumab[a]

		Clesrovimab		Nirsevimab		Palivizumab	
Virus ID	RSV Subtype	EC_{50} (ng/mL)	Fold Change[b]	EC_{50} (ng/mL)	Fold Change[b]	EC_{50} (ng/mL)	Fold Change[b]
RSV A							
RSV A2	A	3.4	-	2.0	-	184.3	-
BCM-R04505	A – contemp.	9.6	2.8	3.9	2.0	254.8	1.4
RSV A D440G	A	3.8	1.1	1.0	0.5	35.2	0.2
RSV A G446E	A	>10,000	>2,941.2[e]	3.6	1.8	159.3	0.9
RSV A G446R [c]	A	ND	-	ND	-	ND	-
RSV A G446W	A	>10,000	>2,941.2[e]	1.4	0.7	25.3	0.1
NS[d]	A – contemp.	6.4	-	2.8	-	ND	ND
RSV A G446R[d]	A	>10,000	>1,562.5[e]	0.4	0.1	ND	ND
RSV B							
RSV B Washington	B	7.7	-	12.6	-	153.1	-
BCM-C03347 K42R	B – contemp.	7.8	1.0	3.2	0.3	252.9	1.7
RSV B K445R	B	4.3	0.6	0.2	0.02	421.9	2.8
RSV B G446E	B	>10,000	>1,298.7[e]	0.3	0.02	227.3	1.5
RSV B G446R[c]	B	ND	-	ND	-	ND	-
RSV B G446W	B	>10,000	>1,298.7[e]	0.4	0.03	361.0	2.4
NS[d]	B – contemp.	4.8	-	2.5	-	ND	ND
RSV A I432V[d]	B	15.5	3.2	0.7	0.3	ND	ND

Source: (Merck 2025b; Merck 2025d)
[a] As a negative control, DD1L was used (mAb specific for dengue virus); no activity was seen for this mAb up to 10,000 ng/mL for any virus tested
[b] Fold change was calculated from the EC_{50} value for each strain divided by the EC_{50} value for the reference strain of the same subtype
[c] Variants encoding the G446R substitution could not be rescued in the first experiment
[d] Data for RSV A G446R and RSV B I432V were provided from a separate experiment
[e] ≥5-fold increase in EC_{50} value
Abbreviations: contemp, contemporary strain (see Table 145); EC_{50}, half-maximal effective concentration; mAb, monoclonal antibody; ND, not determined (virus rescue failed); NS, not stated; RSV, respiratory syncytial virus

Conclusion

The cell culture cross-resistance data for clesrovimab concurred with the binding activity data (see Section 20.3) for Site II or Site Ø knockout proteins, and the alanine scanning data (see Section 20.2) for Site II or Site Ø residue changes, which indicated that clesrovimab activity is not affected by palivizumab or nirsevimab resistance-associated substitutions. However, the Applicant did not conduct a comprehensive assessment of resistance-associated substitutions identified for these two antibodies, and for nirsevimab in particular, which has a broader indication than palivizumab, it will be important to evaluate other known resistance-associated substitutions.

The nirsevimab product Prescribing Information currently includes the following additional F protein substitutions which confer >100-fold loss of susceptibility to nirsevimab:

- RSV A: N67I+N208Y
- RSV B: K65Q+K68N, K68N+N201S, K68N+N208S, N201S, N201T, L203I, N208D

The Applicant also provided cross-resistance data for clesrovimab resistance-associated substitutions G446E, G446R, and G446W. Nirsevimab retained activity against RSV A and RSV

B harboring these substitutions, and palivizumab retained activity against G446E and G446W (G446R was not assessed). However, resistance control RSV variants harboring nirsevimab or palivizumab resistance-associated substitutions were not included in these experiments.

20.7. Animal Models

A nonlethal cotton rat model of RSV infection was used to assess the prophylactic antiviral activity of clesrovimab parental antibody RB-1, and the influence of the effector function of RB-1 on antiviral activity. For these studies, the parental antibody was used, which lacks the YTE modifications to the Fc region, because the YTE substitutions increase binding to the rat neonatal receptor and decrease antibody exposure (Dall'Acqua et al. 2002).

20.7.1. RSV Cotton Rat Challenge Studies of Antiviral Activity

The following was derived from a study report submitted by the Applicant (Merck 2024f). An initial pilot study was conducted in the cotton rat model of RSV A infection, followed by a more detailed using RSV A and RSV B study to determine the EC_{50} and EC_{90} values of RB-1 for reducing RSV titers in lung tissue. The RSV F protein Site Ø targeting antibody, D25, and Site II targeting antibody, palivizumab, were used as controls in these experiments.

Methodology

Pilot Study RSV-118

For the pilot study using RSV A2, RB-1 (EC_{50} value =58pM [8.6 ng/mL], Table 144 was evaluated alongside palivizumab and D25 control antibodies (EC_{50} values =2,800pM [416.8] and 72pM [10.8 ng/mL], respectively) (Zhu et al. 2017). The study groups are shown in Table 153. RB-1 and palivizumab were tested at doses of 5.0, 2.5, 0.25, and 0.025 mg/kg, and D25 at doses of 2.5, 1.25, and 0.125 mg/kg, in groups of five female cotton rats (b) (4) . A control group of five animals was included, which did not receive any antibody. An average weight of the cotton rats was determined on Day 0 using a group of six animals selected randomly. Antibody was administered IM on Day 0, and a blood sample taken on Day 1 for evaluation of serum concentrations of each mAb. Following blood collection, animals were each exposed intranasally to 1×10^5 PFU RSV strain A2 in 100-µL volume. After 4 days following viral challenge, animals were euthanized, and lung tissue collected for assessment of RSV titers.

Table 153. Group Designation, Dose Levels, and Dosing Schedule Against RSV Strain A2, Pilot Study RSV-118

Group	Number of Animals	Treatment	Dose (mg/kg)	Route	Day of Dosing
1	5	RB-1	5.0	IM	0
2	5	RB-1	2.5	IM	0
3	5	RB-1	0.25	IM	0
4	5	RB-1	0.025	IM	0
5	5	Palivizumab	5.0	IM	0
6	5	Palivizumab	2.5	IM	0
7	5	Palivizumab	0.25	IM	0
8	5	Palivizumab	0.025	IM	0
9	5	D25	2.5	IM	0
10	5	D25	1.25	IM	0
11	5	D25	0.125	IM	0
12	5	Control	None	None	N/A

Source: Table 7, page 20, (Merck 2024f)
Abbreviations: IM, intramuscular; N/A, not applicable; RSV, respiratory syncytial virus

RSV Challenge Study RSV-128

For the challenge study RSV-128, RB-1 and D25 antibodies were assessed against RSV A2 and RSV B 18537 strains (EC_{50} values for RB-1=58pM [8.6 ng/mL] [RSV A2] and 36pM [5.4 ng/mL] [RSV B 18537]) (Table 144). EC_{50} values for D25=72pM [10.8 ng/mL] [RSV A2] and 48pM [7.1 ng/mL] [RSV B9320]; (Zhu et al. 2017). The study groups are shown in Table 154. Each antibody was assessed at doses of 2.5, 0.83, 0.28, 0.09, 0.03 mg/kg in groups of five female cotton rats, and a control group (n=5) included with no mAb administered. On Day 0, mAbs were administered IM, and animals were challenged on Day 1 with 1×10^5 PFU RSV A2 or RSV B 18537 strains in 100-µL volume. Animals were euthanized 4 days following viral challenge, and lung tissue collected for assessment of viral titers.

Table 154. Group Designation, Dose Levels, and Dosing Schedule, Using RSV A2 or RSV B 18537[a], Study RSV-128

Group	Number of Animals	Treatment	Dose Level (mg/kg)	Route	Day of Dosing
1	5	RB-1	2.5	IM	0
2	5	RB-1	0.83	IM	0
3	5	RB-1	0.28	IM	0
4	5	RB-1	0.09	IM	0
5	5	RB-1	0.03	IM	0
6	5	D25	2.5	IM	0
7	5	D25	0.83	IM	0
8	5	D25	0.28	IM	0
9	5	D25	0.09	IM	0
10	5	D25	0.03	IM	0
11	5	Control	None	None	N/A

Source: Tables 8 and 9, pages 21 and 22, (Merck 2024f)
Group designations and dosing the same for both RSV strains
Abbreviations: IM, intramuscular; N/A, not applicable; RSV, respiratory syncytial virus

Sample Collection and Processing

One day (24±4 hours) following mAb administration, blood was collected and processed for serum; for Studies RSV-128 and RSV-159, blood was also collected from euthanized rats on Day 4 postchallenge. Left lung lobes were excised for all experiments from euthanized rats on Day 4 postchallenge, and for Studies RSV-128 and RSV-159, nose turbinates were also collected. All samples were clarified by centrifugation, flash frozen, and stored at -70°C until use.

RSV Plaque Assay

A plaque assay was used to determine the RSV titers in lung tissue. Samples were tested in duplicate on 24-well plates with confluent HEp-2 cells at different dilutions (neat, 1:10, and 1:100). The methodology for the plaque assay was the same as described in Section 20.6.1, using a 0.75% methylcellulose overlay, and fixing and staining after 5 days incubation at 37°C with crystal violet solution containing 5% glutaraldehyde.

Immunoassay for Determining Serum Concentration of Antibodies

An immunoassay was used to determine the serum concentrations of antibodies from blood collected on Day 1 prior to viral challenge. Prefusion F protein was coated onto 96-well plates at 4°C overnight, and plates blocked with 3% milk in PBS-Tween 20 for 1 hour at room temperature. Serum samples were diluted 1:50, then serially diluted 4-fold, and added to the plates, along with 3-fold serially diluted control antibodies RB-1, palivizumab and D25. Plates were incubated for 2 hours at room temperature, then washed and treated with horseradish peroxidase-conjugated antihuman IgG for 1 hour at room temperature. The substrate SuperBlu Turbo tetramethylbenzidine was added, and plates read at 450nM on Molecular Devices VersaMax instrument.

Results

Pilot Study RSV-118

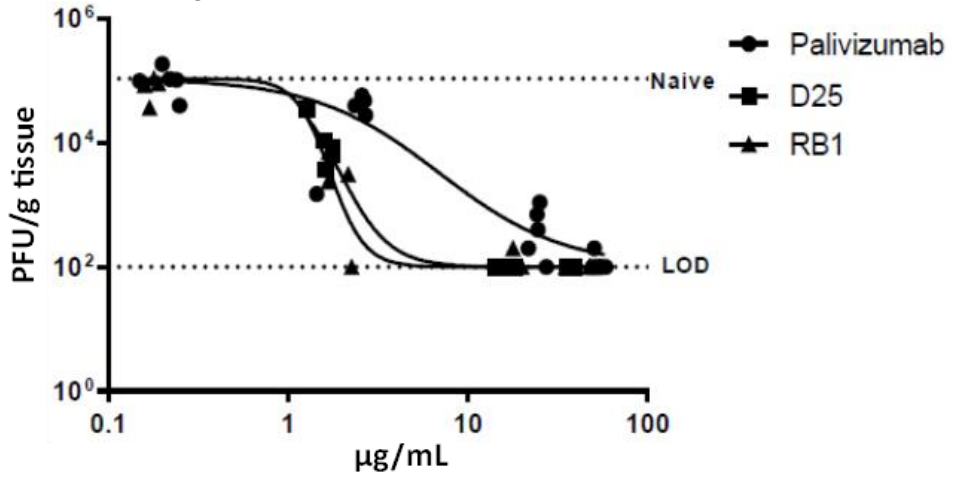
Viral titers in lung tissue assessed following challenge in cotton rats infected with RSV A2 were used to calculate EC_{50} values, shown in Table 155. Dose-response curves are shown in Figure 38. For clesrovimab parental antibody RB-1, there was a dose-response, with an EC_{50} value that was similar to that of D25, and approximately 4-fold lower than seen for palivizumab.

Table 155. EC_{50} Values Determined From Lung RSV Titers in Cotton Rats Dosed With mAbs, 1 Day Prior to Challenge With RSV A2, Study RSV-118

Anti-RSV Antibody	Lung EC_{50} Value (µg/mL)	95% CI (µg/mL)
Clesrovimab parental antibody RB-1	1.719	1.401 to 1.873
D25	1.956	1.811 to 2.274
Palivizumab	6.940	4.202 to 11.800

Source: Table 13, page 29, (Merck 2024f)
Abbreviations: CI, confidence interval; EC_{50}, half-maximal effective concentration; mAb, monoclonal antibody; RSV, respiratory syncytial virus

Figure 38. Dose-Response Curves of Lung RSV Titers in Cotton Rats Dosed With mAbs, 1 Day Prior to Challenge With RSV A2



Source: Figure 1, page 31, (Merck 2024f)
µg/mL = microgram per milliliter
Abbreviations: LOD, limit of detection; mAb, monoclonal antibody; PFU, plaque-forming units; RSV, respiratory syncytial virus

Cotton rats were administered either clesrovimab parental antibody RB-1 or palivizumab at 0.025, 0.25, 2.5, and 5 mg/kg, or anti-RSV antibody D25 at 0.125, 1.25, and 2.5 mg/kg based on the average animal weight by IM injection on the day of dosing. Blood was collected for evaluation of serum antibody concentrations the following day. Immediately after blood sample collections, each animal was sedated and challenged intranasally with 1×10^5 PFU of RSV A2 strain. Four days postchallenge, animals were euthanized, blood collected for evaluation of antibody concentrations, and lung tissue collected to assess antibody efficacy by measuring RSV infectious titers in pulmonary tissues. Depicted are the $\log_{10}$ PFU per gram of tissue for each strain for lung tissues for RB-1, palivizumab, and D25 against the $\log_{10}$ of Day 1 serum concentrations in µg/mL. Points represent observed data.

RSV Challenge Study RSV-128

For the more detailed cotton rat study RSV-128, clesrovimab parental antibody RB-1 was compared with D25 antibody, and rats were challenged with RSV A2 or RSV B 18537 strains. For this study, serum concentrations of antibodies were assessed on Day 1, prior to virus challenge, and lung and nasal RSV titers determined by plaque assay (Table 156). For each antibody, there was a dose response (Figure 39), and EC_{50} and EC_{90} values were determined.

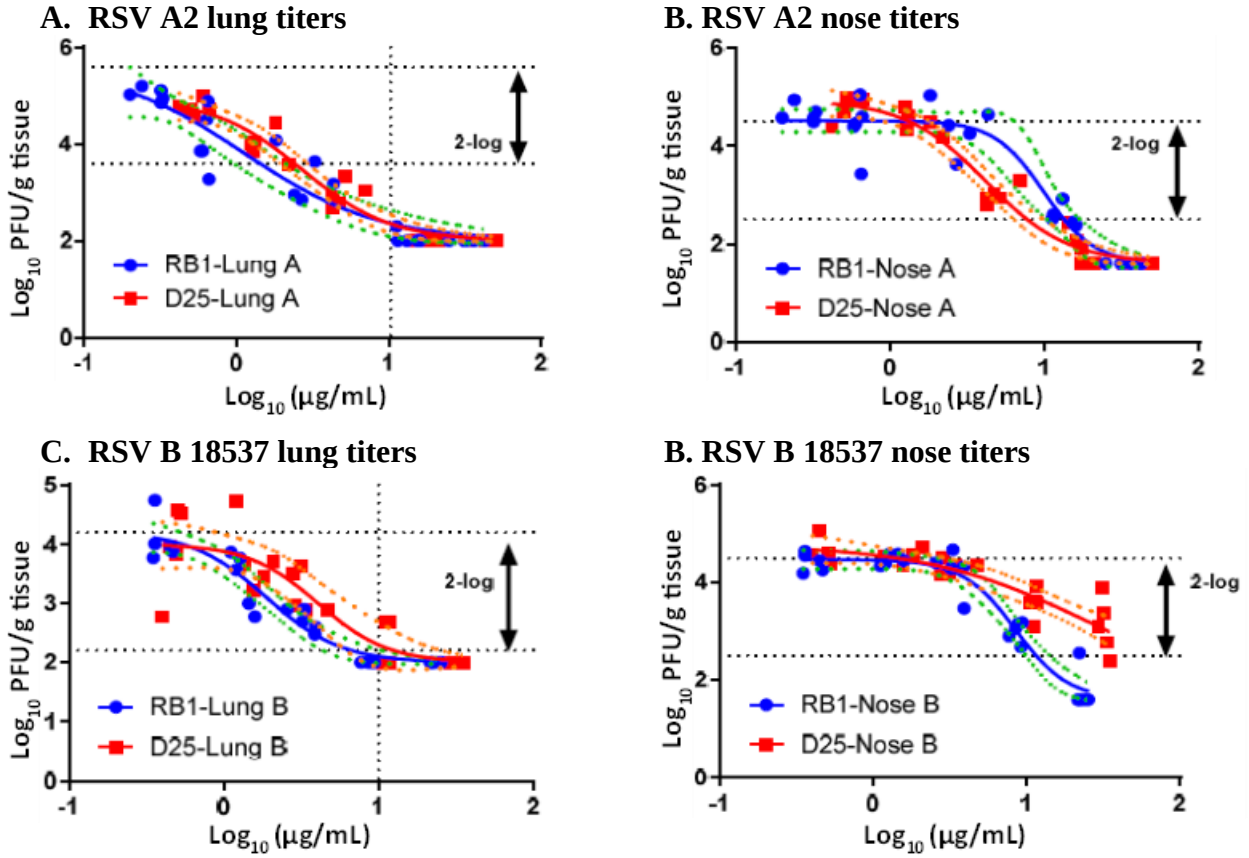
Similar EC_{50} and EC_{90} values were determined for RB-1 and D25 antibodies in both lung and nose tissue, although these values were approximately 2-fold higher for D25 against RSV B 18537. Based on serum antibody exposure, an RB-1 serum concentration of approximately 10 µg/mL was sufficient to reduce RSV A or RSV B lung titers by at least 2 $\log_{10}$ PFU/mL (Figure 39). It should be noted that 2 $\log_{10}$ is a 99% reduction in titers, so it is not clear whether the EC_{90} values reported by the Applicant actually represent EC_{99} values.

Table 156. EC_{90} and EC_{50} Values Determined From Lung RSV Titers in Cotton Rats Dosed With mAbs, 1 Day Prior to Challenge With RSV A2 or RSV B 18537, Study RSV-128

	EC_{90} (µg/mL)		EC_{50} (µg/mL)	
Anti-RSV Antibody	**Lung**	**Nose**	**Lung**	**Nose**
RSV A2				
Clesrovimab parental antibody RB-1	10.3	22.6	1.1	9.9
D25	11.8	16.1	2.7	4.2
RSV B 18537				
Clesrovimab parental antibody RB-1	6.4	20.4	1.9	8.5
D25	12.8	>50.0	4.1	25.7

Source: Table 14, page 29, (Merck 2024f)
Abbreviations: EC_{50}, half-maximal effective concentration; EC_{90}, 90% maximal effective concentration; mAb, monoclonal antibody; RSV, respiratory syncytial virus

Figure 39. Dose-Response Curves of Lung and Nasal RSV Titers in Cotton Rats Dosed With mAbs, 1 Day Prior to Challenge With RSV A2 or RSV B 18537, Study RSV-128



Source: Figure 2, page 32, (Merck 2024f)
Cotton rats were administered either clesrovimab parental antibody RB-1 or D25 antibody at 2.5, 0.83, 0.28, 0.09, or 0.03 mg/kg based on the average animal weight by intramuscular (IM) injection on the day of dosing. Blood was collected for evaluation of serum antibody concentrations the following day. Immediately after blood sample collections, each animal was sedated and challenged intranasally with 1×105 PFU of RSV A2 or RSV B 18537 strains. Four days postchallenge, animals were euthanized, blood collected for evaluation of antibody concentrations, and nose and lung tissue collected to assess antibody efficacy by measuring RSV infectious titers in nasal and pulmonary tissues. Depicted are the $\log_{10}$ PFU per gram of tissue for each strain for lung and nose tissues for RB-1 and D25 against the $\log_{10}$ of Day 1 serum concentrations in µg/mL. Points represent observed data. Lines represent nonlinear regression fit of the inhibitory sigmoidal dose-response analysis with variable slope depicted with 95% confidence bands.
In each panel, data for the RB-1 antibody is represented by a solid circle (blue) and for the D25 antibody is represented by a solid square (red). Panel A depicts lung tissue after RSV A2 challenge. Panel B depicts nose tissue after RSV A2 challenge. Panel C depicts lung tissue after RSV B 18537 challenge. Panel D depicts nose tissue after RSV B 18537 challenge.
Abbreviations: mAb, monoclonal antibody; PFU, plaque-forming units; RSV, respiratory syncytial virus

Conclusion

In cotton rat models of RSV infection, clesrovimab parental antibody RB-1 reduced virus titers in lung and nasal tissue in a dose-dependent manner. From dose-response curves, EC_{50} and EC_{90} values were determined, showing similar antiviral activity as the Site Ø targeting antibody D25 (precursor to nirsevimab), although approximately 2-fold increased activity against RSV B 18537.

It should be noted that these experiments used RB-1 rather than clesrovimab which has YTE modifications that decrease exposure. The YTE modifications may also impact effector function (Dall'Acqua et al. 2006). Hence, the antiviral effect observed in these cotton rat studies may overestimate the effect that might be predicted for clesrovimab in humans.

20.7.2. Evaluation of Clesrovimab Effector Function in a Cotton Rat Model of RSV Infection

The following was derived from a study report submitted by the Applicant (Merck 2024f). A modified version of RB-1 was generated to include Fc LALA substitutions (Lund et al. 1991), which reduce binding to IgG Fcγ receptors and C1q. The RB-1 and RB-1-LALA antibodies were compared for antiviral activity in the cotton rat model of RSV infection.

Methods

Study RSV-159 assessed the LALA-modified RB-1 antibody in cotton rats infected with RSV A2. Dosing groups (n=5 female cotton rats in each group) and schedules are shown in Table 157; two experiments were conducted using the same study design. For RB-1 and RB-1-LALA, the doses were based on the average animal weight on the day of dosing, and were 0.03, 0.09, 0.28, 0.83, or 2.5 mg/kg. A control group of five animals was included which did not receive antibody treatment.

Antibody was administered IM on Day 0, and on Day 1, blood samples taken for determining serum antibody concentrations. Following blood collection, each animal was intranasally dosed with 1×10^5 PFU RSV A2 in 100 µL volume. At 4 days postchallenge, lung and nose tissue were collected for assessment of viral titers by plaque assay, using the same methodology described in Section 20.7.1.

Table 157. Group Designation, Dose Levels, and Dosing Schedule Against RSV A2, Experiments 1 and 2, Study RSV-159

Group	Number of Animals	Treatment	Dose Level (mg/kg)	Route	Day of Dosing
1	5	RB-1	0.03	IM	0
2	5	RB-1	0.09	IM	0
3	5	RB-1	0.28	IM	0
4	5	RB-1	0.83	IM	0
5	5	RB-1	2.5	IM	0
6	5	RB-1-LALA	0.03	IM	0
7	5	RB-1-LALA	0.09	IM	0
8	5	RB-1-LALA	0.28	IM	0
9	5	RB-1-LALA	0.83	IM	0
10	5	RB-1-LALA	2.5	IM	0
11	5	Control	None	None	N/A

Source: Table 10, page 23, (Merck 2024f)
Abbreviations: IM, intramuscular; LALA, Fc substitutions L234A and L235A; N/A, not applicable; RSV, respiratory syncytial virus

Results

The clesrovimab parental antibody RB-1 and RB-1-LALA were compared in the cotton rat model of RSV infection, using RSV A2 strain. Two experiments were conducted using the same study design. In lung and nose tissue, there was a dose-dependent antiviral response. From the dose-response curves (Figure 40), EC_{50} values were determined (Table 158). Similar EC_{50} values were seen for Experiments 1 and 2, which were approximately 10-fold higher in nose compared with lung tissue. RB-1 and RB-1-LALA had similar EC_{50} values across experiments and for lung

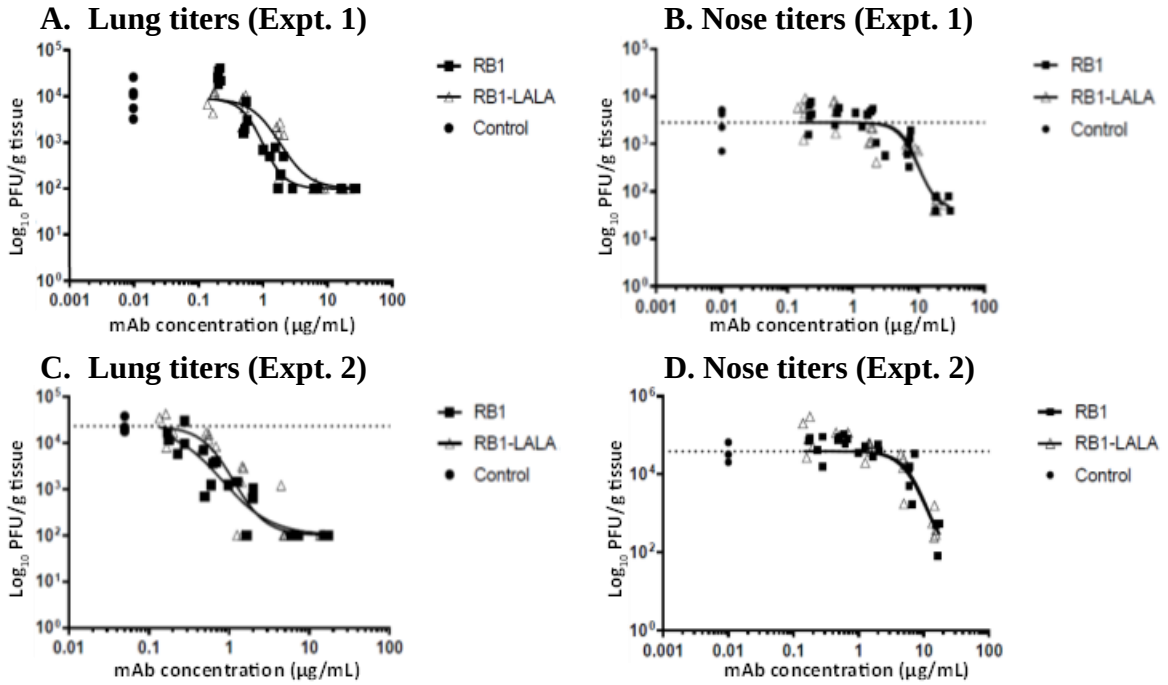
and nose tissue, indicating that at least for this model, there was no clear impact of the LALA modifications on antiviral activity.

Table 158. EC_{50} Values Determined From Lung and Nasal RSV Titers in Cotton Rats Dosed With RB-1 or LALA-RB-1, 1 Day Prior to Challenge With RSV A2, Study RSV-159

		Lung		Nose	
Anti-RSV Antibody	Experiment No.	EC_{50} (µg/mL)	95% CI (µg/mL)	EC_{50} (µg/mL)	95% CI (µg/mL)
Clesrovimab parental antibody RB-1	1	1.069	0.8298 to 1.377	9.848	7.582 to 12.79
	2	0.830	0.647 to 1.074	11.61	9.724 to 13.86
LALA-modified RB-1	1	1.999	1.536 to 2.602	10.7	7.959 to 12.75
	2	1.138	0.862 to 1.558	11.04	8.803 to 13.85

Source: Table 15 and Table 16, page 30, (Merck 2024f)
Abbreviations: CI, confidence interval; EC_{50}, half-maximal effective concentration; LALA, Fc substitutions L234A and L235A; No., number; RSV, respiratory syncytial virus

Figure 40. Dose-Response Curves of Lung and Nasal RSV Titers in Cotton Rats Dosed With RB-1 or RB-1-LALA, 1 Day Prior to Challenge With RSV A2, Study RSV-159



Source: Figure 3, page 33, and Figure 4, page 34, (Merck 2024f)
In two separate experiments, cotton rats were administered either antibody RB-1 or LALA-modified RB-1 antibody (RB-1-LALA) by intramuscular injection at 0.03, 0.09, 0.28, 0.83, or 2.5 mg/kg based on the average animal weight on the day of dosing. Blood was collected for evaluation of serum antibody concentration the following day; the antibody concentration determined is plotted on the x-axis in each panel. Immediately after blood sample collections, each animal was sedated and challenged intranasally with 1×105 PFU of RSV A2. Four days postchallenge, animals were euthanized, and nose and lung tissue collected to assess antibody efficacy by measuring RSV infectious titers in both the nasal and pulmonary tissues. Depicted are the log_{10} PFU per gram of lung and nasal tissue for each antibody. Panel A and Panel B depict lung titers and nasal titers, respectively, after RSV challenge in Experiment 1. Panel C and Panel D depict lung titers and nasal titers, respectively, after RSV challenge in Experiment 2.
Abbreviations: LALA, Fc substitutions L234A and L235A; mAb, monoclonal antibody; PFU, plaque-forming units; RSV, respiratory syncytial virus

Conclusion

In a cotton rat prophylaxis model of RSV A2 infection, clesrovimab parental antibody RB-1 and LALA-modified RB-1 showed dose-dependent antiviral activity, as determined from lung and

nose titers, which was similar for both antibodies. These data indicate that effector function is not necessarily needed for antiviral activity, at least in the cotton rat model. However, there may be differential effects between cotton rat and humans, depending on relative binding to Fcγ and C1q receptors.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Five clinical sites (Drs. Baker, Zar, Franckling-Smith, Etchegaray, and Novoa Pizarro), as well as the Applicant – Merck Sharp & Dohme, LLC – were inspected in support of BLA 761432. These sites were selected based on the enrollment of large numbers of study participants and high rates of treatment responders. The clinical investigator inspections covered Trials MK-1654-004 (Drs. Baker, Zar, Etchegaray, and Novoa Pizarro) and MK-1654-007 (Dr. Franckling-Smith), and the Applicant inspection covered both protocols. The clinical investigator inspections have the following findings:

Underreporting of AEs

For Trial MK-1654-004, two AEs (vomiting and not eating well) at the site of Dr. Baker and three AEs (nasal mucus/sneezing, mild colic, and defecation problem) at the site of Dr. Novoa Pizarro were not reported to the FDA. For Protocol MK-1654-007, one AE (increasing ringworm) at the site of Dr. Franckling-Smith was not reported.

The AEs that were not reported, including the AEs of vomiting and not eating well (which occurred in a single participant in the placebo group) and the AE of increasing ringworm (which occurred in a single participant in the clesrovimab group), are unlikely to have any impact on the assessment of the safety of clesrovimab. Further, given that at each implicated clinical site there was only a single participant with unreported AEs, these findings do not suggest a more pervasive underreporting issue.

Underreporting of RSV-Associated MALRI

At the site of Dr. Etchegaray, source documents showed that Participant #(b) (6) (in the placebo group) had RSV-positive RT-PCR test results on Day 56 with cough and wheezing, therefore meeting criteria for RSV-associated MALRI. This case was not reported in the data line listings submitted by the Applicant. Because Participant #(b) (6) was randomized to the placebo group, the failure to report this case should favor placebo over clesrovimab.

Otherwise, the inspections found that the primary efficacy and safety data for Trial MK-1654-004 and the safety issues of interest to the review division for Trial MK-1654-007 were verifiable. Overall, the inspections indicate that these studies appear to have been conducted

adequately, and the data generated by these inspected CI sites and reported by the Applicant appear acceptable in support of the respective indication.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the (Applicant's draft PI) (Table 159). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 159. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to (Applicant's Draft PI)
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	N/A
2 DOSAGE AND ADMINISTRATION	The following edits were made to Section 2.1: **2.1 Recommended Dosage** (b) (4) The recommended dose for neonates and infants born during or entering their first RSV season is 105 mg administered as a single intramuscular (IM) injection. For neonates and infants born during the RSV season, administer ENFLONSIA once starting from birth. For infants born outside the RSV season, administer ENFLONSIA once prior to the start of their first RSV season considering (b) (4) the duration of protection by ENFLONSIA. *[See Clinical Pharmacology (12.2).]* Infants Undergoing Cardiac Surgery With Cardiopulmonary Bypass For infants undergoing cardiac surgery with cardiopulmonary bypass during the RSV season, an additional 105 mg dose administered as an IM injection is recommended as soon as the infant is stable after surgery to ensure adequate clesrovimab-cfor serum levels. In Section 2.2, the following notable changes were made: The third administration step was modified to recommend use of a 22- to 25-gauge needle rather than (b) (4) A fourth administration step was added (Discard syringe into a sharps container). In the "Co-administration with Childhood Vaccines and Immunoglobulin Products" subsection, the following sentence was added: "There is no information regarding co-administration of ENFLONSIA with other immunoglobulin products."
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	The following warning was added under this section. See Sections 18.2 and 18.3 for additional detail.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to (Applicant's Draft PI)
	5.2 RSV Diagnostic Test Interference Clesrovimab-cfor may interfere with some immunologically based RSV diagnostic assays (i.e., rapid antigen tests) as observed in laboratory studies. Confirmation using a reverse transcriptase polymerase chain reaction (RT-PCR) assay is recommended when rapid antigen assay results are negative and clinical observations are consistent with RSV infection *[see Drug Interactions (7.1)].*
6 ADVERSE REACTIONS	The numbers of study participants and the rates of adverse reactions were updated to reflect the protocol-defined APaT population. These changes were small and did not impact the conclusions regarding safety.
7 DRUG INTERACTIONS	The following edits were made to interference with diagnostic assay. See Sections 18.2 and 18.3 for additional detail. **7.1 Interference With ~~RT-PCR or~~ Rapid Antigen Detection RSV Diagnostic Assays** Clesrovimab (b) (4) cfor may interfere with (b) (4) ~~)~~some immunologically-based RSV diagnostic assays. (b) (4) (i.e., rapid antigen (b) (4) ~~,~~tests) as observed in laboratory studies. Confirmation using a RT-PCR assay is recommended when rapid antigen RSV diagnostic assay results (b) (4) ~~-~~are negative (b) (4) and clinical observations are consistent with RSV infection~~,~~ (b) (4) ~~.~~ Clesrovimab-cfor does not interfere with RT-PCR diagnostic assays *[see Warnings and Precautions (5.2)].*
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	N/A
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	N/A
12 CLINICAL PHARMACOLOGY	**12.2 Pharmacodynamics** Exposure-response relationship information added. See Section 14.5.2 for additional detail. Exposure-Response Relationship In the Phase 2b/3 trial evaluating the recommended dose of clesrovimab-cfor (a single dose of 105 mg) in healthy preterm and full-term infants (Trial MK-1654-004), no significant relationship was observed between AUC (from Day 1 to Day 150) and clinical outcomes (i.e., RSV-associated MALRI). **12.3 Pharmacokinetics** Geometric mean area under the time concentration curve from Day 1 to Day 150, peak concentration, and the concentration at Day 150 were added. See Sections 14.2 and 14.5 for additional detail. Removed data (b) (4)

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to (Applicant's Draft PI)
	[redacted] (b) (4)
	12.4 Microbiology See Sections 18 and 20 for additional detail. Antiviral Activity • Removed [redacted] (b) (4) . • Added geographic information regarding historical and contemporary RSV isolates which were assessed. (Section 20.4). • Added median values of clesrovimab activity against clinical isolates, and separated data for historical and contemporary isolates. Also provided likely explanation for higher values seen for contemporary isolates. (Section 20.4). Antiviral Resistance *In Cell Culture* • Reworded to be consistent with language used by the Division (i.e., "variants" instead of "MARMs", "substitutions" instead of "mutations"). • Added details about clesrovimab loss of susceptibility to resistance-associated substitutions selected in cell culture for RSV A and RSV B. (Section 20.6). *In Surveillance Trials* • Reworded to be consistent with language used by the Division. • Deleted [redacted] (b) (4) • Added age range of individuals in surveillance study (Section 18.1). *In Clinical Trials* • Added frequency of clesrovimab-binding substitutions seen in clesrovimab versus placebo participants in clinical trials (Section 18.4). • Added susceptibility data for resistance-associated substitutions seen in clinical trials (Section 20.6). • Added binding-site substitutions seen in clinical trials for which no phenotypic data were available (Section 18.4). • Noted lack of association of binding-site substitutions and clinical outcomes, and added the one instance in each trial where a substitution was seen in a hospitalized individual (Section 18.4). Cross-Resistance • Reworded to be consistent with language used by the Division. • Noted that not all nirsevimab resistance-associated substitutions had been assessed for cross-resistance (Section 20.6) • Added that nirsevimab and palivizumab retained activity against clesrovimab resistant RSV variants (Section 20.6).

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to (Applicant's Draft PI)
	12.6 Immunogenicity • Included rates of participants who were ADA-positive on Day 150. • Included statement that impact of ADA on efficacy is unknown due to low rates of MALRI and ADA. Refer to Section 14.4 for additional detail.
13 NONCLINICAL TOXICOLOGY	N/A
14 CLINICAL STUDIES	The following (b) (4) were removed (b) (4) In addition, the results of all efficacy endpoints for Trial MK-1654-004 and Trial MK-1654-007 were updated using the protocol-defined FAS population. These changes were small and did not impact the conclusions regarding efficacy.
17 PATIENT COUNSELING INFORMATION	Counseling information on hypersensitivity reaction including anaphylaxis and dosing information was added under this subsection based on the Warnings and Precautions.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	N/A

Source: Comparison of original PI submitted October 10, 2024 and the final, agreed-upon PI.
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): ADA, antidrug antibody; APaT, all-participants as-treated; FAS, full analysis set; LRI, lower respiratory infection; MALRI, medically attended lower respiratory infection; MARM, monoclonal antibody-resistant viral mutant; N/A, not applicable; PI, Prescribing Information; RSV, respiratory syncytial virus

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- USPI
- PPI
- Carton and container labeling

24. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) and commitments (PMCs) have been negotiated with the Applicant and are agreed upon. Please refer to the PMR/506B PMC Development Templates submitted to DARRTS on June 4, 2025 for additional details (DARRTS°ID:°5603154 2025).

Required Pediatric Assessments Under the Pediatric Research Equity Act (21 U.S. Code 355c)

PMR Set 4841-1

The following pediatric assessment was reviewed and agreed upon by the Pediatric Review Committee:

Conduct a study in children up to 24 months of age with underlying conditions who are at increased risk for RSV disease.

PMR 4841-1 Schedule Milestone

Final report submission: August 2026

Postmarketing Requirements Under 505(o)

PMR Set 4841-2

PMR Description

Conduct a surveillance study of current and emerging RSV variants from global locations, with F protein sequencing and identification of clesrovimab binding-site substitutions and their frequency. These surveillance activities should include active collection and characterization of RSV samples from global regions (i.e., North America [United States/Canada], Europe, rest of world), and will target at least 100 samples from each region when fully operational, as well as periodic analysis of sequences from public databases (i.e., GISAID, NCBI, GenBank). The surveillance study should also determine the cell culture neutralization activity of clesrovimab against those RSV clesrovimab binding epitope variants carrying substitutions (VAF >10%) and with unknown impact on clesrovimab susceptibility that are capable of growing in cell culture. Phenotypic characterization will include RSV variants whose prevalence is ≥5% within an RSV season (or over two consecutive years in public databases) and/or ≥3-fold increase above 1% from the previous season across all sequenced samples from all sites within a global region. RSV variants of interest for phenotypic testing will include those carrying substitutions of unknown impact on clesrovimab susceptibility, detected in Site IV, adjacent to the clesrovimab binding epitope (within ≤5 Å distance), or outside Site IV at highly conserved positions (≥99% in GenBank).

Submit interim reports on an annual basis and conduct public sequence database analysis for as long as strain surveillance is ongoing. In addition, after confirmation of the results, the Agency should be notified within 2 months of receipt of new phenotypic data for variants or individual

substitutions showing ≥5-fold reduction in susceptibility, and no later than 15 days for substitutions showing ≥100-fold reduction in susceptibility.

PMR 4841-2 Schedule Milestones

Strain Surveillance Study

- Draft Protocol Submission: December 2025
- Final Protocol Submission: July 2026
- Interim Report Submission: July 2028
- Interim Report Submission: July 2029
- Interim Report Submission: July 2030
- Interim Report Submission: July 2031
- Interim Report Submission: July 2032
- Interim Report Submission: July 2033
- Final Report Submission: July 2034

Public Sequence Database Analysis

- Interim Report Submission: July 2025
- Interim Report Submission: July 2026
- Interim Report Submission: July 2027
- Interim Report Submission: July 2028
- Interim Report Submission: July 2029
- Interim Report Submission: July 2030
- Interim Report Submission: July 2031
- Interim Report Submission: July 2032
- Interim Report Submission: July 2033
- Final Report Submission: July 2034

PMR Set 4841-3

PMR Description

Conduct a study to assess F protein substitutions in cell culture neutralization assays, in the background subtype in which they were identified based on non-clinical, surveillance, and clinical studies of clesrovimab. The list of substitutions is provided below:

RSV A: N380S, N426H, N428D, R429H, S436F, V447M, Y457H, K465R, S466N, K470R

Also: test S443T if RSV B S443L shows reduced susceptibility to clesrovimab, and test K445R if RSV B K445N shows reduced susceptibility.

RSV B: I402V, K433R, F435S, V442M, S443L, K445N, G446V, V452E

Also: test V447I if RSV A V447M shows reduced susceptibility to clesrovimab.

PMR 4841-3 Schedule Milestones

- Draft Protocol Submission: December 2025
- Final Protocol Submission: July 2026
- Interim Report: July 2027
- Interim Report: July 2028
- Final Report Submission: July 2029

The Applicant agreed to notify the Agency within 2 months of receipt of new, confirmed, phenotypic data for variants or individual substitutions showing ≥5-fold reduction in susceptibility, and no later than 15 days for substitutions showing ≥100-fold reduction in susceptibility.

Postmarketing Commitment (506B Reportable)

PMC Set 4841-4

PMC Description

Conduct a study to assess the cell culture neutralization of clesrovimab against RSV with substitutions that confer >100-fold reduction in susceptibility to nirsevimab, as reported in the BEYFORTUS™ USPI:

RSV A: N67I+N208Y

RSV B: K68N+N201S, K68N+N208S, L203I, N208D

PMC 4841-4 Schedule Milestone

- Final Report Submission: August 2027

25. Financial Disclosure

Table 160. Covered Clinical Trials: MK-1654-002, MK-1654-004, and MK-1654-007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2162		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator: 1 Sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 2 Two (2) subinvestigators did not return the form with requested information. Due Diligence attempts were made on 10-23-2023, 10-30-2023, 10-31-2023, 11-01-2023, and 06-27-2024.		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Journal Articles

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27. Review Team

Table 161. Reviewers of Integrated Assessment

Role	Name(s)
Clinical Reviewer	Yugenia Hong-Nguyen, MD
Clinical Team Leader Cross-Disciplinary Team Leader	Aimee Hodowanec, MD
Pharmacology Toxicology Reviewer	Maocheng Yang, PhD, DABT
Pharmacology Toxicology Team Leader	Christopher Ellis, PhD
Division Director (Pharmacology/Toxicology)	Hanan Ghantous, PhD, DABT
Clinical Virology Reviewers	Michael Thomson, PhD Eric Donaldson, PhD
Clinical Virology Team Leader	Jules O'Rear, PhD
OCP Reviewer(s)	Yi Zhang, PhD Elyes Dahmane, PhD
OCP Team Leader(s)	Su-Young Choi, PhD Justin Earp, PhD
Division Director (OCP)	Kellie Reynolds, PharmD
Biometrics Reviewer	Ling Zhang, PhD
Biometrics Secondary Reviewer	Wen Zen, PhD
Supervisory Mathematical Statistician (OB)	Scott Komo, DrPH
Chemistry, Manufacturing and Controls - Application Team Lead	Nailing Zhang, PhD
Associate Director for Labeling	Stacey Min, PharmD
Regulatory Project Manager	Nina Mani, PhD, MPH
Chief Project Management Staff	Karen Winestock
Director of Regulatory Operations for Infectious Diseases	Maureen Dillon-Parker, MS, RAC
Deputy Director (Safety)	Poonam Mishra, MD, MPH
Division Director (Clinical)	Wendy Carter, DO
Office Director (Acting)	Adam Sherwat, MD

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 162. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ RBPM	Shazma Aftab, PharmD
Office of Product Quality Assessment (OPQA) Drug Product/Drug Substance Reviewer	Dilip Devineni, PhD
OPQA Immunogenicity Reviewer	Davinna Ligons, PhD
OPMA Drug Product Micro/Facility Reviewer	Maria Gutierrez-Hoffman, PhD
OPMA Drug Substance Micro/Facility Reviewer	Ralph Bernstein, PhD
OPMA Micro/Facility Quality Application Lead	Virginia Carroll, PhD
OPQA Labeling Reviewer	Liming Lu, PharmD, RPh
OPQA Review Chief	Maria Teresa Gutierrez-Lugo, PhD
CDRH (OPEQ/OHT3/DHT3C – Injection Team	Cassandra O'Donnell, PhD Rong Guo, PhD Shruti Mistry, PhD
CDRH (DMD\BAC2b) – In vitro Diagnostics	Daisy Torres-Miranda, PhD
DMPP	Maria Nguyen, MSHS, BSN, RN Barbara Fuller, PharmD
OPDP	Wendy Lubarsky, PharmD Sam Skariah, PharmD
OSI	Elena Boley, MD Philip Kronstein, MD Jenn Sellers, MD
OSE/DMEPA	Melina Fanari, RPh Yevgeniya Kogan, PharmD, BCSCP Idalia Rychlik, PharmD Keith Christopher, PhD Matthew Barlow, RN, BSN Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP Carlos M Mena-Grillasca, BS Pharm Mishale Mistry, PharmD, MPH
OSE/DRISK	Timothy Bernheimer, PharmD Naomi Boston, PharmD Laura Zendel, PharmD
OND/OID/DAV- Clinical Virology Reviewer	Sheli Radoshitzky, PhD

Abbreviations: BAC2b, Bacterial Respiratory and Medical Countermeasure Branch; CDRH, Center for Devices and Radiological Health; DAV, Division of Antivirals; DEPI, Division of Epidemiology; DHT3C, Drug Delivery and General Hospital Devices, and Human Factors; DMD, Division of Microbiology Devices; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DRISK, Division of Risk Management; OHT3, Office of Gastrorenal, ObGyn, General Hospital, and Urology Devices; OID, Office of Infectious Diseases; OND, Office of New Drugs; OPDP, Office of Prescription Drug Promotion; OPEQ, Office of Product Evaluation and Quality; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OPQA, Offices of Product Quality Assessment; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; RBPM, regulatory business process manager

27.1. Reviewer Signatures

Table 27-163 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Maocheng Yang OID DPTID	Sections: None, 7.1, 8.4, All, None, None	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Maocheng Yang**			**Digitally signed by Maocheng Yang** **Date: 6/5/2025 2:13 PM EDT** **GUID: 202565181332**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Elyes Dahmane OCP DPM	Sections: 6.1, 6.3.1, 14.3	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Elyes Dahmane**			**Digitally signed by Elyes Dahmane** **Date: 6/5/2025 2:13 PM EDT** **GUID: 202565181352**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Virology Discipline Secondary Reviewer	Eric Donaldson OID DAV	Sections: 18, 20, 5, 6, 7	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Eric Donaldson			**Digitally signed by Eric Donaldson** **Date: 6/5/2025 2:14 PM EDT** **GUID: 202565181432**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Virology Discipline Primary Reviewer	Michael Thomson OID DAV	Sections: 18, 20, 5, 6, 7	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Michael Thomson			**Digitally signed by Michael Thomson** **Date: 6/5/2025 2:18 PM EDT** **GUID: 202565181837**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Christopher Ellis OID DPTID	Sections: 7.1, 8.4, 13.1, 13.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Christopher Ellis			**Digitally signed by Christopher Ellis** **Date: 6/5/2025 2:22 PM EDT** **GUID: 202565182234**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Wen Zeng OB DBIV	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Wen Zeng			**Digitally signed by Wen Zeng** **Date: 6/5/2025 2:24 PM EDT** **GUID: 20256518244**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Ling Zhang OB DBIV	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Based on the comprehensive statistical analysis of the submitted data, including the primary and secondary efficacy analyses and sensitivity analyses, I recommend approval of this BLA761432 from a statistical perspective, as the results demonstrate statistically significant and clinically meaningful efficacy with an acceptable safety profile that supports the proposed indication.
Signature: Ling Zhang			**Digitally signed by Ling Zhang** **Date: 6/5/2025 2:26 PM EDT** **GUID: 202565182622**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Yugenia Hong-Nguyen OID DAV	Sections: 1-4, 6, 7, 8-12, 15-16, 17-19, 20-21, 22, 23-36	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yugenia Hong-Nguyen			**Digitally signed by Yugenia Hong-Nguyen** **Date: 6/5/2025 2:32 PM EDT** **GUID: 202565183248**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Justin Earp OCP DPM	Sections: 5, 6.3, 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Justin Earp			**Digitally signed by Justin Earp** **Date: 6/5/2025 2:39 PM EDT** **GUID: 202565183930**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Virology Discipline Tertiary Reviewer	Julian O Rear OID DAV	Sections: 18, 20, 5, 6, 7	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Julian O Rear			**Digitally signed by Julian O Rear** **Date: 6/5/2025 2:57 PM EDT** **GUID: 202565185726**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Nina Mani ORO DROID	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Nina Mani			**Digitally signed by Nina Mani** **Date: 6/5/2025 3:03 PM EDT** **GUID: 20256519337**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Yi Zhang OCP DIDP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yi Zhang			**Digitally signed by Yi Zhang** **Date: 6/5/2025 3:25 PM EDT** **GUID: 20256519258**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Su-Young Choi OCP DIDP	Sections: 5,6,8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Su-Young Choi

Digitally signed by Su-Young Choi

Date: 6/5/2025 3:26 PM EDT
GUID: 202565192628

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Primary Reviewer	Nailing Zhang OPQAIII DPQAXV	Sections: 9, None	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Nailing Zhang

Digitally signed by Nailing Zhang

Date: 6/5/2025 3:26 PM EDT
GUID: 202565192659

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Secondary Reviewer	Nailing Zhang OPQAIII DPQAXV	Sections: 9, None	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Nailing Zhang

Digitally signed by Nailing Zhang

Date: 6/5/2025 3:27 PM EDT
GUID: 202565192753

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Aimee Hodowanec OID DAV	Sections: 1-4, 6-12, 15-21, and 23-26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Aimee Hodowanec

Digitally signed by Aimee Hodowanec

Date: 6/5/2025 3:27 PM EDT
GUID: 202565192756

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Tertiary Reviewer	Aimee Hodowanec OID DAV	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Aimee Hodowanec

Digitally signed by Aimee Hodowanec

Date: 6/5/2025 3:28 PM EDT
GUID: 202565192837

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Secondary Reviewer	Aimee Hodowanec OID DAV	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Aimee Hodowanec

Digitally signed by Aimee Hodowanec

Date: 6/5/2025 3:34 PM EDT
GUID: 202565193453

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Primary Reviewer	Aimee Hodowanec OID DAV	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Aimee Hodowanec**

Digitally signed by Aimee Hodowanec

Date: 6/5/2025 3:41 PM EDT
GUID: 202565194125

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Karen Winestock ORO DROID	Sections: 12, 13, 1	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	

Signature: **Karen Winestock**

Digitally signed by Karen Winestock

Date: 6/5/2025 3:41 PM EDT
GUID: 202565194147

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Scott Komo OB DBIV	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Scott Komo			**Digitally signed by Scott Komo** **Date: 6/5/2025 4:05 PM EDT** **GUID: 20256520545**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Terry Miller OID DPTID	Sections: Section 7.1, 8.4, 13.1, 13.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Terry Miller			**Digitally signed by Terry Miller** **Sign on behalf of** **Date: 6/5/2025 4:25 PM EDT** **GUID: 202565202557**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Kellie Reynolds OCP DIDP	Sections: 5; 6.1; 6.3.1; 6.3.3; 6.3.5; 8.1; 8.3; 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Kellie Reynolds

Digitally signed by Kellie Reynolds

Date: 6/6/2025 5:59 AM EDT
GUID: 20256695944

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Tertiary Reviewer	Maureen Dillon Parker ORO DROID	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Maureen Dillon Parker

Digitally signed by Maureen Dillon Parker

Date: 6/6/2025 7:59 AM EDT
GUID: 202566115959

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AIMEE C HODOWANEC
06/06/2025 01:15:48 PM

WENDY W CARTER
06/06/2025 01:22:01 PM

ADAM I SHERWAT
06/09/2025 08:11:36 AM